



(86) Date de dépôt PCT/PCT Filing Date: 2010/02/02
(87) Date publication PCT/PCT Publication Date: 2010/08/12
(85) Entrée phase nationale/National Entry: 2011/08/02
(86) N° demande PCT/PCT Application No.: EP 2010/000630
(87) N° publication PCT/PCT Publication No.: 2010/089084
(30) Priorité/Priority: 2009/02/04 (EP09001488.7)

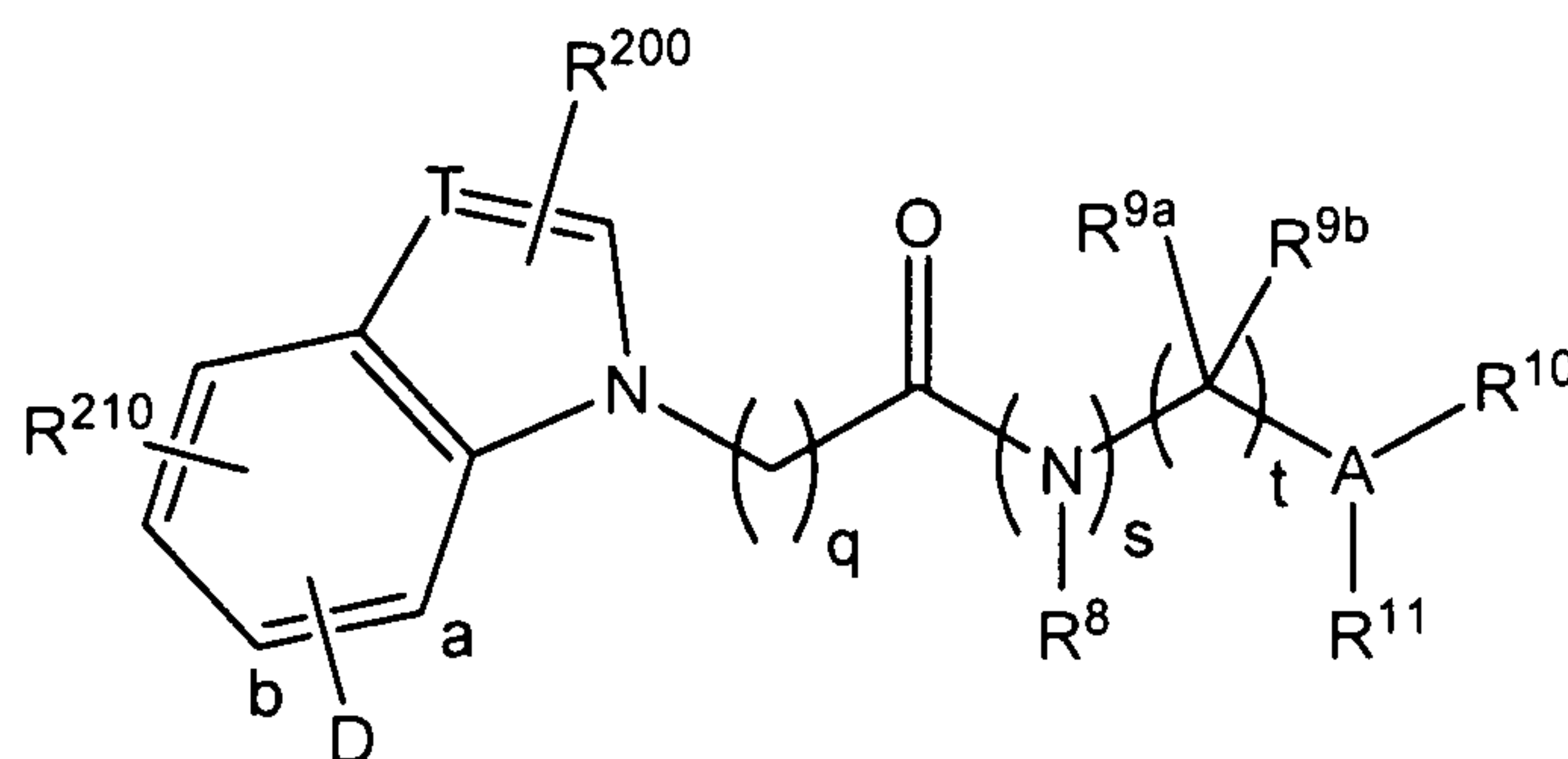
(51) Cl.Int./Int.Cl. *C07D 401/14* (2006.01),
A61K 31/454 (2006.01), *A61K 31/4545* (2006.01),
A61K 31/497 (2006.01), *A61P 25/00* (2006.01),
A61P 29/00 (2006.01), *C07D 403/12* (2006.01),
C07D 409/12 (2006.01), *C07D 471/10* (2006.01),
C07D 487/10 (2006.01)

(71) Demandeur/Applicant:
GRUENENTHAL GMBH, DE

(72) Inventeurs/Inventors:
SCHUNK, STEFAN, DE;
REICH, MELANIE, DE;
ENGELS, MICHAEL, BE;
GERMANN, TIENO, DE; ...

(54) Titre : COMPOSES D'INDOL SUBSTITUES EN TANT QUE MODULATEURS DU RECEPTEUR 1 DE LA
BRADYKININE

(54) Title: SUBSTITUTED INDOLE COMPOUNDS AS BRADYKININ RECEPTOR 1 MODULATORS



(I)

(57) Abrégé/Abstract:

The invention relates to substituted indole compounds of general formula (I), methods for the production thereof, medicaments containing said compounds, and the use of substituted indole compounds for the production of medicaments.

(72) **Inventeurs(suite)/Inventors(continued):** JOSTOCK, RUTH, DE; HEES, SABINE, DE

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

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES
PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG(19) Weltorganisation für geistiges Eigentum
Internationales Büro(43) Internationales Veröffentlichungsdatum
12. August 2010 (12.08.2010)(10) Internationale Veröffentlichungsnummer
WO 2010/089084 A1

(51) Internationale Patentklassifikation:

C07D 401/14 (2006.01) A61K 31/454 (2006.01)
 C07D 403/12 (2006.01) A61K 31/4545 (2006.01)
 C07D 409/12 (2006.01) A61K 31/497 (2006.01)
 C07D 471/10 (2006.01) A61P 25/00 (2006.01)
 C07D 487/10 (2006.01) A61P 29/00 (2006.01)

(21) Internationales Aktenzeichen: PCT/EP2010/000630

(22) Internationales Anmeldedatum:
2. Februar 2010 (02.02.2010)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
09001488.7 4. Februar 2009 (04.02.2009) EP

(71) Anmelder (für alle Bestimmungsstaaten mit Ausnahme von US): GRÜNENTHAL GMBH [DE/DE]; Zieglerstrasse 6, 52078 Aachen (DE).

(72) Erfinder; und

(75) Erfinder/Anmelder (nur für US): SCHUNK, Stefan [DE/DE]; Augustastraße 9, 52070 Aachen (DE). REICH, Melanie [DE/DE]; Nizzaallee 39, 52072 Aachen (DE). ENGELS, Michael [DE/BE]; Jokerstraat 9, B-2300 Turnhout (BE). GERMANN, Tieno [DE/DE]; Lindenstrasse 115, 52080 Aachen (DE). JOSTOCK, Ruth [DE/DE]; Hostetstrasse 35, 52223 Stolberg (DE).

HEES, Sabine [DE/DE]; Kirchberg 6 a, 52076 Aachen (DE).

(81) Bestimmungsstaaten (soweit nicht anders angegeben, für jede verfügbare nationale Schutzrechtsart): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

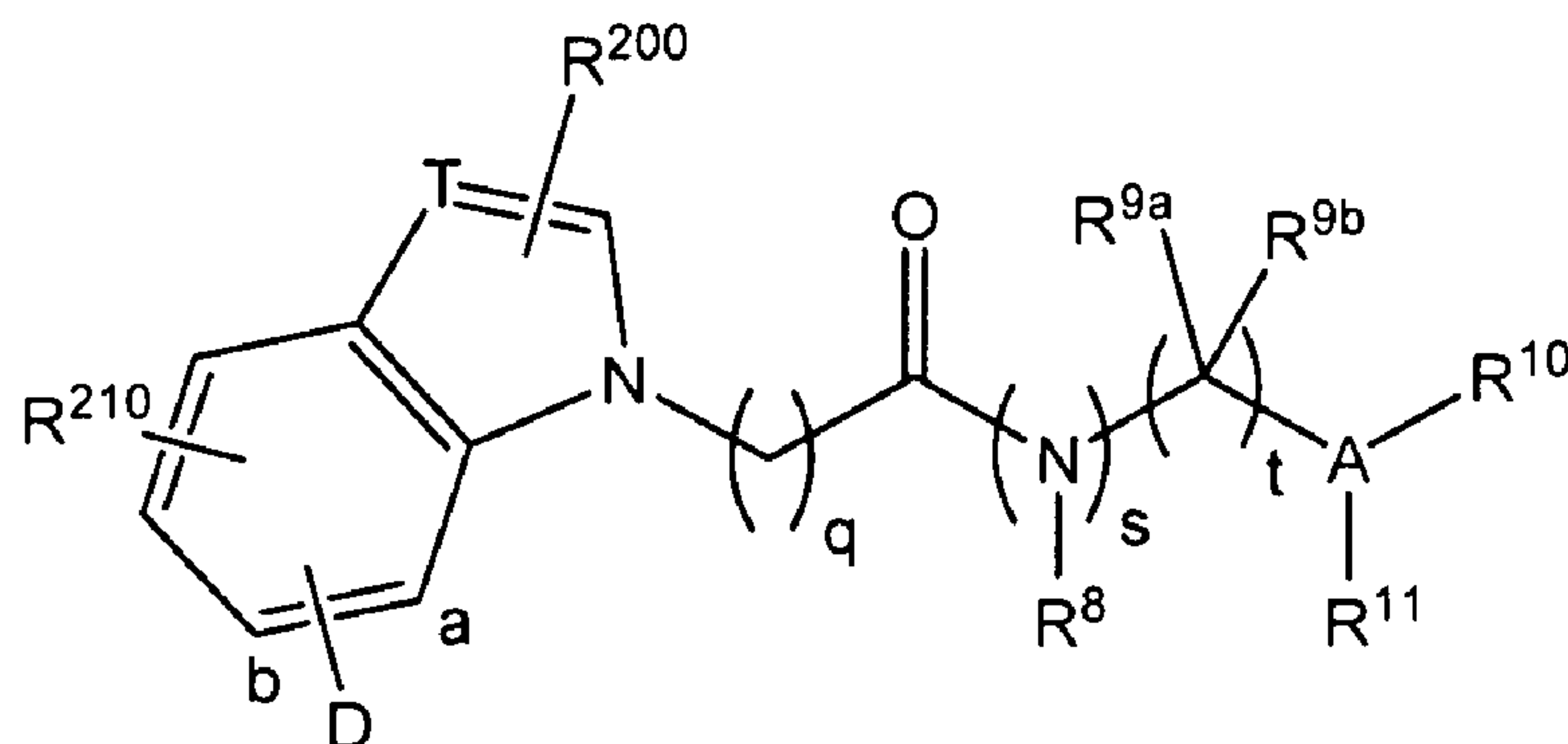
(84) Bestimmungsstaaten (soweit nicht anders angegeben, für jede verfügbare regionale Schutzrechtsart): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:

— mit internationalem Recherchenbericht (Artikel 21 Absatz 3)

(54) Title: SUBSTITUTED INDOLE COMPOUNDS AS BRADYKININ RECEPTOR 1 MODULATORS

(54) Bezeichnung : SUBSTITUIERTE INDOL-VERBINDUNGEN ALS BRADYKININ REZEPTOR 1 MODULATOREN



(I)

(57) Abstract: The invention relates to substituted indole compounds of general formula (I), methods for the production thereof, medicaments containing said compounds, and the use of substituted indole compounds for the production of medicaments.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft substituierte Indol -Verbindungen der allgemeinen Formel (I), Verfahren zu deren Herstellung, Arzneimittel enthaltend diese Verbindungen und die Verwendung von substituierten Indol -Verbindungen zur Herstellung von Arzneimitteln.

GRA3454-WO
22nd December 2009

Substituted indole compounds as bradykinin receptor 1 modulators

The present invention relates to substituted indole compounds, processes for the preparation thereof, medicinal products containing these compounds and the use of substituted indole compounds for the preparation of medicinal products.

In contrast to the constitutive expression of the bradykinin 2 receptor (B2R), the bradykinin 1 receptor (B1R) is not expressed or is only weakly expressed in most tissues. Nevertheless, expression of the B1R can be induced on various cells. By way of example, in the course of inflammation reactions a rapid and pronounced induction of the B1R takes place on neuronal cells, but also on various peripheral cells, such as fibroblasts, endothelial cells, granulocytes, macrophages and lymphocytes. Thus, in the course of inflammation reactions a switch from a B2R to a B1R dominance occurs on the cells involved. The cytokines interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF α) are substantially involved in this B1R up-regulation (Passos et al. J. Immunol. 2004, 172, 1839-1847). After activation with specific ligands, B1R-expressing cells can subsequently themselves secrete inflammation-promoting cytokines, such as IL-6 and IL-8 (Hayashi et al., Eur. Respir. J. 2000, 16, 452-458). This leads to inwards migration of further inflammation cells, for example neutrophilic granulocytes (Pesquero et al., PNAS 2000, 97, 8140-8145). The bradykinin B1R system can contribute to the chronification of diseases via these mechanisms. This is demonstrated by a large number of animal studies (overviews in Leeb-Lundberg et al., Pharmacol Rev. 2005, 57, 27-77 and Pesquero et al., Biol. Chem. 2006, 387, 119-126). In humans too, an increased expression of the B1R is seen, for example on enterocytes and macrophages in the affected tissue of patients with inflammatory bowel diseases (Stadnicki et al., Am. J. Physiol. Gastrointest. Liver Physiol. 2005, 289, G361-366) and on T lymphocytes of patients with multiple sclerosis (Prat et al., Neurology. 1999; 53, 2087-2092), or an activation of the bradykinin B2R-B1R system is seen in the course of infections with *Staphylococcus aureus* (Bengtson et al., Blood 2006, 108, 2055-2063). Infections with *Staphylococcus aureus* are responsible for disease profiles such as superficial infections of the skin through to septic shock.

GRA3454-WO
22nd December 2009

Based on the pathophysiological relationships described, there is great therapeutic potential for the use of B1R antagonists against acute and in particular chronic inflammatory diseases. They include diseases of the respiratory tract (bronchial asthma, allergies, COPD/chronic obstructive pulmonary disease, cystic fibrosis, etc.), inflammatory bowel diseases (ulcerative colitis, CD/Crohn's disease, etc.), neurological diseases (multiple sclerosis, neurodegeneration, etc.), inflammations of the skin (atopic dermatitis, psoriasis, bacterial infections, etc.) and mucous membranes (Behcet's disease, chronic pelvic pain, prostatitis, etc.), rheumatic diseases (rheumatoid arthritis, osteoarthritis, etc.), septic shock and reperfusion syndrome (following heart attack or stroke).

The bradykinin (receptor) system is moreover also involved in the regulation of angiogenesis (potential as an angiogenesis inhibitor in cases of cancer and macula degeneration in the eye), and B1R-knockout mice are protected from the induction of obesity by a particularly high-fat diet (Pesquero et al., *Biol. Chem.* 2006, 387, 119-126). B1R antagonists are therefore also suitable for the treatment of obesity.

B1R antagonists are particularly suitable for the treatment of pain, in particular inflammatory pain and neuropathic pain (Calixto et al., *Br. J. Pharmacol* 2004, 1-16), and here in particular diabetic neuropathy (Gabra et al., *Biol. Chem.* 2006, 387, 127-143). They are also suitable for the treatment of migraine.

In the development of B1R modulators there is the problem, however, that the human and the rat B1R receptor differ so widely that many compounds which are good B1R modulators on the human receptor have only a poor or no affinity for the rat receptor. This makes animal pharmacology studies considerably more difficult, since many studies are usually conducted on the rat. However, if there is no activity on the rat receptor, neither action nor side-effect can be investigated on the rat. This has already meant that transgenic animals with human B1 receptors have been produced for animal pharmacology studies (Hess et al., *Biol. Chem* 2006; 387(2):195-201). Working with transgenic animals is, however, more expensive than working with the unmodified animals.

GRA3454-WO
22nd December 2009

The patent applications WO 2008/040492 and WO 2008/046573 describe compounds which in *in-vitro* assays exhibit an antagonistic action both on the human B1 receptor and on the B1 receptor of the rat.

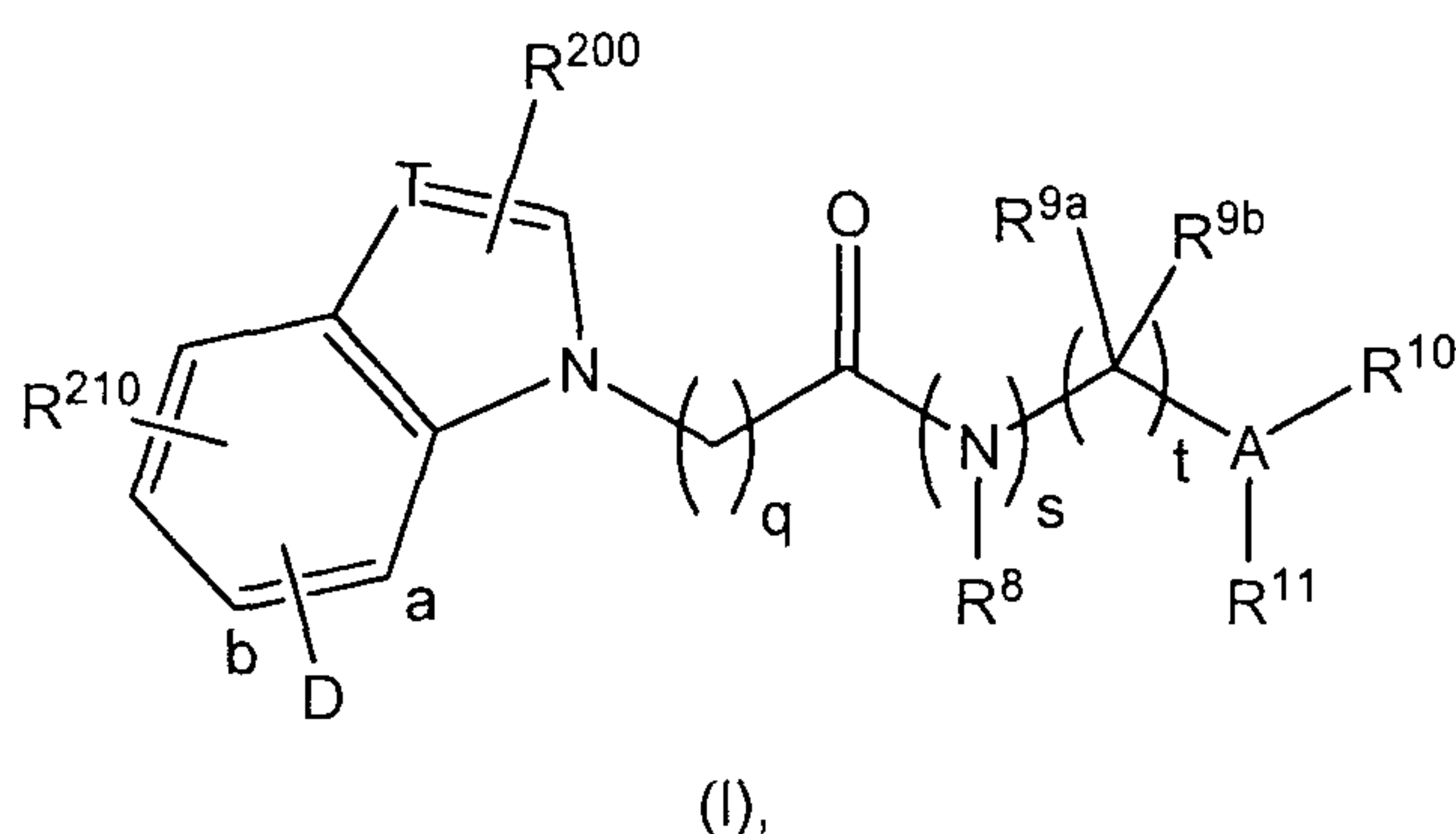
The patent applications WO 2007/140383 and WO 2007/101007 describe compounds which in *in-vitro* assays exhibit an antagonistic action on the macaque B1 receptor. Experimental data on the activity on the human B1 receptor or the B1 receptor of the rat is not disclosed.

There is therefore still a need for novel B1R modulators, wherein B1R modulators which bind both to the rat receptor and to the human receptor offer particular advantages.

An object of the present invention was therefore to provide novel compounds which are suitable in particular as pharmacological active ingredients in medicinal products, preferably in medicinal products for the treatment of disorders or diseases which are at least partly mediated by B1R receptors.

This object is achieved by the substituted indole compounds according to the invention.

The invention therefore provides substituted indole compounds having the general formula (I)



wherein

T stands for CH or N;

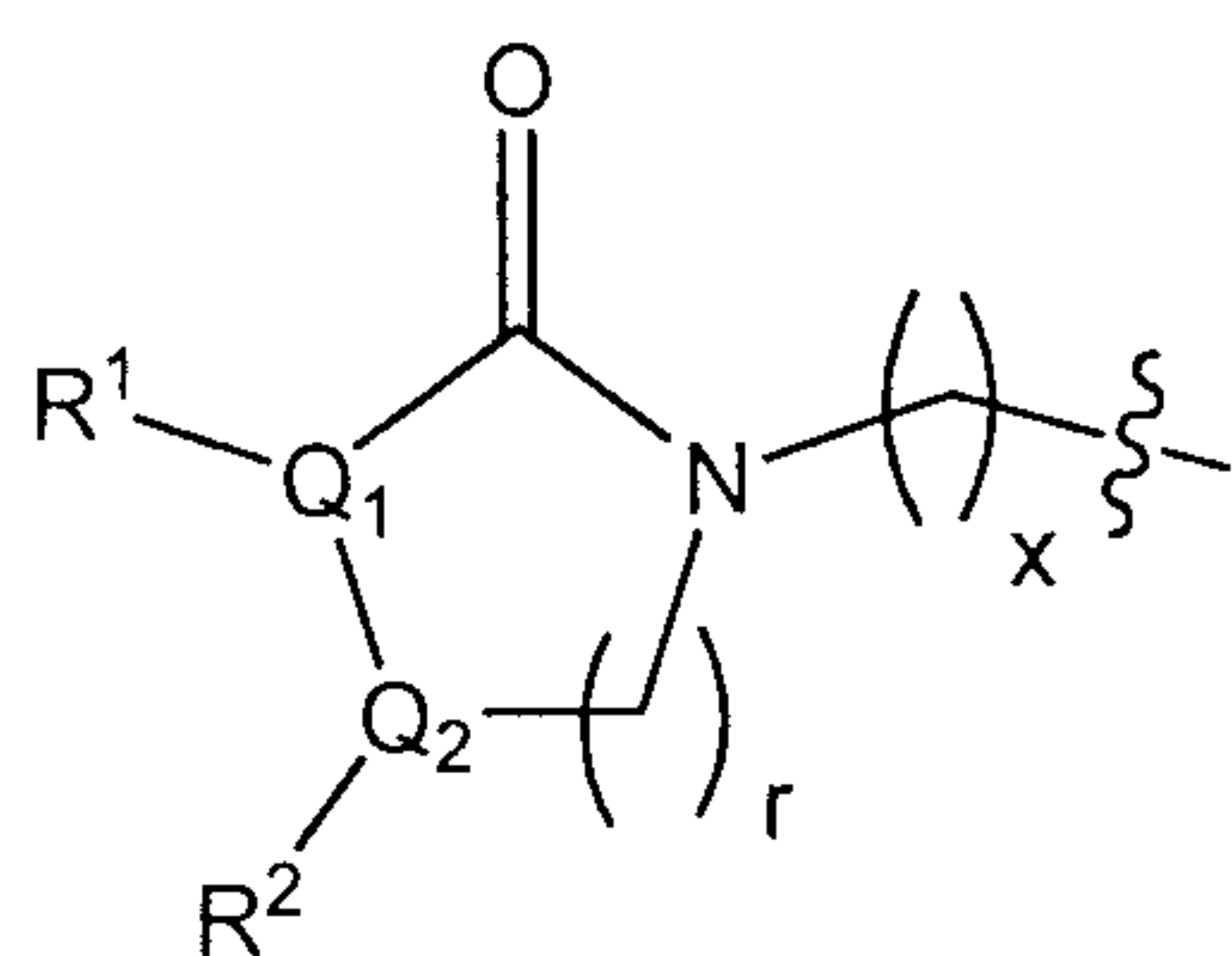
GRA3454-WO
22nd December 2009

$q = 1, 2 \text{ or } 3$;

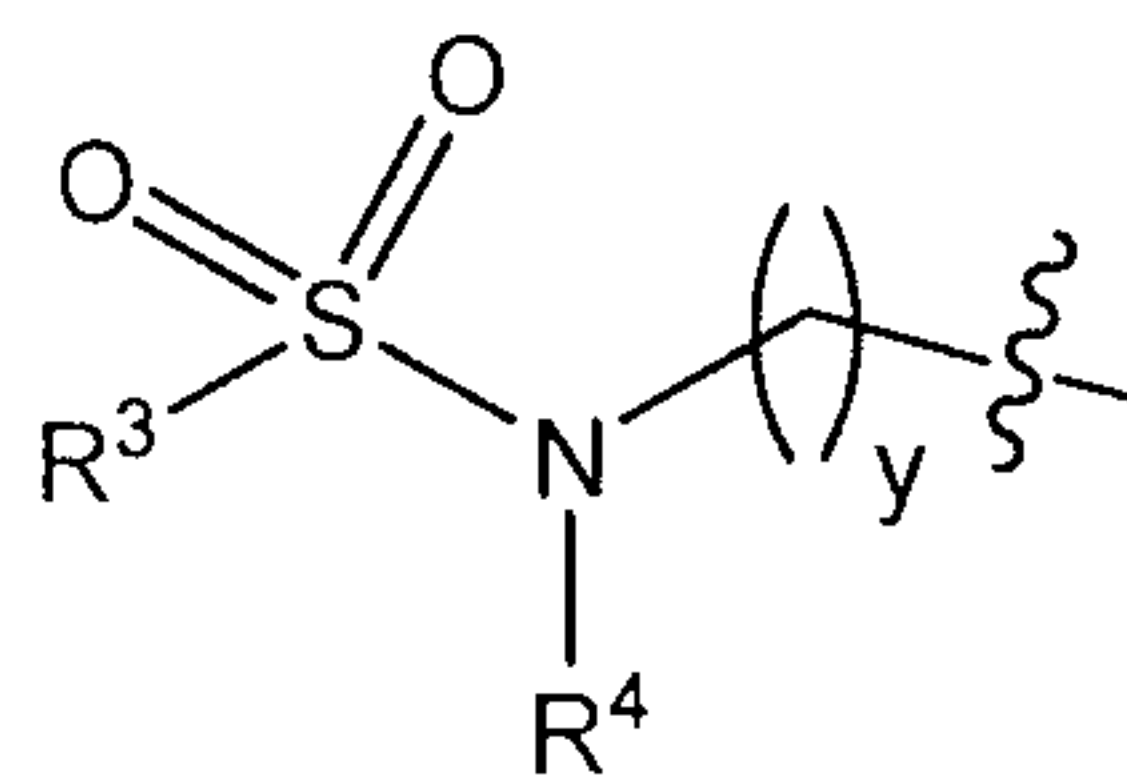
$s = 0 \text{ or } 1$;

$t = 0, 1, 2 \text{ or } 3$;

D in position a or b is bound to the indole skeleton and stands for one of the following radicals D1 or D2



D1



D2;

x and y , mutually independently, stand for 0 or 1;

r stands for 1, 2 or 3;

Q_1 and Q_2 mutually independently stand for C, CH or N;

R^1 and R^2 together with the $-Q_1-Q_2-$ group linking them form a cyclic compound, which can be substituted at one or more of its carbon ring members with one or more, for example 2 or 3, radicals mutually independently selected from the group consisting of F, Cl, Br, I, CF_3 , C_{1-6} alkyl, $O-C_{1-6}$ alkyl, OH, OCF_3 , SH, SCF_3 , aryl and heteroaryl and/or can be anellated with at least one aryl or heteroaryl, wherein the cyclic compound is saturated, mono- or polyunsaturated, for example diunsaturated, or aromatic, is 4-, 5-, 6- or 7-membered, can optionally contain one or more, for example 2 or 3, heteroatoms or heteroatom groups mutually independently selected from the group consisting of N, NR^{50} , O, S, $S=O$ and $S(=O)_2$; wherein the radical R^{50} denotes H, C_{1-6} alkyl, $-C(=O)-R^{51}$, C_{3-8} cycloalkyl, aryl, heteroaryl or a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-3} alkylene group, and R^{51} denotes C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl or a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-3} alkylene group;

GRA3454-WO
22nd December 2009

R^3 stands for aryl, heteroaryl or an aryl or heteroaryl bound by a C_{1-3} alkylene group, wherein aryl and heteroaryl can each be anellated with a 4-, 5-, 6- or 7-membered cyclic compound, wherein the cyclic compound is in each case saturated or mono- or polyunsaturated, for example diunsaturated, but is not aromatic and can be substituted at one or more of its carbon ring members with one or more radicals mutually independently selected from the group consisting of F, Cl, Br, I, $-CF_3$, $-O-CF_3$, C_{1-6} alkyl and $O-C_{1-6}$ alkyl and can optionally contain one or more, for example 2 or 3, heteroatoms or heteroatom groups mutually independently selected from the group consisting of N, NR^{50a} , O, S, $S=O$ and $S(=O)_2$, wherein R^{50a} denotes H, C_{1-6} alkyl, $-C(=O)-R^{51a}$, C_{3-8} cycloalkyl, aryl, heteroaryl or a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-3} alkylene group and R^{51a} denotes C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl or a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-3} alkylene group;

R^4 stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or for a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

R^{200} stands for 0 to 2 substituents, which are mutually independently selected from the group consisting of F, Cl, Br, I, CF_3 , OCF_3 , OH, $O-C_{1-6}$ alkyl, C_{1-6} alkyl, aryl and heteroaryl and/or two adjacent substituents R^{200} form an anellated aryl or heteroaryl;

R^{210} stands for 0 to 3 substituents which are mutually independently selected from the group consisting of F, Cl, Br, I, CF_3 , OCF_3 , OH, $O-C_{1-6}$ alkyl, C_{1-6} alkyl, aryl and heteroaryl;

R^8 stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or for a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

R^{9a} and R^{9b} mutually independently denote H, F, Cl, OH, C_{1-6} alkyl, $O-C_{1-6}$ alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

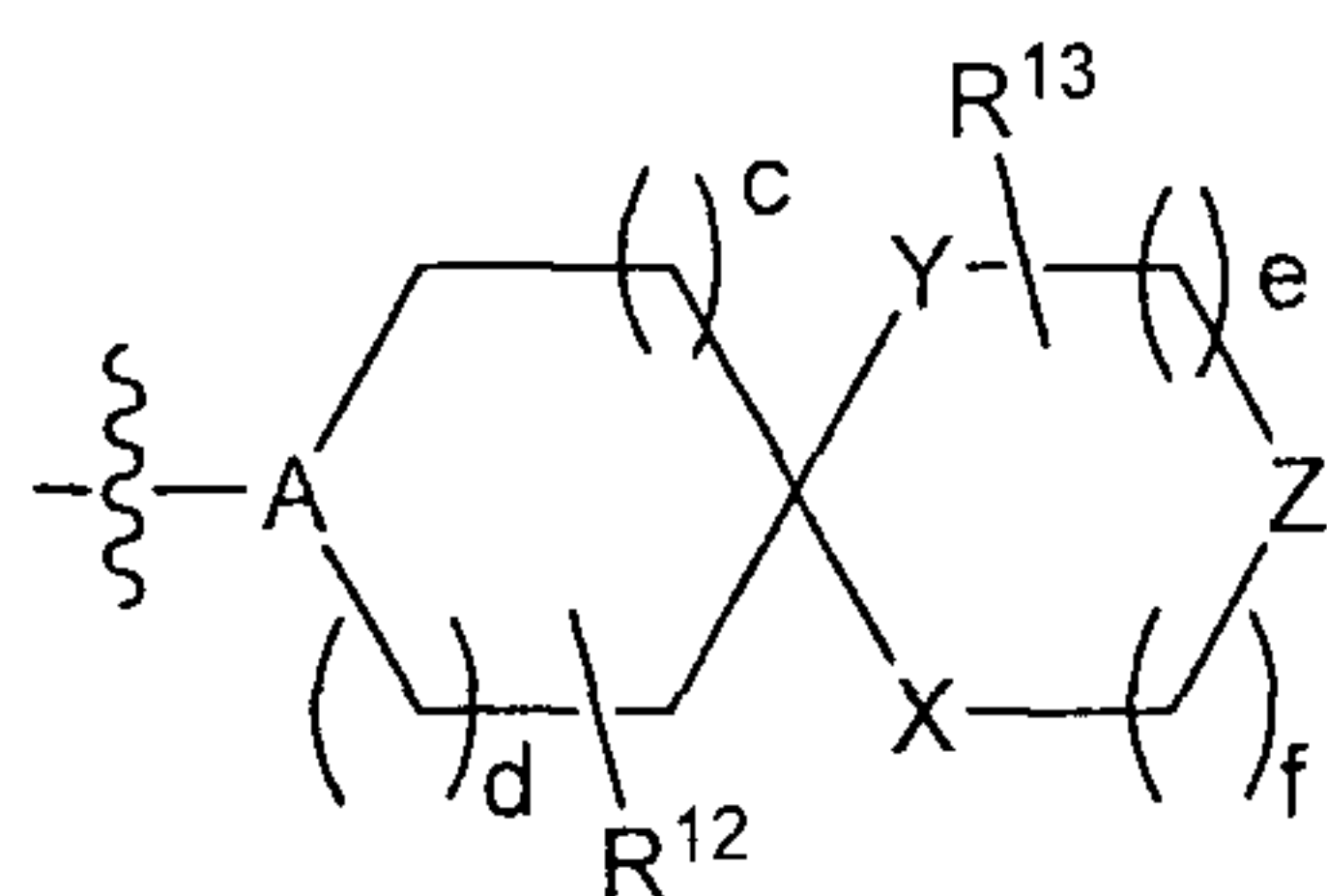
A stands for N or CH;

with the proviso that if s stands for 1 and t stands for 0 then A stands for CH; and

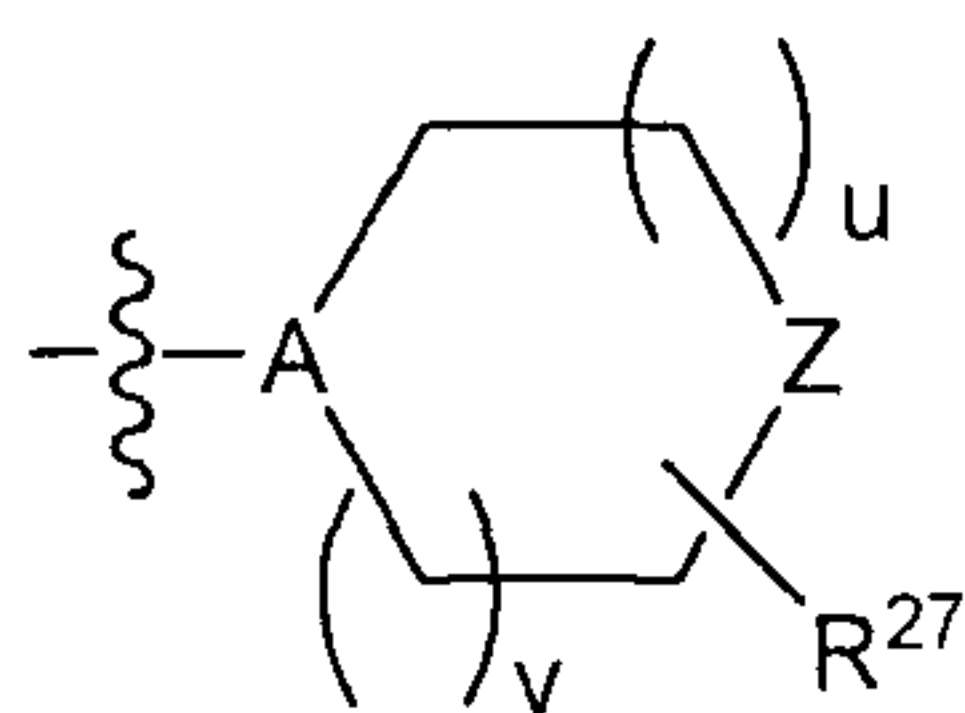
GRA3454-WO
22nd December 2009

with the proviso that if s and t each stand for 0 then A stands for N;

the radicals R^{10} and R^{11} with inclusion of A represent a spirocyclic or cyclic group according to one of the general formulae (II) or (III),



(II)



(III)

wherein

c, d, e, f, u and v mutually independently denote 0, 1 or 2;

R^{12} , R^{13} and R^{27} mutually independently stand for 0 to 4 substituents which are mutually independently selected from the group consisting of F, Cl, OH, =O, C_{1-6} alkyl, O- C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl and C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

and/or two of the 0 to 4 substituents R^{27} together represent a C_{1-3} alkylene bridge such that the cyclic compound represented in the general formula (III) assumes a bicyclically bridged form;

and/or two adjacent substituents out of the 0 to 4 substituents R^{13} form an anellated aryl or heteroaryl;

and/or two adjacent substituents out of the 0 to 4 substituents R^{27} form an anellated aryl or heteroaryl;

X stands for $CR^{14a}R^{14b}$, NR^{15} or O;

GRA3454-WO
22nd December 2009

Y stands for $\text{CR}^{16a}\text{R}^{16b}$, NR^{17} or O;

with the proviso that X does not denote NR^{15} if Y denotes NR^{17} ; and

with the proviso that X and Y do not simultaneously denote O;

wherein

R^{14a} , R^{14b} , R^{16a} and R^{16b} mutually independently denote H, F, Cl, OH, C_{1-6} alkyl, O- C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or stand for a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group,

and/or R^{14a} and R^{14b} can together stand for =O and/or R^{16a} and R^{16b} can together stand for =O;

R^{15} and R^{17} mutually independently stand for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denote a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

Z in the general formula (II) stands for $\text{CR}^{18a}\text{R}^{18b}$, NR^{19} or O;

or

Z in the general formula (II), if X stands for O and f stands for 0, denotes $-(\text{C}(\text{R}^{124})-\text{C}(\text{R}^{125}))$ -, wherein

R^{124} and R^{125} together with the carbon atoms linking them form a fused aryl or heteroaryl; or

Z in the general formula (II), if X stands for O and f stands for 0, denotes $=(\text{N}(\text{CR}^{126}))$ -, wherein the N atom is singly bound to the O atom, and

R^{126} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

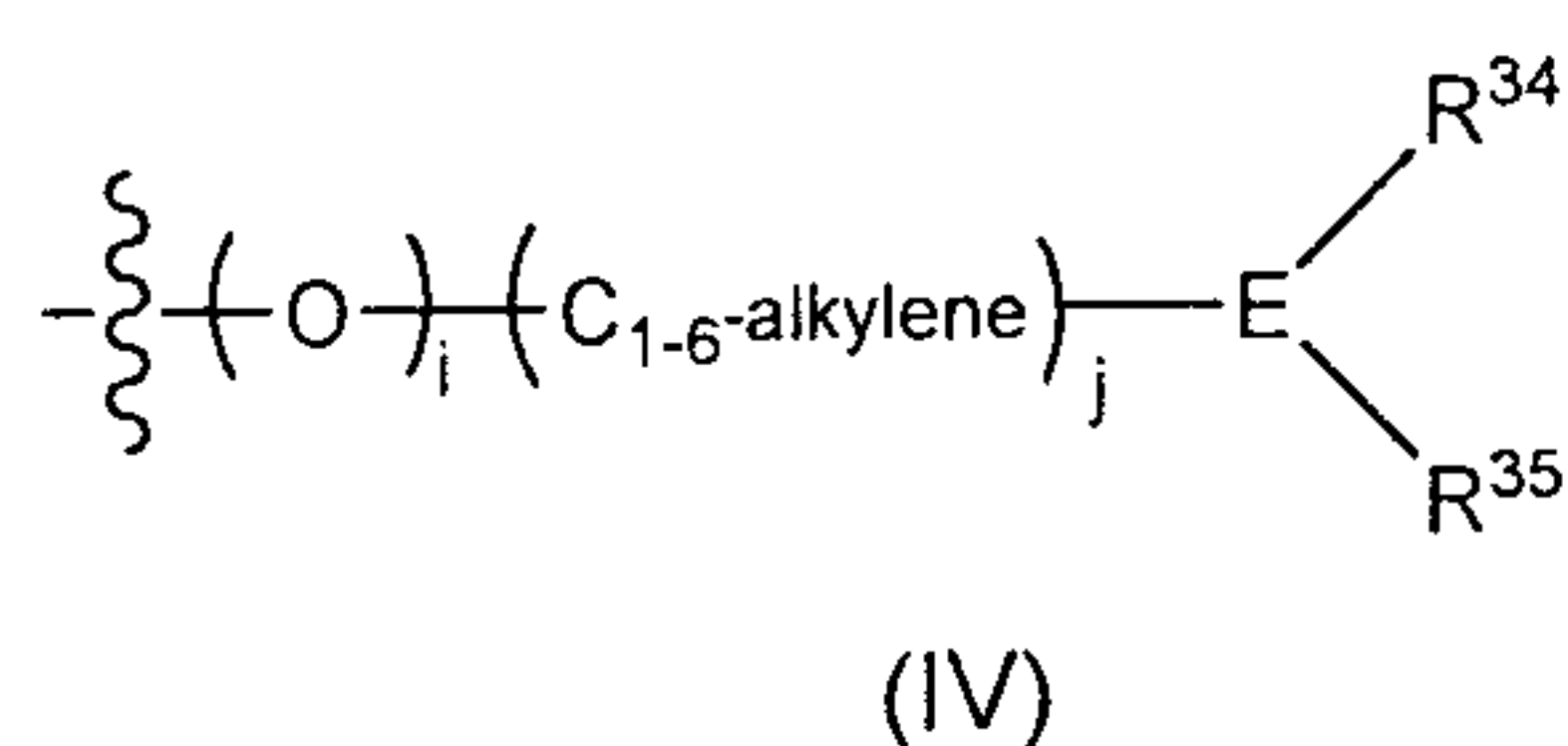
GRA3454-WO
22nd December 2009

Z in the general formula (III) stands for $\text{CR}^{18a}\text{R}^{18b}$, NR^{19} , O, S, S(=O) or S(=O)_2 ;

wherein

R^{18a} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group,

or R^{18a} stands for a group according to the general formula (IV),



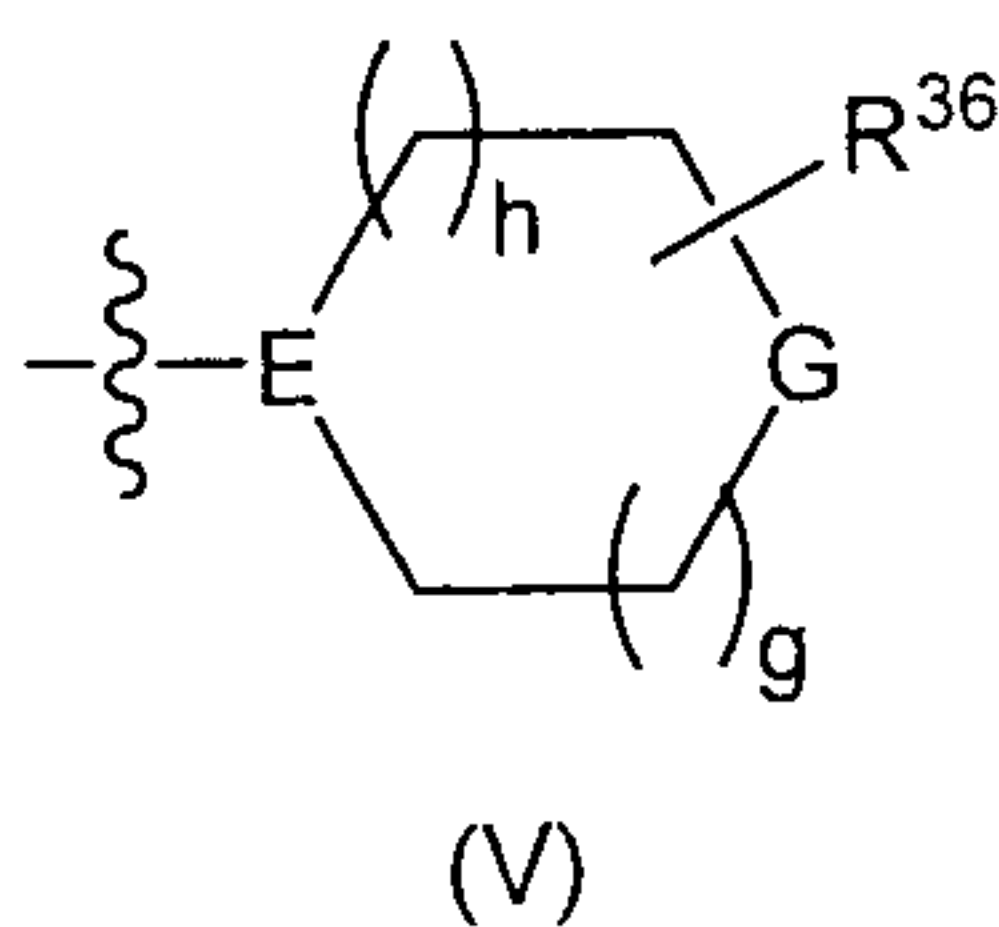
wherein

i and j mutually independently stand for 0 or 1;

E stands for N or CH, with the proviso that if i stands for 1 and j stands for 0 then E stands for CH,

R^{34} and R^{35} mutually independently denote H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or an aryl, heteroaryl or C_{3-8} cycloalkyl bound by a C_{1-3} alkylene group; or R^{34} and R^{35} with inclusion of E form a 5- or 6-membered aryl or heteroaryl;

or R^{34} and R^{35} with inclusion of E form a saturated heterocyclic compound according to the general formula (V),



GRA3454-WO
22nd December 2009

wherein

h and g mutually independently denote 0, 1 or 2;

G stands for $\text{CR}^{37a}\text{R}^{37b}$, NR^{38} , O, S, S=O or S(=O)_2 , with the proviso that if E stands for CH then G does not stand for $\text{CR}^{37a}\text{R}^{37b}$;

R^{36} stands for 0 to 4 substituents which are mutually independently selected from the group consisting of F, Cl, Br, I, OH, SH, =O, O- C_{1-6} alkyl, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl and C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

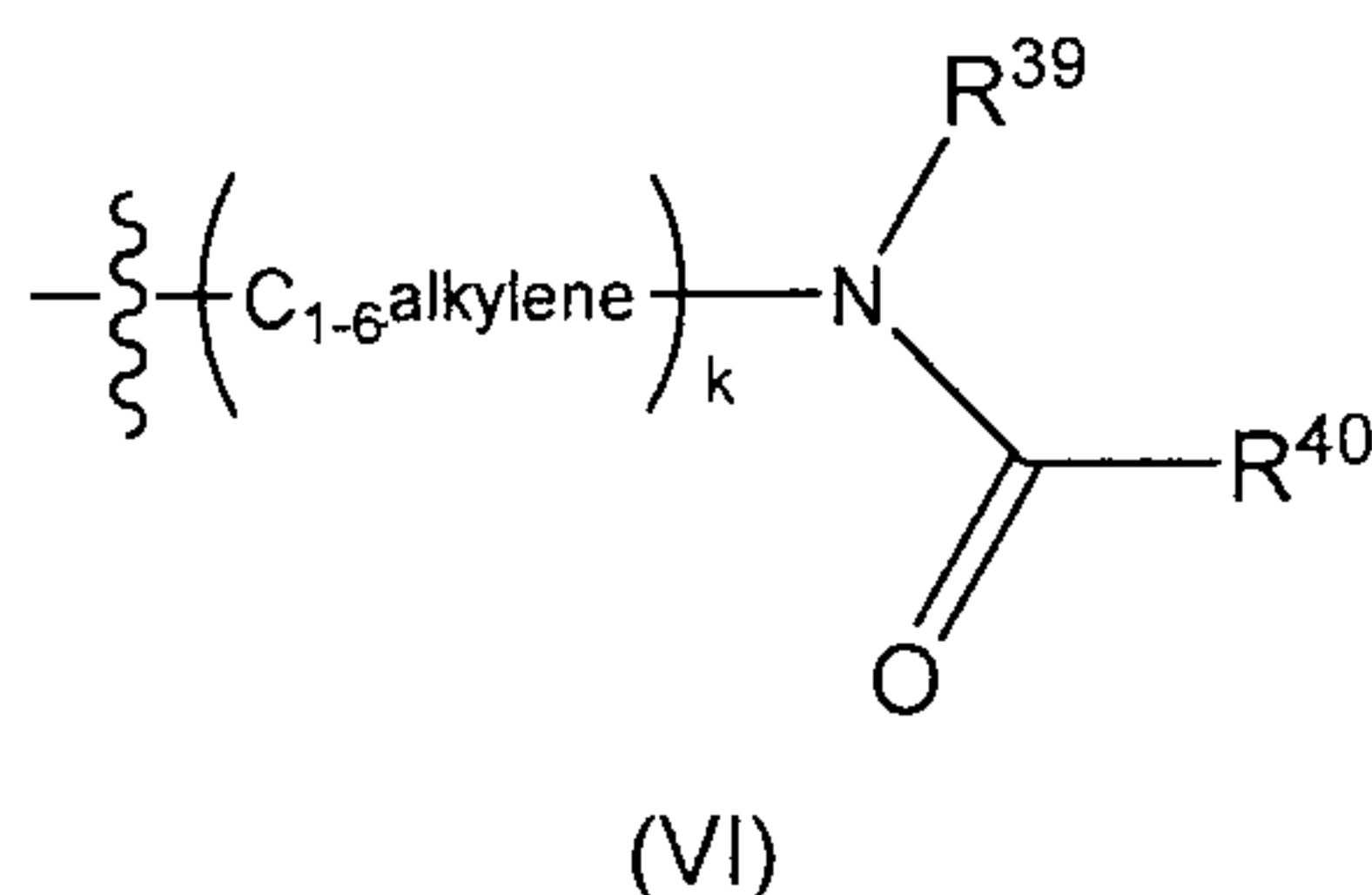
and/or two adjacent substituents R^{36} together represent an anellated aryl or heteroaryl;

R^{37a} and R^{37b} mutually independently denote H, F, Cl, Br, I, OH, SH, =O, O- C_{1-6} alkyl, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or stand for a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

R^{38} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes an aryl, heteroaryl or C_{3-8} cycloalkyl bound by a C_{1-3} alkylene group;

R^{18b} stands for H, OH, C_{1-6} alkyl, C_{3-8} cycloalkyl, O- C_{1-6} alkyl, O-(C_{3-8} cycloalkyl), (C_{1-6} alkylene)-O- C_{1-6} alkyl, (C_{1-6} alkylene)-O-(C_{3-8} cycloalkyl), aryl, heteroaryl, O-aryl or O-heteroaryl or denotes an aryl, O-aryl, heteroaryl or O-heteroaryl bound by a C_{1-6} alkylene group;

or R^{18b} stands for a group according to the general formula (VI),



wherein

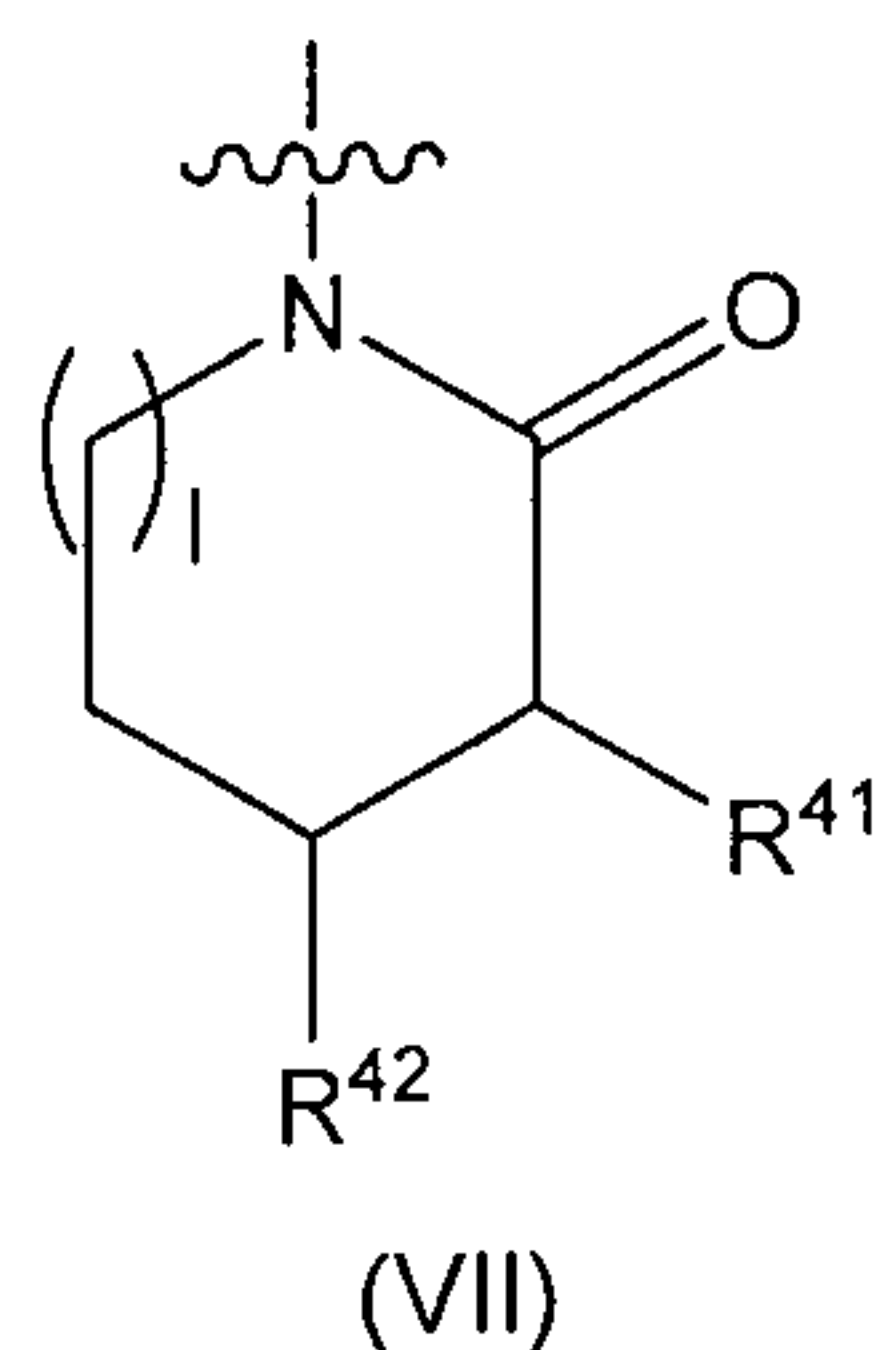
GRA3454-WO
22nd December 2009

k stands for 0 or 1;

R^{39} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-3} alkylene group;

R^{40} stands for C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group; or

R^{39} and R^{40} together with the N-C(=O) group linking them form a ring according to the general formula (VII),



wherein

I stands for 0, 1 or 2;

and R^{41} and R^{42} together with the carbon atoms linking them form an anellated aryl or heteroaryl;

R^{19} stands for H; or $(P)_z-R^{22}$,

wherein

z stands for 0 or 1;

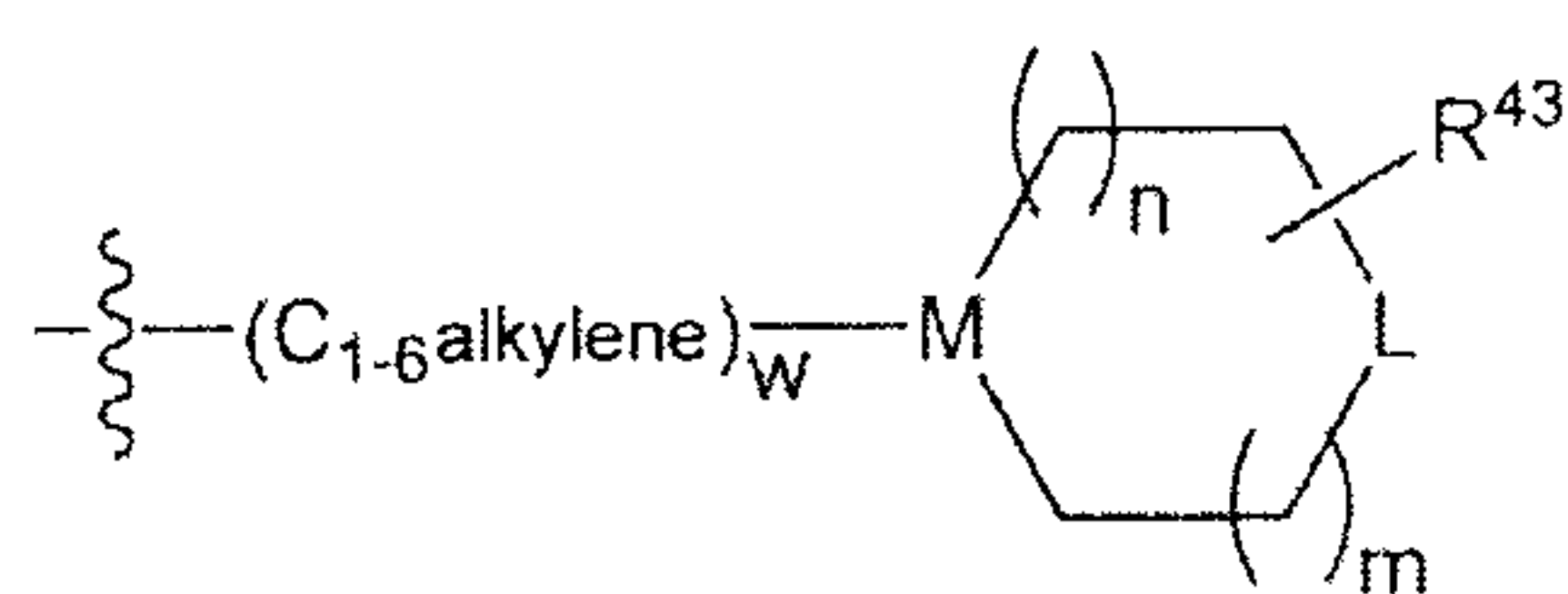
P stands for $(C=O)$, $S(=O)_2$ or $C(=O)-N(R^{24})$, wherein the N atom in the $C(=O)-N(R^{24})$ group is linked to R^{22} , wherein

GRA3454-WO
22nd December 2009

R^{24} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl or for an aryl, heteroaryl or C_{3-8} cycloalkyl bound by a C_{1-3} alkylene group;

R^{22} stands for C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes an aryl or heteroaryl bound by a C_{1-6} alkylene group; or

R^{22} stands for a group according to the general formula (VIII), wherein



(VIII)

n stands for 0, 1 or 2;

m stands for 0, 1 or 2;

w stands for 0 or 1,

M stands for CH or N;

with the proviso that if P stands for $C(=O)-NR^{24}$ and w stands for 0 then M stands for CH; and

with the proviso that if z and w simultaneously stand for 0 then M stands for CH;

L stands for $CR^{44a}R^{44b}$, NR^{45} , O, S, S=O or $S(=O)_2$;

R^{43} stands for 0 to 4 substituents which are mutually independently selected from the group consisting of F, Cl, OH, =O, C_{1-6} alkyl, O- C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl and C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

GRA3454-WO
22nd December 2009

and/or two adjacent radicals out of the 0 to 4 radicals R^{43} together represent an anellated aryl or heteroaryl;

R^{44a} and R^{44b} mutually independently stand for H, F, Cl, Br, I, OH, C_{1-6} alkyl, O- C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denote a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

or R^{44a} and R^{44b} can together stand for =O;

R^{45} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes an aryl, heteroaryl or C_{3-8} cycloalkyl bound by a C_{1-3} alkylene group;

wherein the aforementioned radicals C_{1-6} alkyl, C_{1-3} alkylene, C_{1-6} alkylene, C_{3-8} cycloalkyl, aryl and heteroaryl can each be unsubstituted or mono- or polysubstituted with identical or different radicals and the aforementioned radicals C_{1-6} alkyl, C_{1-3} alkylene and C_{1-6} alkylene can each be branched or unbranched;

optionally in the form of a single enantiomer or a single diastereomer, the racemate, the enantiomers, the diastereomers, mixtures of enantiomers and/or diastereomers, and each in the form of their bases and/or physiologically compatible salts.

In the general formula (IV) used above, the bonds shown between E and the radicals R^{34} and R^{35} should not be understood exclusively as single bonds; they can also be part of an aromatic system.

Within the meaning of the present invention the term "halogen" preferably stands for the radicals F, Cl, Br and I, in particular for the radicals F and Cl.

Within the meaning of this invention, the expression " C_{1-6} alkyl" includes acyclic saturated hydrocarbon radicals having 1, 2, 3, 4, 5 or 6 C atoms, which can be branched or straight-chain (unbranched) and unsubstituted or mono- or polysubstituted, for example di-, tri-, tetra- or pentasubstituted, with identical or different radicals. The alkyl radicals can preferably be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl,

GRA3454-WO
22nd December 2009

n-pentyl, isopentyl, neopentyl and hexyl. Particularly preferred alkyl radicals can be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl and tert-butyl.

Within the meaning of this invention, the expression "C₃₋₈ cycloalkyl" denotes cyclic saturated hydrocarbons having 3, 4, 5, 6, 7 or 8 carbon atoms, which can be unsubstituted or mono- or polysubstituted, for example di-, tri-, tetra- or pentasubstituted, at one or more ring members with identical or different radicals. C₃₋₈ cycloalkyl can preferably be selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Within the meaning of this invention, the expression "aryl" denotes aromatic hydrocarbons, in particular phenyls and naphthyls. The aryl radicals can also be fused to other saturated, (partially) unsaturated or aromatic ring systems. Each aryl radical can be present in unsubstituted or mono- or polysubstituted form, for example di-, tri-, tetra- or pentasubstituted, wherein the aryl substituents can be identical or different and can be at any desired and possible position of the aryl. Aryl can advantageously be selected from the group consisting of phenyl, 1-naphthyl and 2-naphthyl, which can be unsubstituted or mono- or polysubstituted, for example with 2, 3, 4 or 5 radicals.

Within the meaning of the present invention, the expression "heteroaryl" stands for a 5-, 6- or 7-membered cyclic aromatic radical containing at least 1, optionally also 2, 3, 4 or 5 heteroatoms, wherein the heteroatoms can be identical or different and the heteroaryl can be unsubstituted or mono- or polysubstituted, for example di-, tri-, tetra- or pentasubstituted, with identical or different radicals. The substituents can be bound to any desired and possible position of the heteroaryl. The heterocyclic compound can also be part of a bicyclic or polycyclic, in particular a mono-, bi- or tricyclic system, which can then in total be more than 7-membered, for example up to 14-membered. Preferred heteroatoms are selected from the group consisting of N, O and S. The heteroaryl radical can preferably be selected from the group consisting of pyrrolyl, indolyl, furyl (furanlyl), benzofuranlyl, thienyl (thiophenyl), benzothienyl, benzothiadiazolyl, benzothiazolyl, benzotriazolyl, benzodioxolanyl, benzodioxanyl, benzooxazolyl, benzooxadiazolyl, imidazothiazolyl, dibenzofuranlyl, dibenzothienyl,

GRA3454-WO
22nd December 2009

phthalazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, oxadiazolyl, triazole, tetrazole, isoxazolyl, pyridinyl (pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, indazolyl, purinyl, indolizinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenazinyl, phenothiazinyl and oxadiazolyl, in particular from the group consisting of thienyl (thiophenyl), pyridinyl (pyridyl), pyrimidinyl, thiazolyl, triazolyl, imidazolyl, oxazolyl, oxadiazolyl, quinazolinyl, quinolinyl and isoquinolinyl, wherein the binding to the general structure (I) can be made via any desired and possible ring member of the heteroaryl radical. The heteroaryl radical can particularly preferably be selected from the group consisting of thienyl, imidazolyl, thiazolyl, triazolyl, pyridinyl and pyrimidinyl.

Within the meaning of the present invention, the expression "C₁₋₃ alkylene group" or "C₁₋₆ alkylene group" includes acyclic saturated hydrocarbon radicals having respectively 1, 2 or 3 or 1, 2, 3, 4, 5 or 6 C atoms, which can be branched or straight-chain (unbranched) and unsubstituted or mono- or polysubstituted, for example di-, tri-, tetra- or pentasubstituted, with identical or different radicals and which link a corresponding radical to the higher-order general structure. The alkylene groups can preferably be selected from the group consisting of -CH₂-, -CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -CH(CH₃)-CH₂-, -CH(CH₂CH₃)-, -CH₂-(CH₂)₂-CH₂-, -CH(CH₃)-CH₂-CH₂-, -CH₂-CH(CH₃)-CH₂-, -CH(CH₃)-CH(CH₃)-, -CH(CH₂CH₃)-CH₂-, -C(CH₃)₂-CH₂-, -CH(CH₂CH₂CH₃)-, -C(CH₃)(CH₂CH₃)-, -CH₂-(CH₂)₃-CH₂-, -CH(CH₃)-CH₂-CH₂-CH₂-, -CH₂-CH(CH₃)-CH₂-CH₂-, -CH(CH₃)-CH₂-CH(CH₃)-, -CH(CH₃)-CH(CH₃)-CH₂-, -C(CH₃)₂-CH₂-CH₂-, -CH₂-C(CH₃)₂-CH₂-, -CH(CH₂CH₃)-CH₂-CH₂-, -CH₂-CH(CH₂CH₃)-CH₂-, -C(CH₃)₂-CH(CH₃)-, -CH(CH₂CH₃)-CH(CH₃)-, -C(CH₃)(CH₂CH₃)-CH₂-, -CH(CH₂CH₂CH₃)-CH₂-, -C(CH₂CH₂CH₃)-CH₂-, -CH(CH₂CH₂CH₂CH₃)-, -C(CH₃)(CH₂CH₂CH₃)-, -C(CH₂CH₃)₂- and -CH₂-(CH₂)₄-CH₂-. The alkylene groups can particularly preferably be selected from the group consisting of -CH₂-, -CH₂-CH₂- and -CH₂-CH₂-CH₂-.

Within the meaning of the present invention the expression "-(O)_{0/1}-C₁₋₆ alkylene group" also includes in addition to the C₁₋₆ alkylene groups described above such groups in which these groups are linked by an oxygen atom to the higher-order structure.

GRA3454-WO
22nd December 2009

Within the meaning of the present invention, the expression "aryl or heteroaryl bound by a C₁₋₃ alkylene group or a C₁₋₆ alkylene group" means that the C₁₋₃ alkylene groups, C₁₋₆ alkylene groups and aryl or heteroaryl have the meanings defined above and the aryl or heteroaryl is bound to the higher-order general structure by a C₁₋₃ alkylene group or C₁₋₆ alkylene group. Benzyl, phenethyl and phenylpropyl are cited by way of example.

Within the meaning of the present invention, the expression "C₃₋₈ cycloalkyl bound by a C₁₋₃ alkylene group or C₁₋₆ alkylene group" means that the C₁₋₃ alkylene group, C₁₋₆ alkylene group and C₃₋₈ cycloalkyl have the meanings defined above and C₃₋₈ cycloalkyl is bound by a C₁₋₃ alkylene group or C₁₋₆ alkylene group to the higher-order general structure.

In connection with "alkyl", "alkylene" and "cycloalkyl", the term "substituted" within the meaning of this invention is understood to mean the substitution of a hydrogen radical with F, Cl, Br, I, CF₃, OCF₃, CN, NH₂, NH-C₁₋₆ alkyl, NH-C₁₋₆ alkylene-OH, C₁₋₆ alkyl, N(C₁₋₆ alkyl)₂, N(C₁₋₆ alkylene-OH)₂, NO₂, SH, S-C₁₋₆ alkyl, C₁₋₆ alkyl, S-benzyl, O-C₁₋₆ alkyl, OH, O-C₁₋₆ alkylene-OH, =O, O-benzyl, C(=O)C₁₋₆ alkyl, CO₂H, CO₂-C₁₋₆ alkyl, phenyl, phenoxy, benzyl, naphthyl, furyl, thienyl and pyridinyl, wherein polysubstituted radicals are understood to mean radicals which are substituted multiple times, for example twice or three times, at different or the same atoms, for example substituted three times at the same C atom, as in the case of CF₃ or -CH₂CF₃, or at different sites, as in the case of CH(Cl)-CH=CH-CHCl₂. The polysubstitution can take place with identical or different substituents, as for example in the case of CH(OH)-CH=CH-CHCl₂. It should be understood in particular to be the substitution of one or more hydrogen radicals with F, Cl, NH₂, OH, phenyl, O-CF₃ or O-C₁₋₆ alkyl, in particular methoxy.

In connection with "aryl" and "heteroaryl", the term "substituted" within the meaning of this invention is understood to mean the mono- or polysubstitution, for example the di-, tri-, tetra- or pentasubstitution, of one or more hydrogen atoms of the corresponding ring system with F, Cl, Br, I, CN, NH₂, NH-C₁₋₆ alkyl, NH-C₁₋₆ alkylene-OH, N(C₁₋₆ alkyl)₂, N(C₁₋₆ alkylene-OH)₂, NH aryl¹, N(aryl¹)₂, N(C₁₋₆ alkyl)aryl¹, pyrrolinyl, piperazinyl, morpholinyl, azetidiny, piperidinyl, thiazolinyl, azepanyl,

GRA3454-WO
22nd December 2009

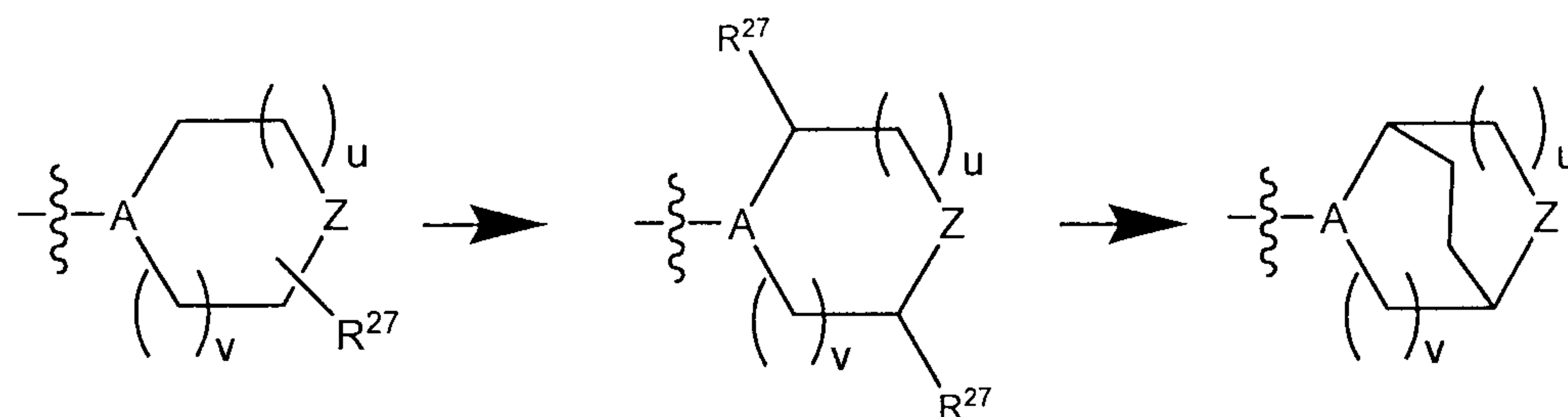
diazepanyl, (C₁₋₃ alkylene)-azetidiny, (C₁₋₃ alkylene)-pyrroliny, (C₁₋₃ alkylene)-piperidiny, (C₁₋₃ alkylene)-morpholiny, (C₁₋₃ alkylene)-piperaziny, (C₁₋₃ alkylene)-thiazoliny, (C₁₋₃ alkylene)-azepanyl, (C₁₋₃ alkylene)-diazepanyl, NO₂, SH, S-C₁₋₆ alkyl, OH, O-C₁₋₆ alkyl, O-C₁₋₆ alkyl-OH, C(=O)C₁₋₆ alkyl, NHSO₂C₁₋₆ alkyl, NHCOC₁₋₆ alkyl, CO₂H, CH₂SO₂ phenyl, CO₂-C₁₋₆ alkyl, OCF₃, CF₃, -O-CH₂-O-, -O-CH₂-CH₂-O-, -O-C(CH₃)₂-CH₂-, unsubstituted C₁₋₆ alkyl, pyrrolidiny, imidazolyl, benzyloxy, phenoxy, phenyl, naphthyl, pyridiny, -C₁₋₃ alkylene-aryl¹, benzyl, thienyl, furyl, wherein aryl¹ stands for phenyl, thiazolyl, thienyl or pyridiny, at one or different atoms, wherein the aforementioned substituents - unless otherwise specified - can themselves be substituted with the cited substituents. The polysubstitution of aryl and heteroaryl can be performed with identical or different substituents. Preferred substituents for aryl and heteroaryl can be selected from the group consisting of -O-C₁₋₃ alkyl, unsubstituted C₁₋₆ alkyl, F, Cl, Br, I, CN, CF₃, OCF₃, OH, SH, -CH₂ azetidiny, -CH₂ pyrrolidiny, -CH₂ piperidiny, -CH₂ piperaziny, -CH₂ morpholiny, phenyl, naphthyl, thiazolyl, thienyl and pyridiny, in particular from the group consisting of F, Cl, CN, CF₃, CH₃, OCH₃, OCF₃ and -CH₂ azetidiny.

In the chemical structural formulae which are used here to describe the compounds according to the invention, the symbol " $\text{R}^a \diagdown$ " is also used to describe one or more substitution models, wherein unlike the representation of a binding to a specific atom, this group is not bound to a specific atom within the chemical structural formula (R^a stands by way of example here for a substituent R having a number represented by the variable "a").

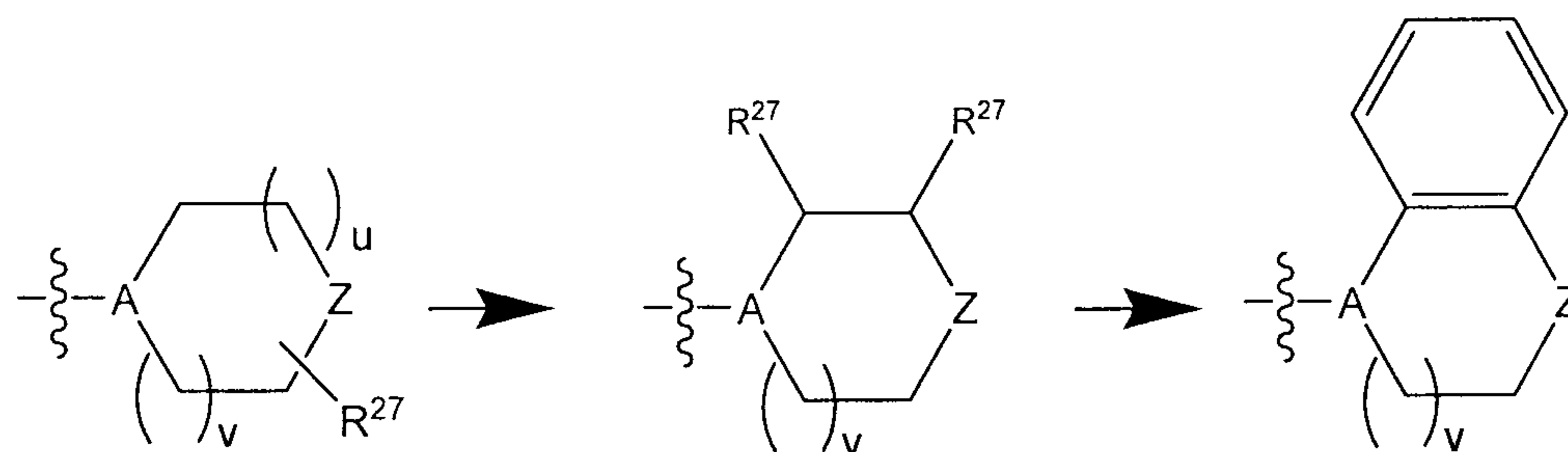
This can be explained by way of example by reference to the group " $\text{R}^{27} \diagdown$ " from the general formula (III) shown above: The definition for R²⁷ indicates that R²⁷ can stand for 0 to 4 substituents. Thus R²⁷ can be absent, or 1, 2, 3 or 4 of the C-bound hydrogen atoms within the substructure represented by the general formula (III) can be replaced by one of the substituents provided in the definition of the radical R²⁷, wherein each of the substituents can be selected mutually independently, in other words they can have different meanings, and C-bound hydrogen atoms can be replaced at one or more C atoms. As explained in the definition of R²⁷, two of the substituents R²⁷ can also together represent a C₁₋₃ alkylene bridge or an anellated aryl or heteroaryl (also referred to as a fused aryl or heteroaryl or anellated/fused aryl

GRA3454-WO
22nd December 2009

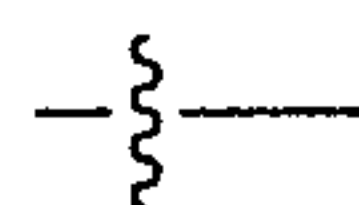
or heteroaryl group), such that R^{27} in the general formula (III) also has the meanings shown below by way of example, in which R^{27} stands for two substituents at different C atoms and in the second example the variable u stands for 1:



or



In the context of the present invention, the symbol



used in formulae represents a linking of a corresponding radical to the higher-order general structure.

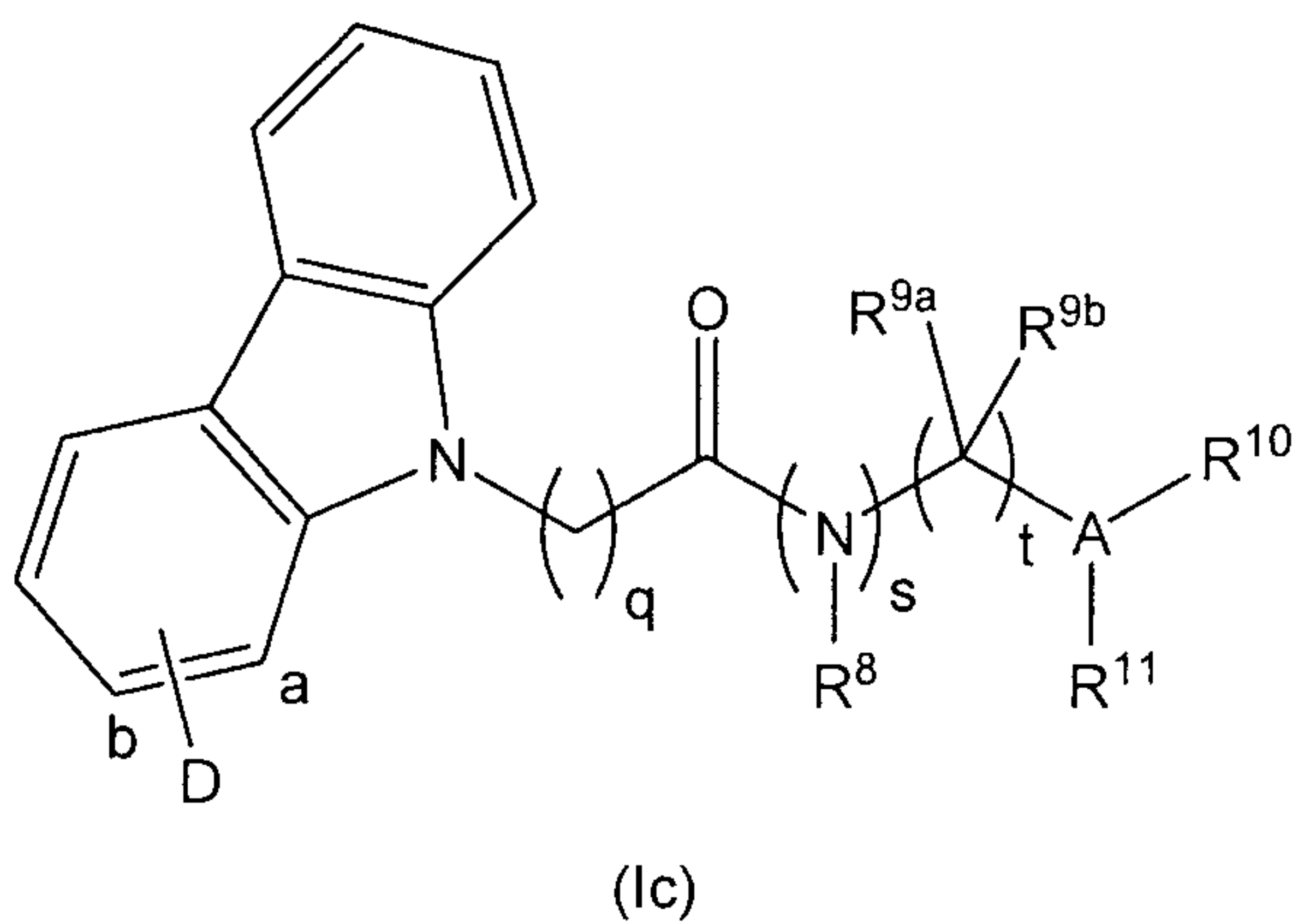
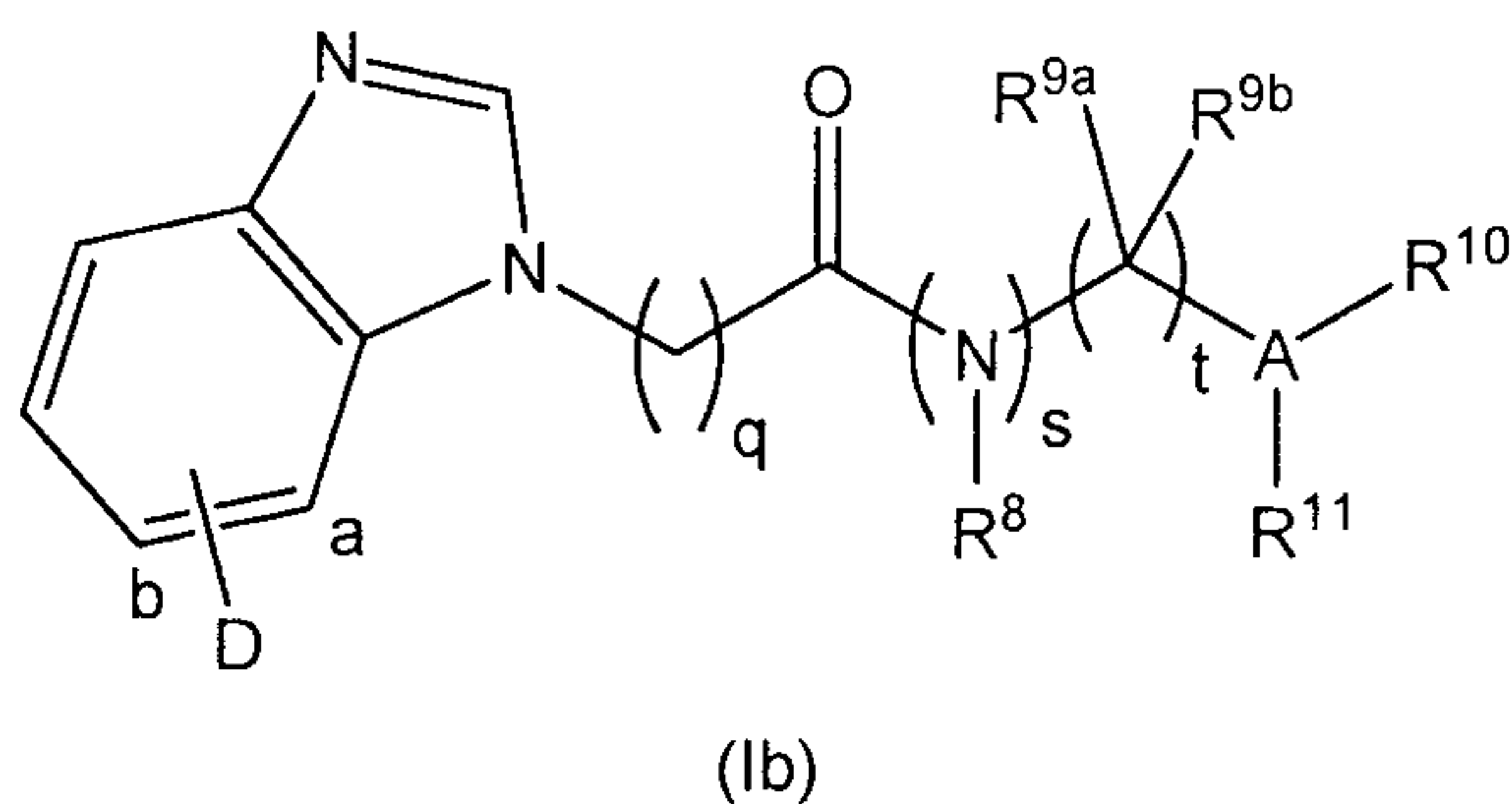
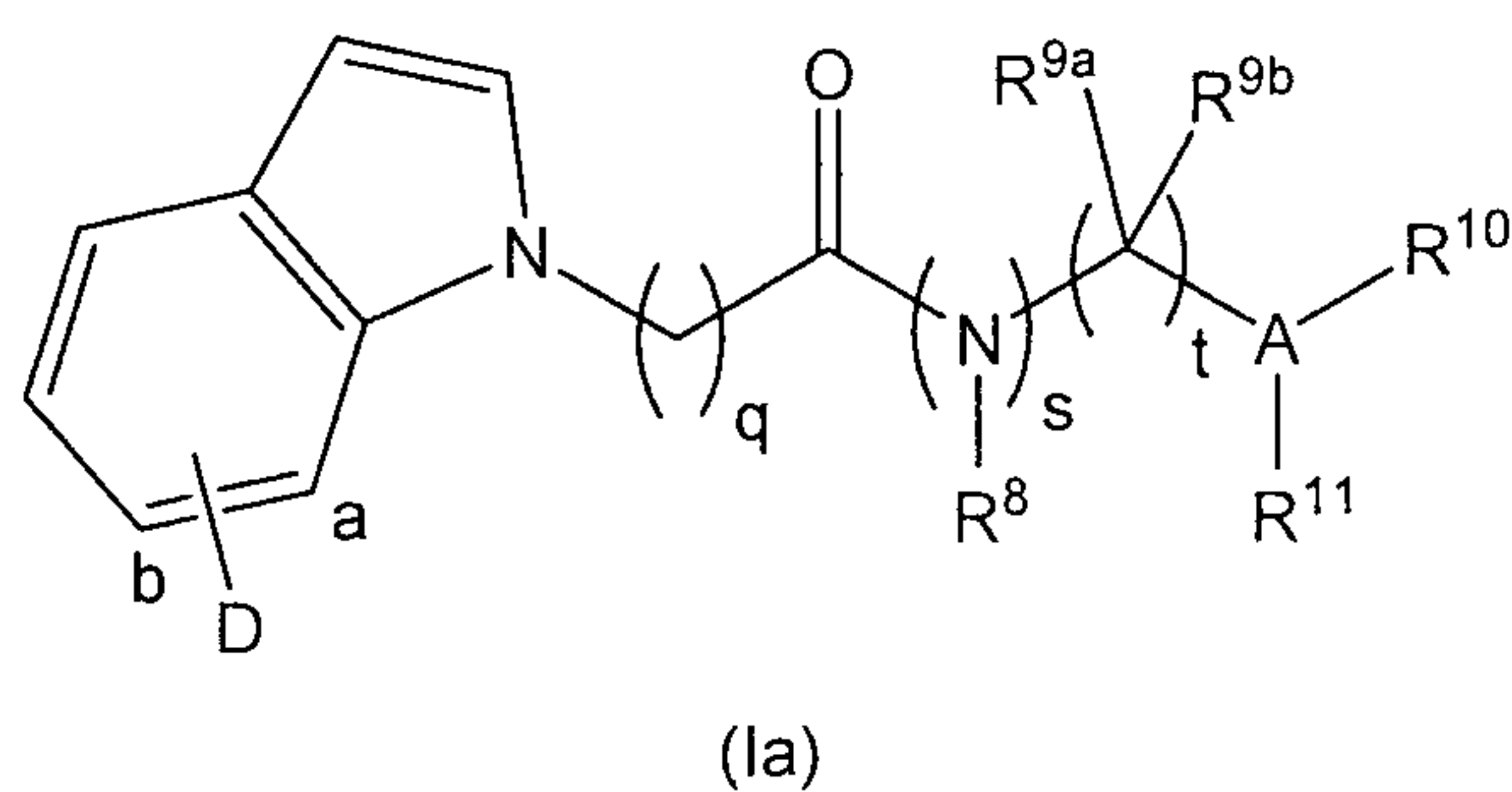
The person skilled in the art understands that identical radicals used for the definition of different substituents are mutually independent.

Within the meaning of this invention the term "physiologically compatible salt" is understood to mean preferably salts of the compounds according to the invention with inorganic or organic acids, which are physiologically - particularly when used in humans and/or mammals - compatible. Examples of suitable acids are hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, maleic acid, lactic acid, citric acid, glutamic acid, 1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[d]isothiazol-3-one (saccharinic acid), monomethylsebacic acid, 5-oxoproline, hexane-1-sulfonic acid,

GRA3454-WO
22nd December 2009

nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, α -lipoic acid, acetylglycine, hippuric acid, phosphoric acid and/or aspartic acid. The salts of hydrochloric acid (hydrochlorides) and of citric acid (citrates) are particularly preferred.

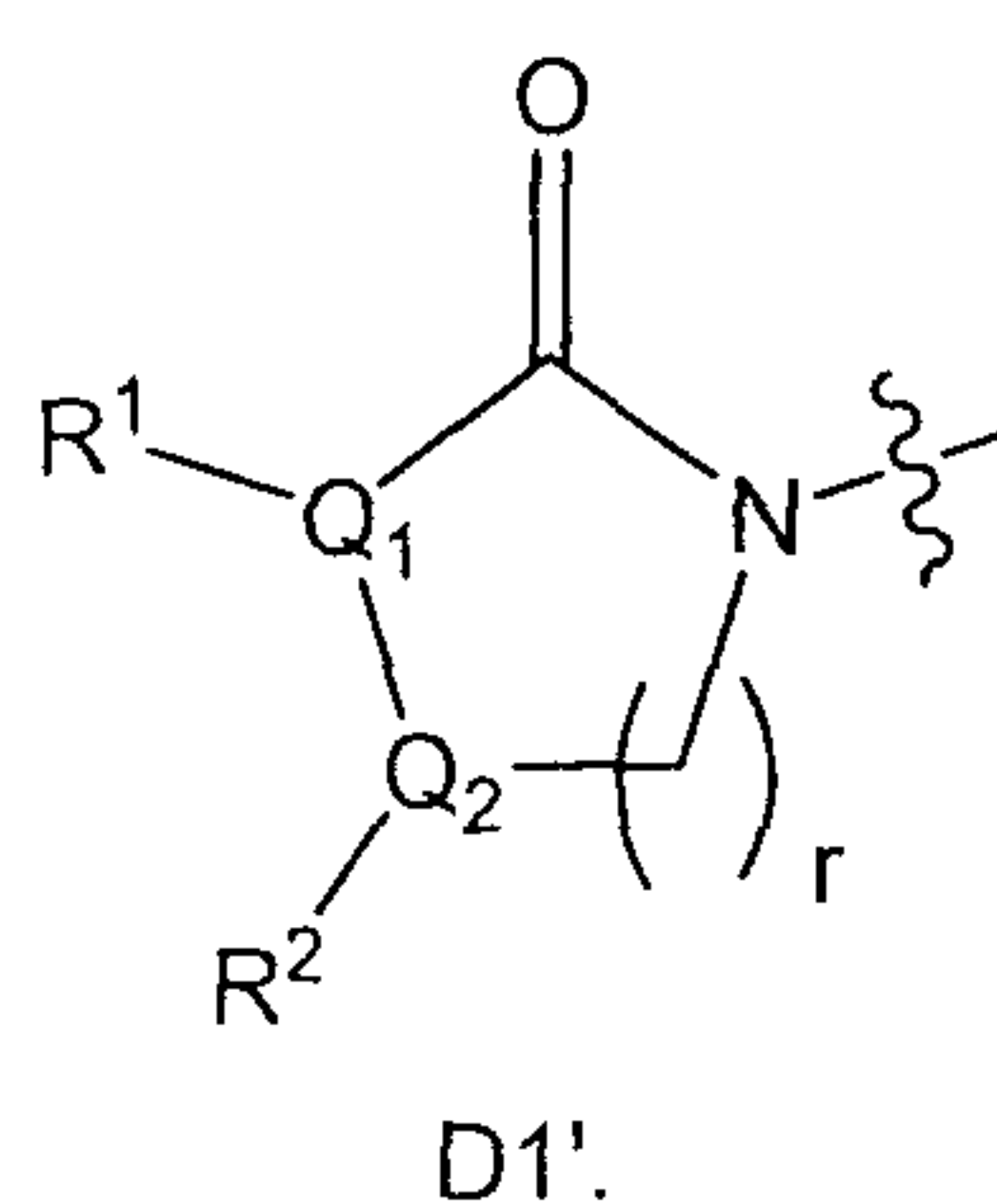
In preferred embodiments of the compounds according to the invention according to the general formula (I) T, R^{200} and R^{210} are selected such that the general formula I assumes one of the general formulae (Ia), (Ib) or (Ic)



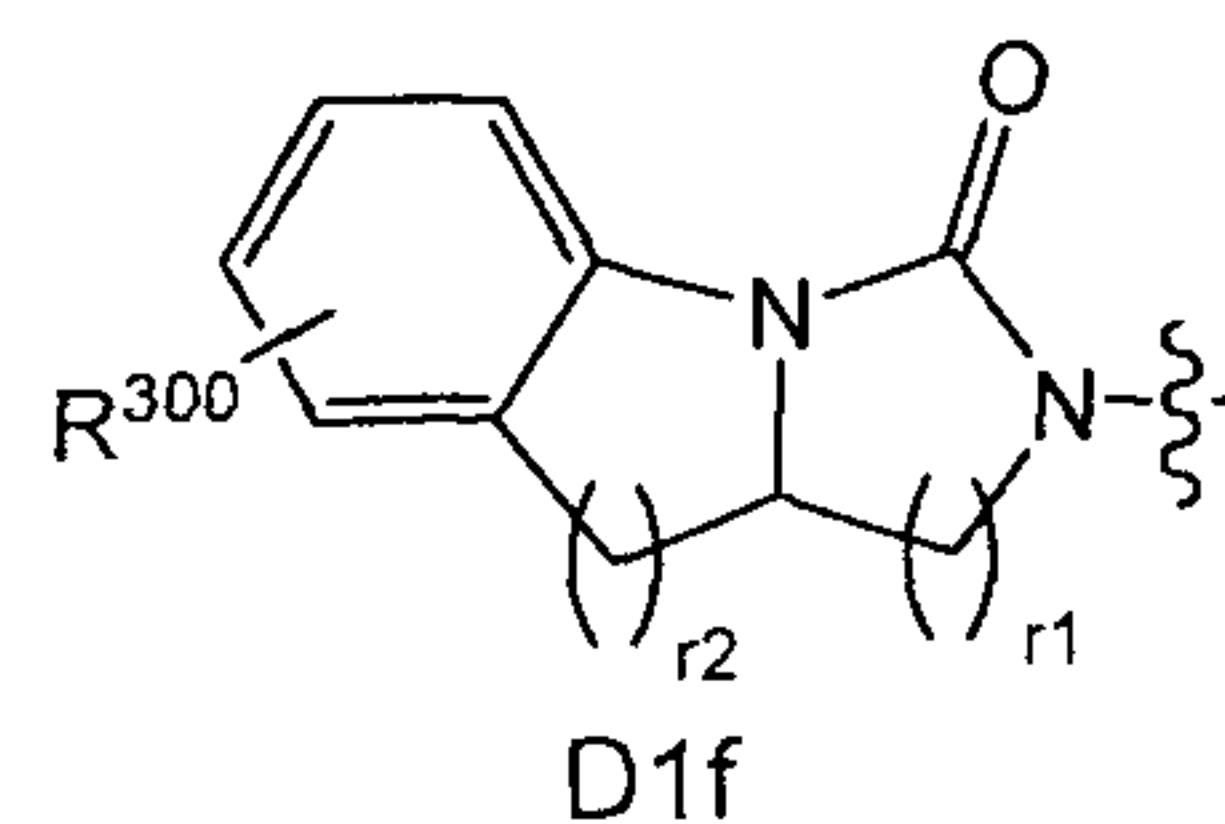
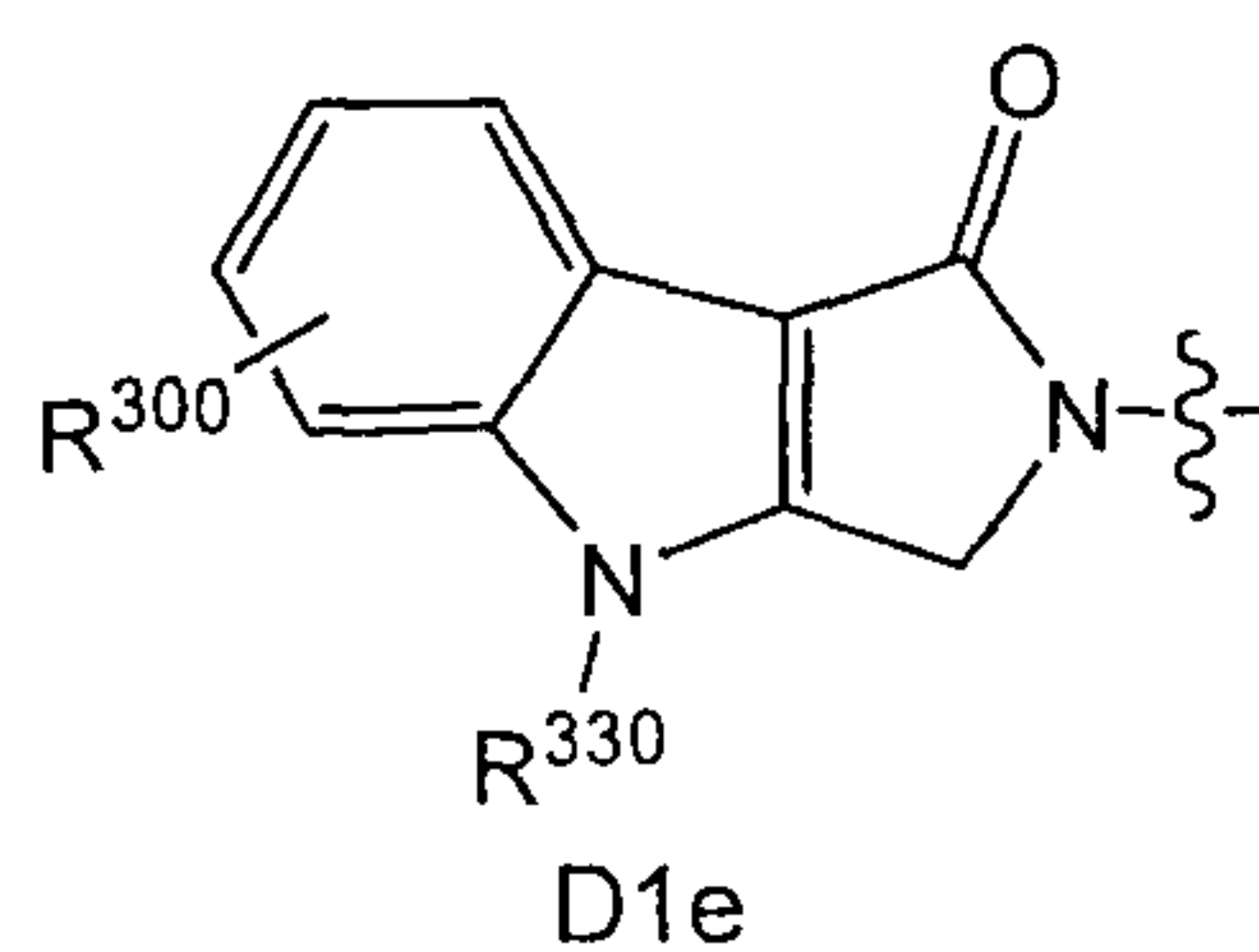
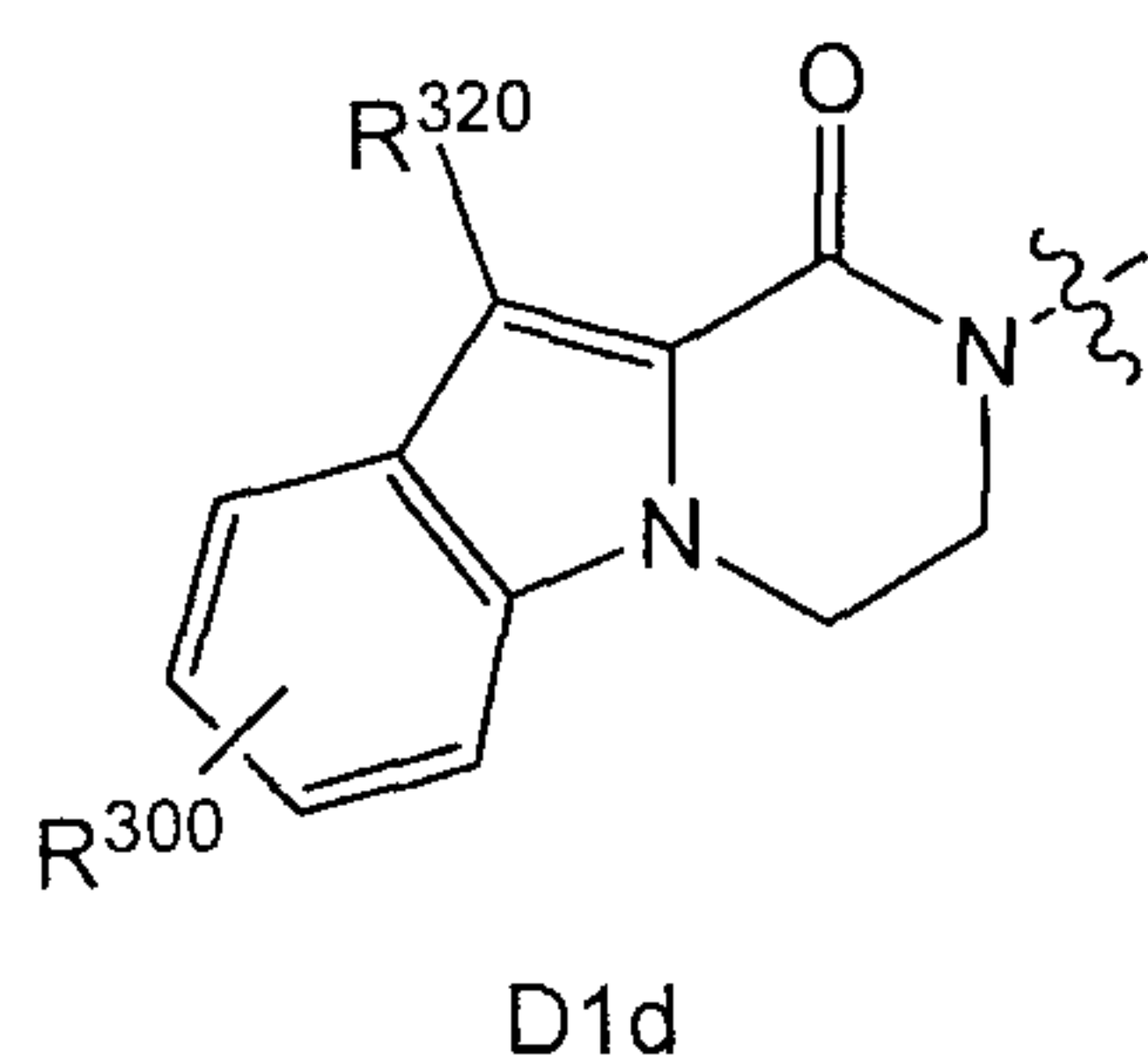
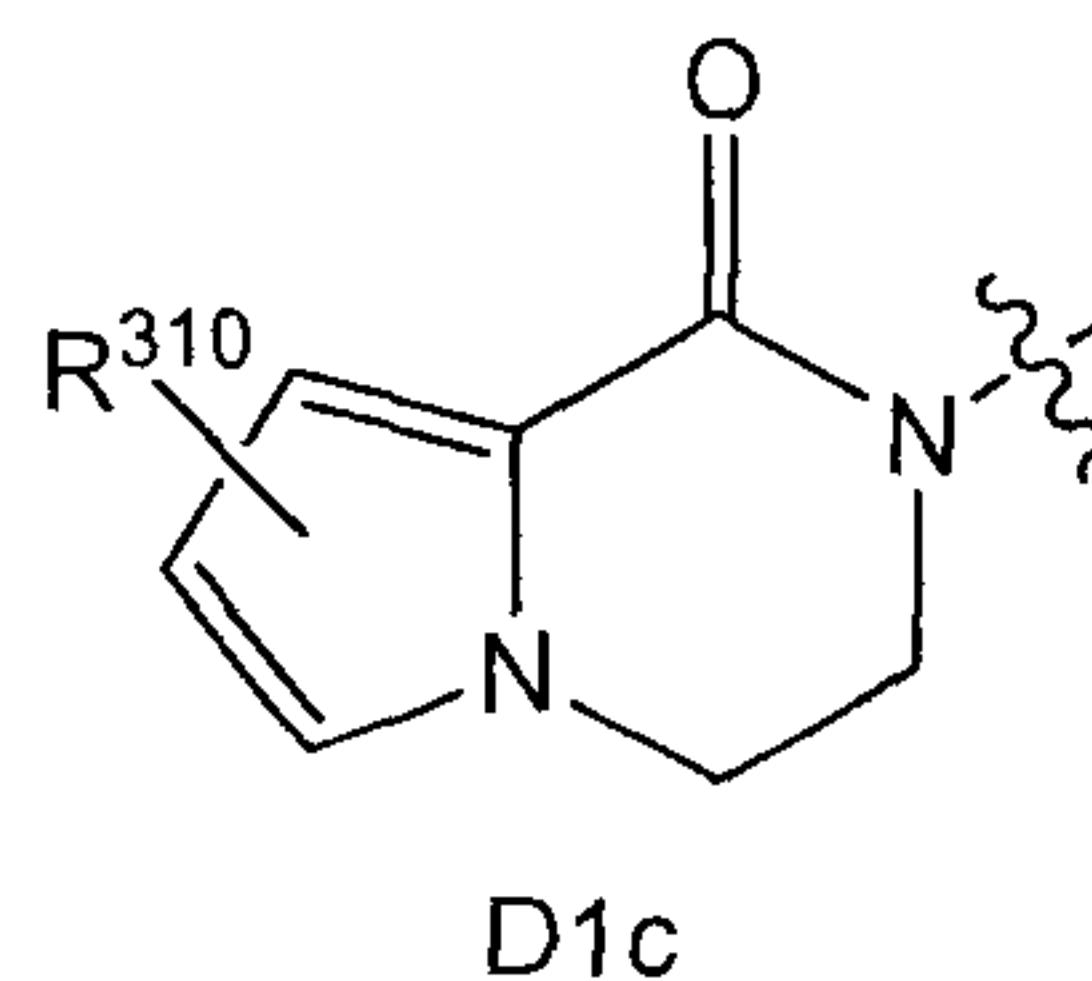
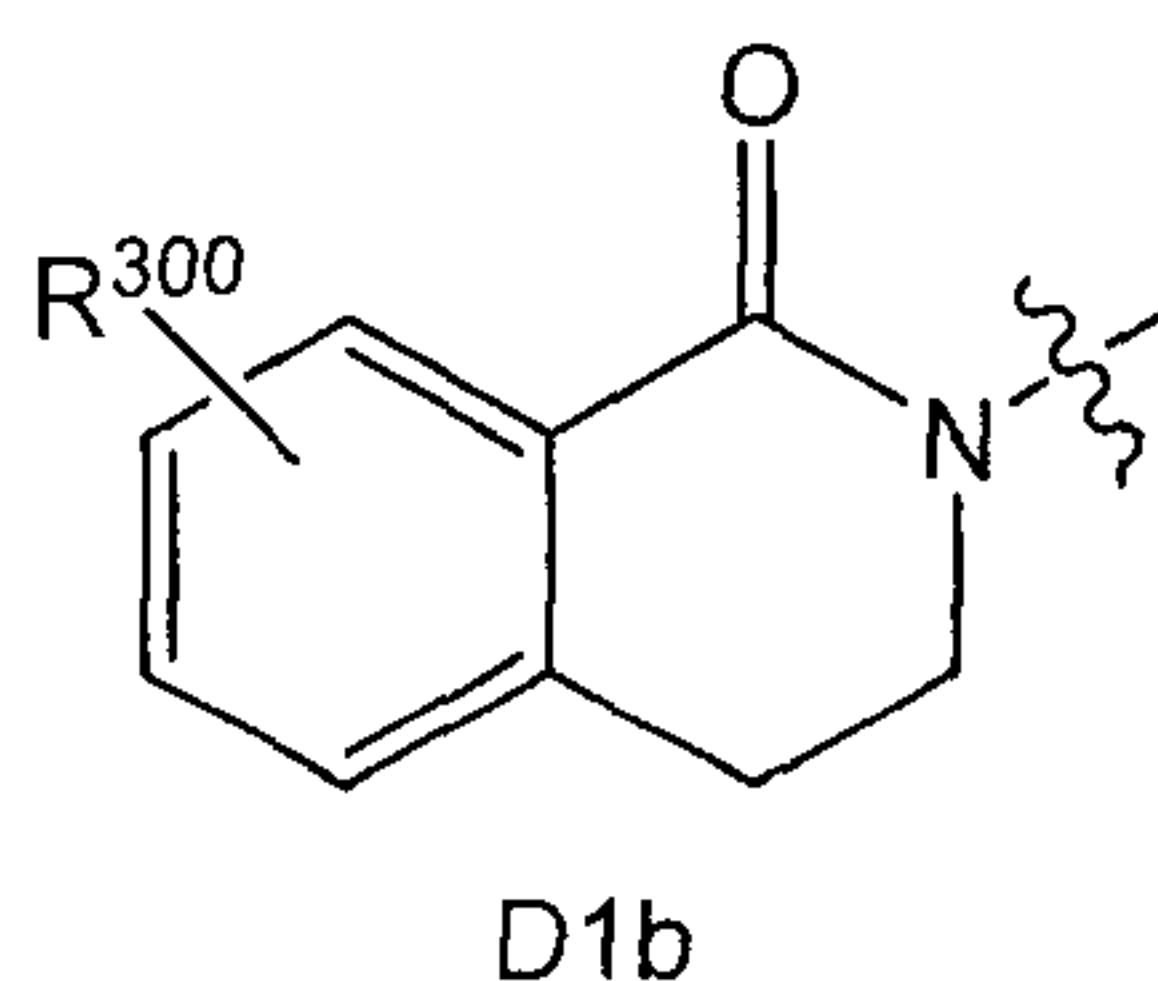
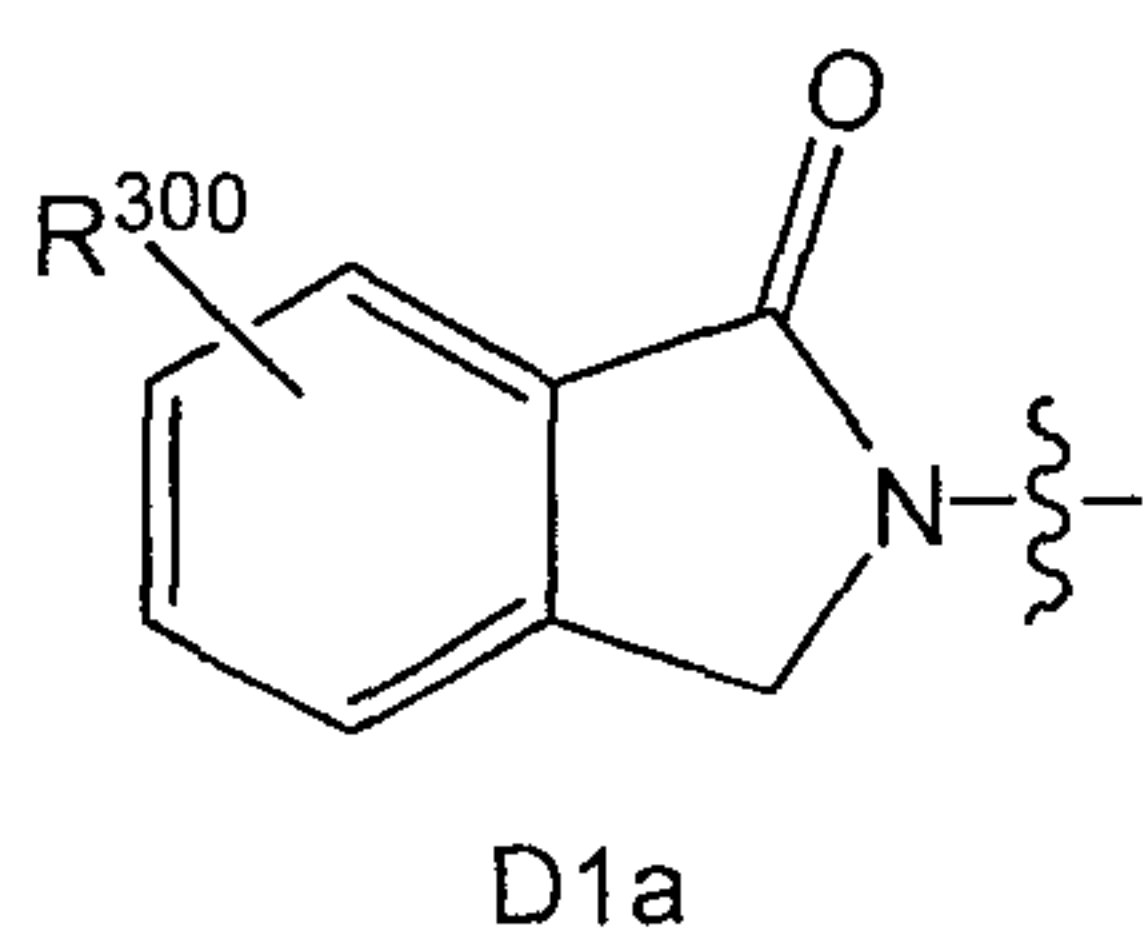
GRA3454-WO
22nd December 2009

wherein the various radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and the preferred embodiments thereof. The general formula (I) can in particular assume the general formula (Ia).

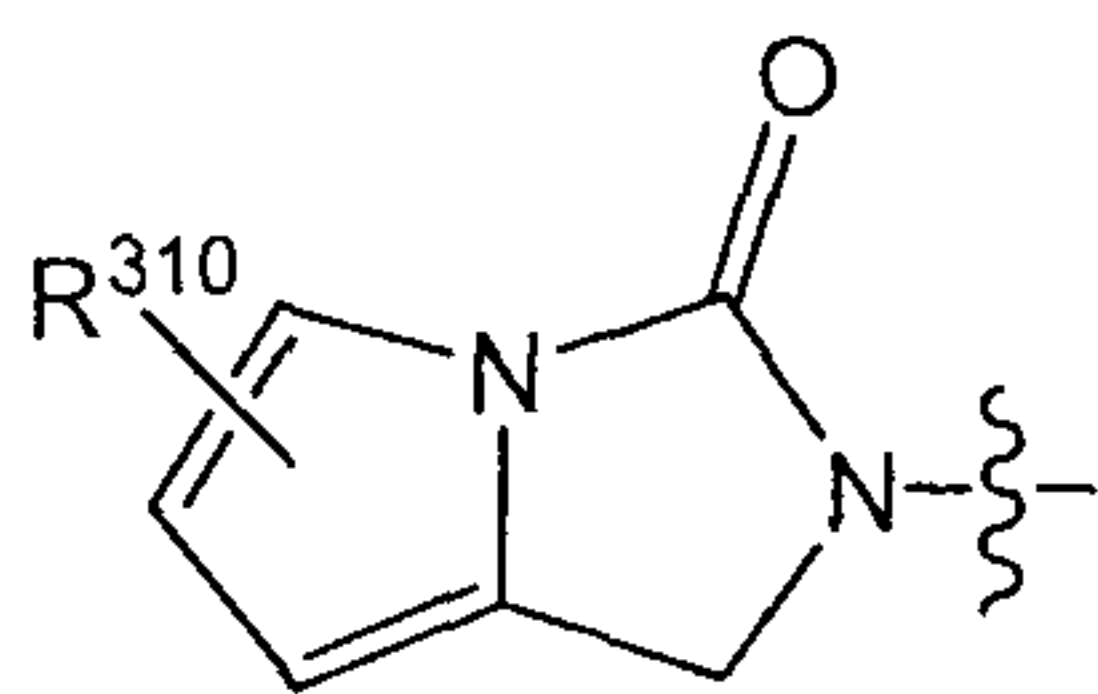
In likewise preferred embodiments of the compounds according to the invention x stands for 0, such that the radical D1 assumes the following form D1':



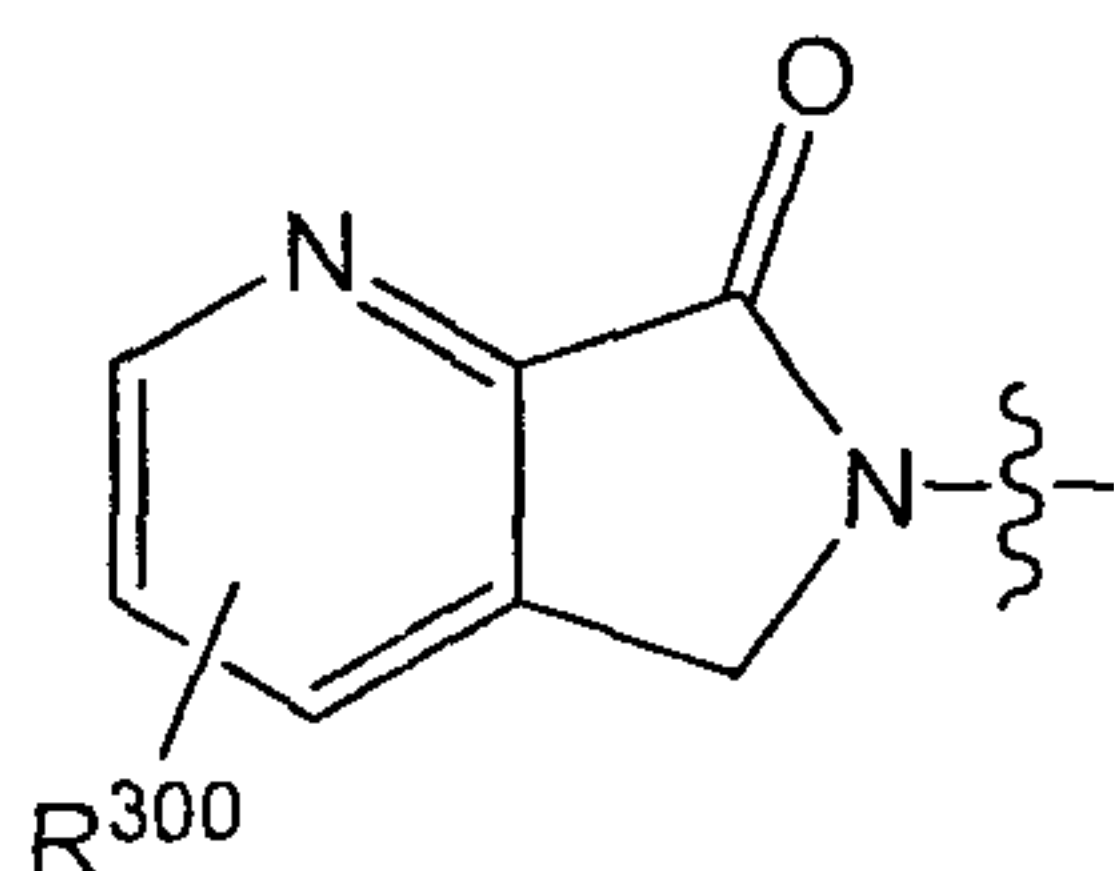
In further preferred embodiments of the compounds according to the invention D stands for a radical selected from the group consisting of



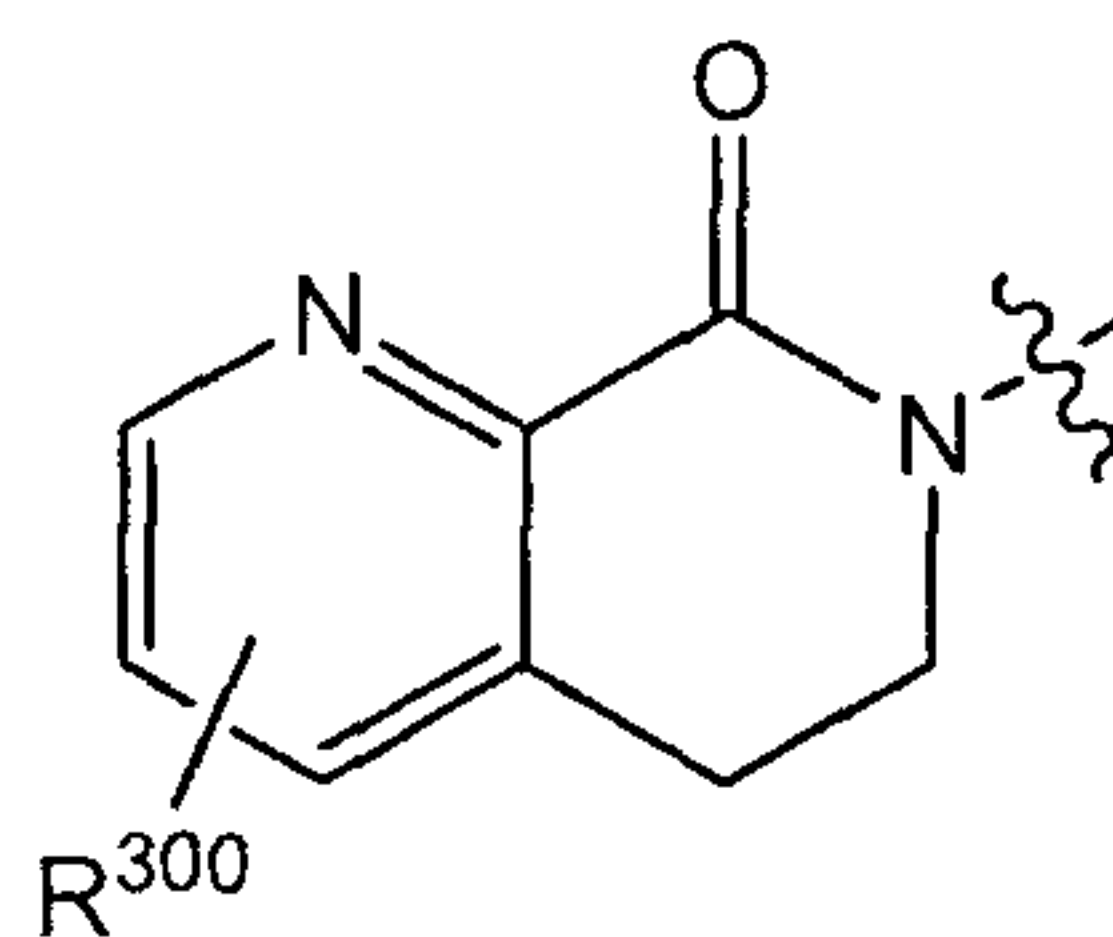
GRA3454-WO
22nd December 2009



D1g

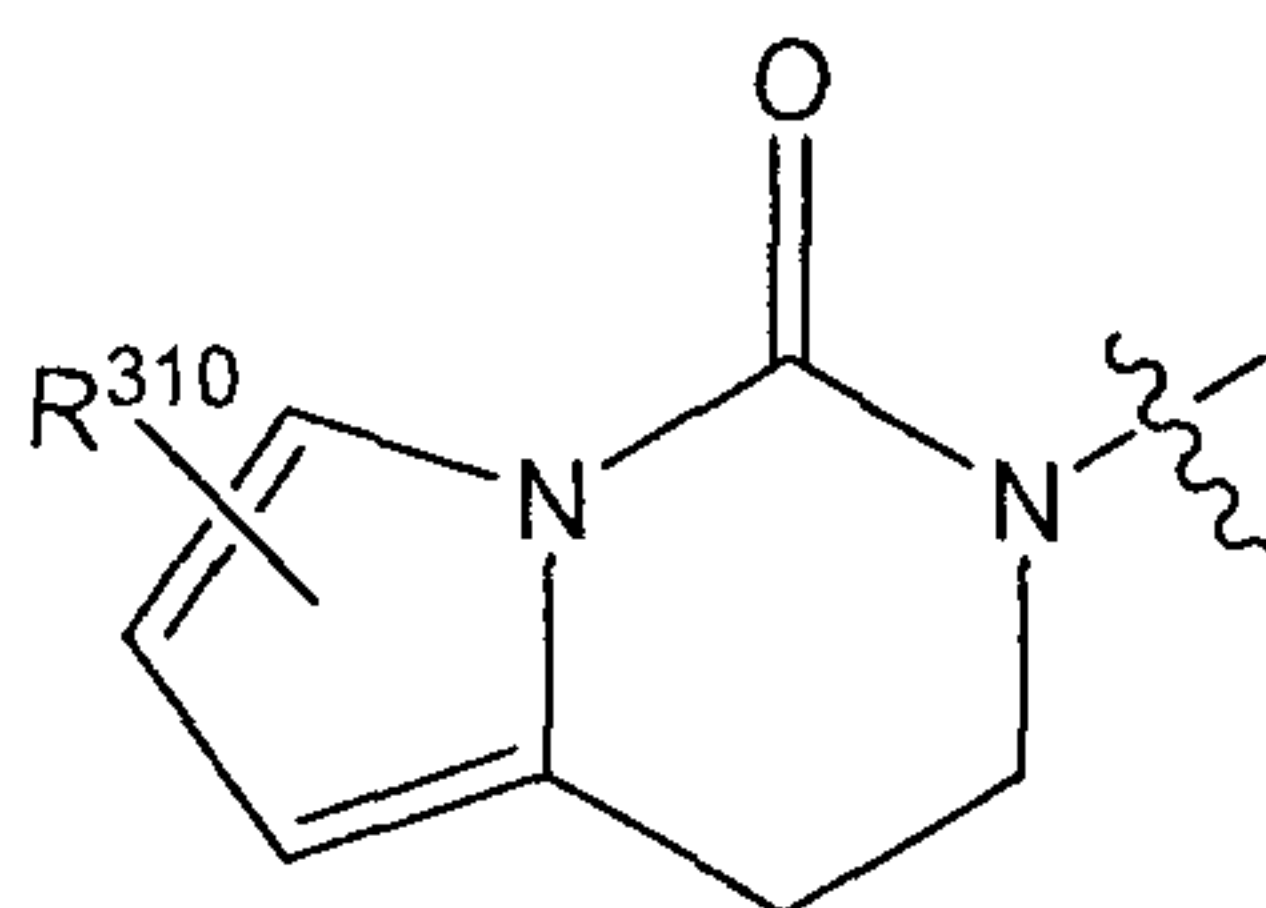


D1h



D1i

and



D1j

wherein

R^{300} stands for 0, 1, 2, 3 or 4 substituents, which are mutually independently selected from the group consisting of F, Cl, Br, I, $-CF_3$, $-O-CF_3$, C_{1-4} alkyl and $O-C_{1-4}$ alkyl;

R^{310} stands for 0, 1, 2 or 3 substituents, which are mutually independently selected from the group consisting of F, Cl, Br, I, $-CF_3$, $-O-CF_3$, C_{1-4} alkyl and $O-C_{1-4}$ alkyl;

R^{320} stands for a substituent selected from the group consisting of H, F, Cl, Br, I, $-CF_3$, $-O-CF_3$ and C_{1-4} alkyl;

R^{330} stands for a substituent selected from the group consisting of H, C_{1-4} alkyl, aryl, $-CH_2$ aryl and heteroaryl;

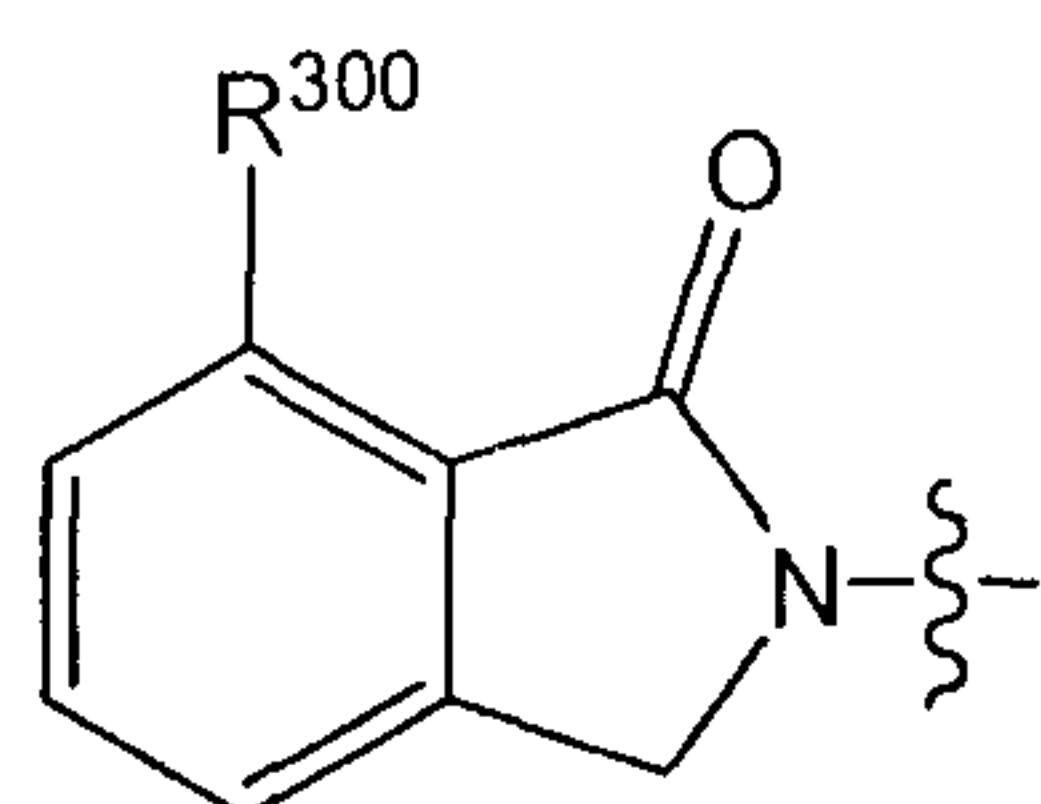
r_1 stands for 1 or 2 and

r_2 stands for 1 or 2.

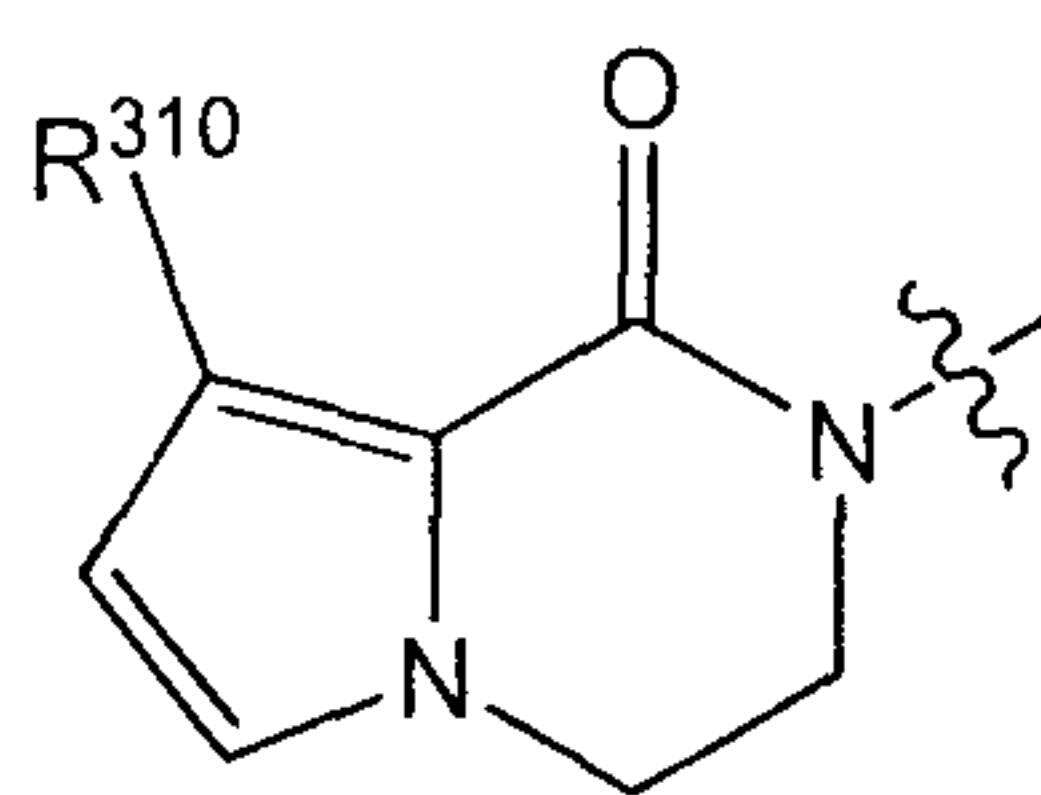
In likewise preferred embodiments of the compounds according to the invention

D stands for a radical selected from the group consisting of

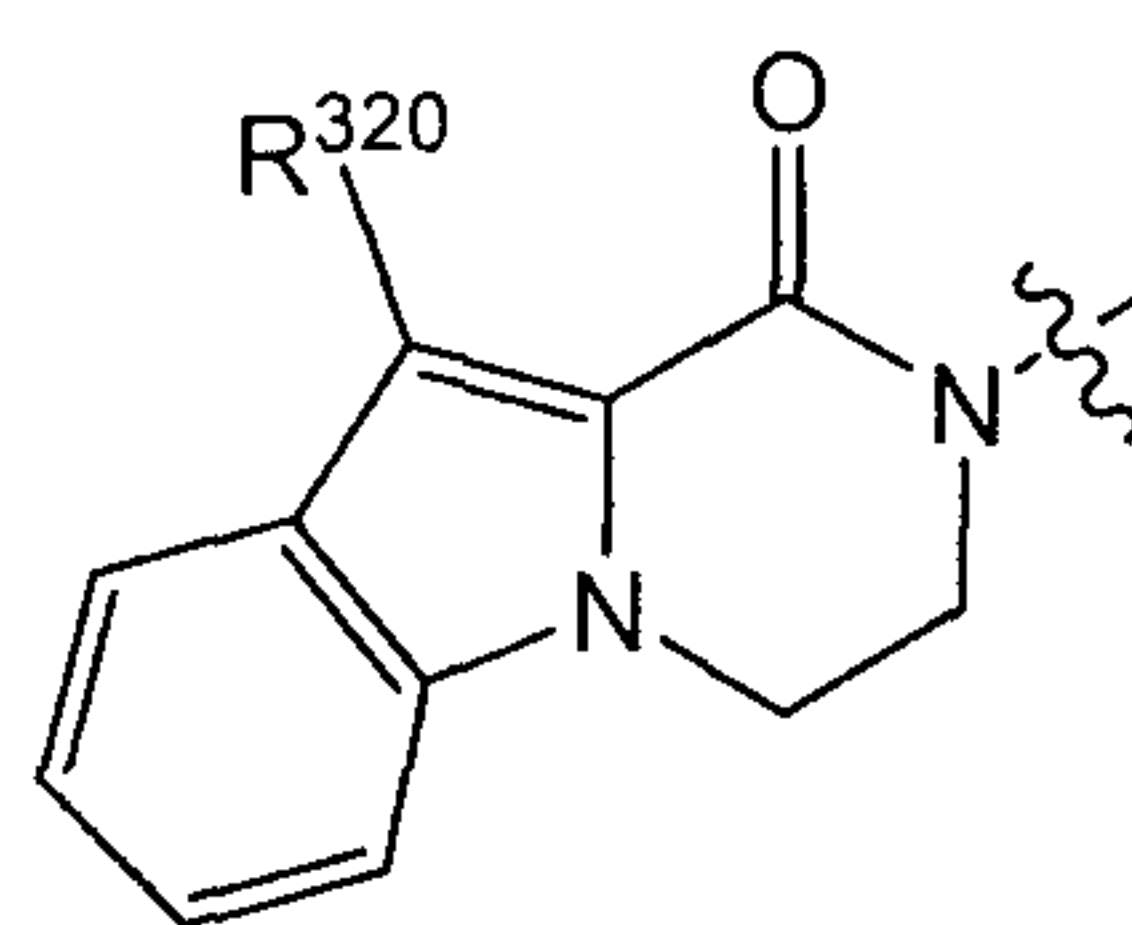
GRA3454-WO
22nd December 2009



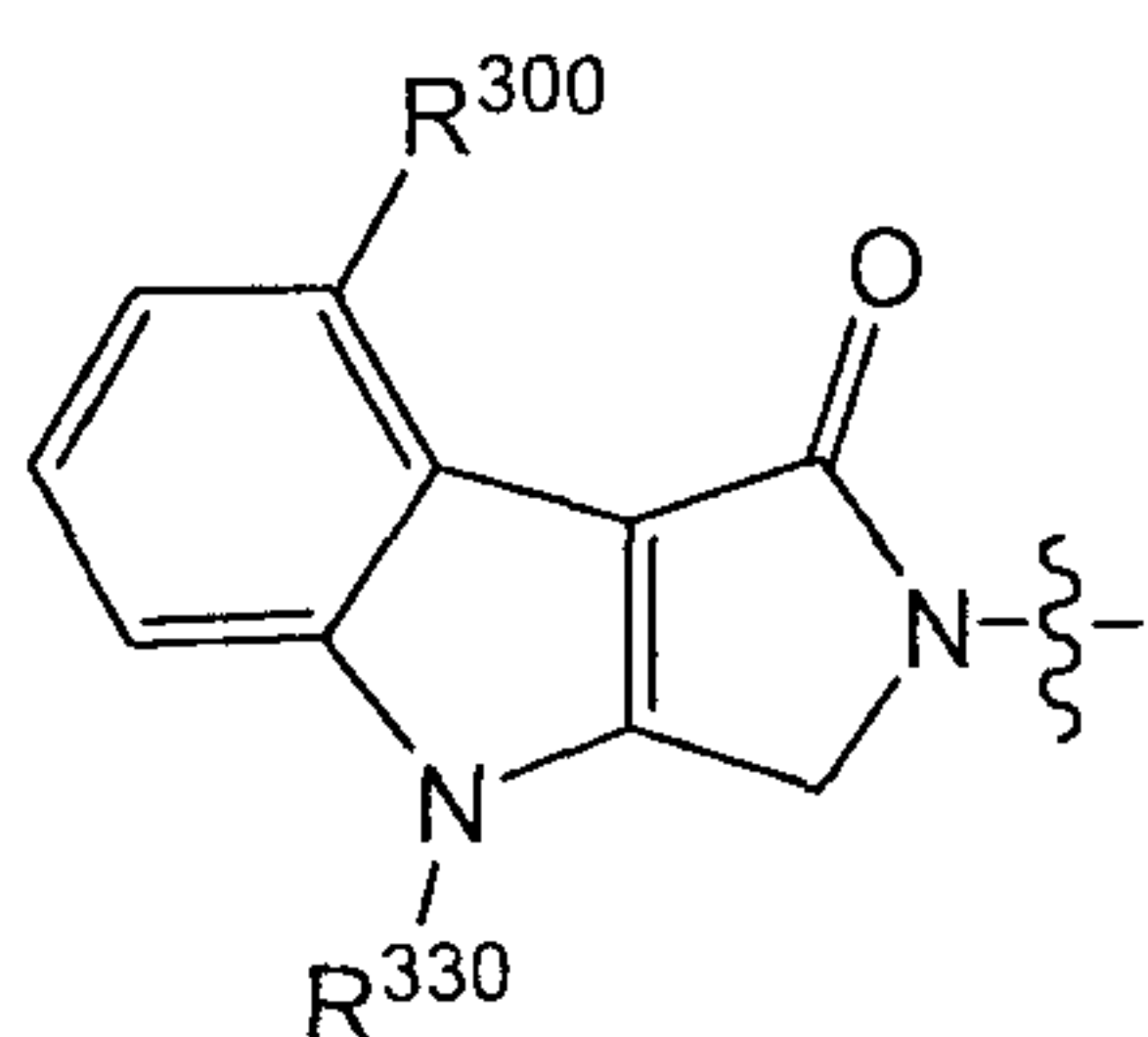
D1a1



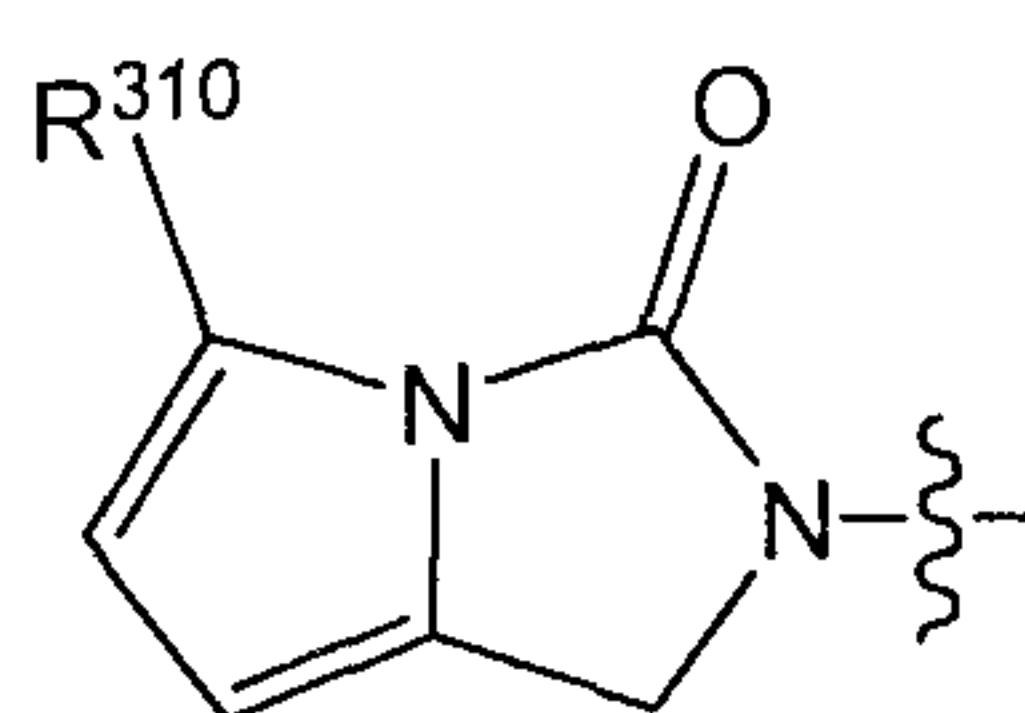
D1c1



D1d1



D1e1



D1g1

and

wherein

R^{300} stands for a substituent which is selected from the group consisting of F, Cl, Br, I, $-CF_3$, $-O-CF_3$, C_{1-4} alkyl and $O-C_{1-4}$ alkyl;

R^{310} stands for a substituent which is selected from the group consisting of F, Cl, Br, I, $-CF_3$, $-O-CF_3$, C_{1-4} alkyl and $O-C_{1-4}$ alkyl;

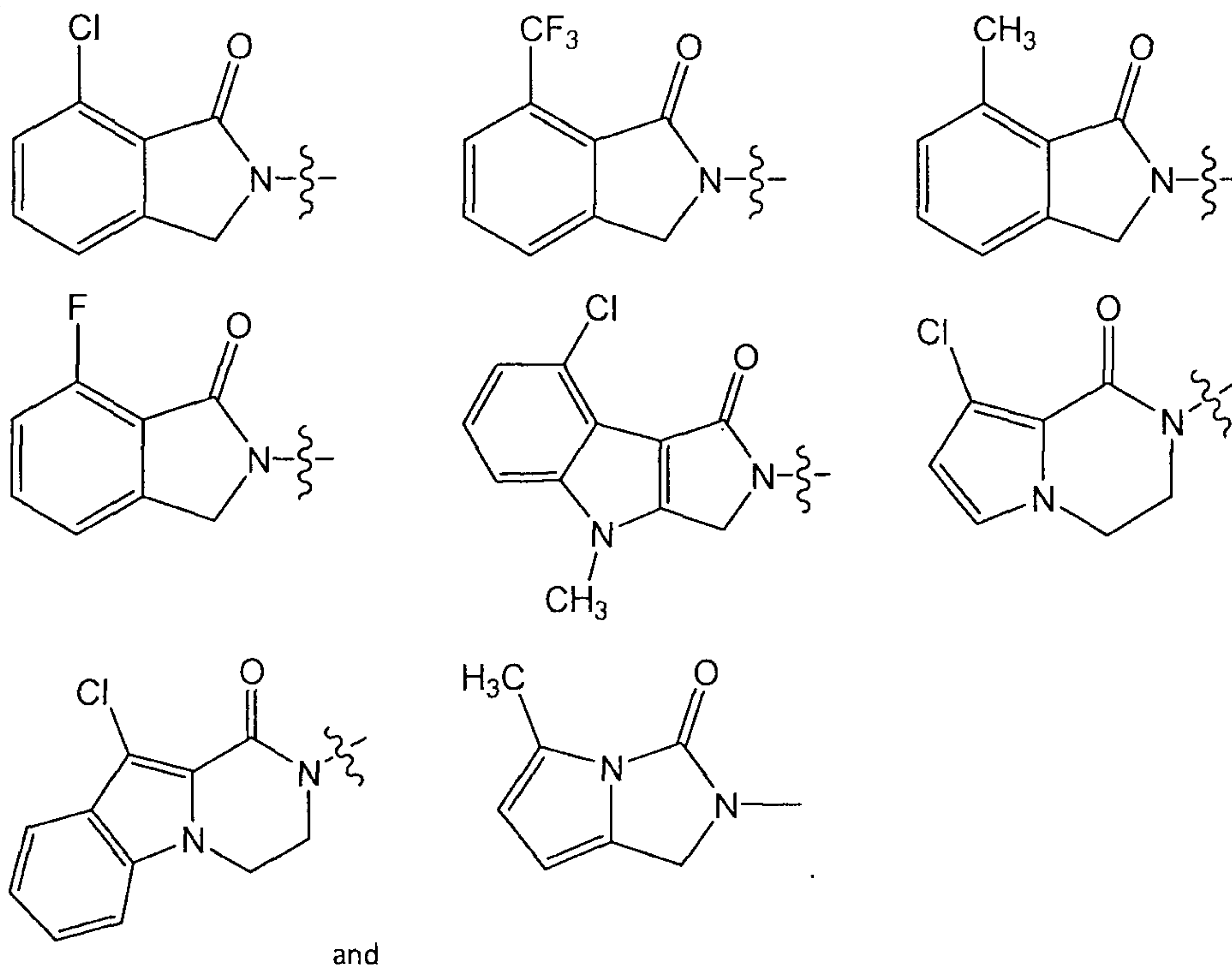
R^{320} stands for a substituent which is selected from the group consisting of H, F, Cl, Br, I, $-CF_3$, $-O-CF_3$ and C_{1-4} alkyl and

R^{330} stands for a substituent which is selected from the group consisting of H, C_{1-4} alkyl, aryl, $-CH_2$ aryl and heteroaryl.

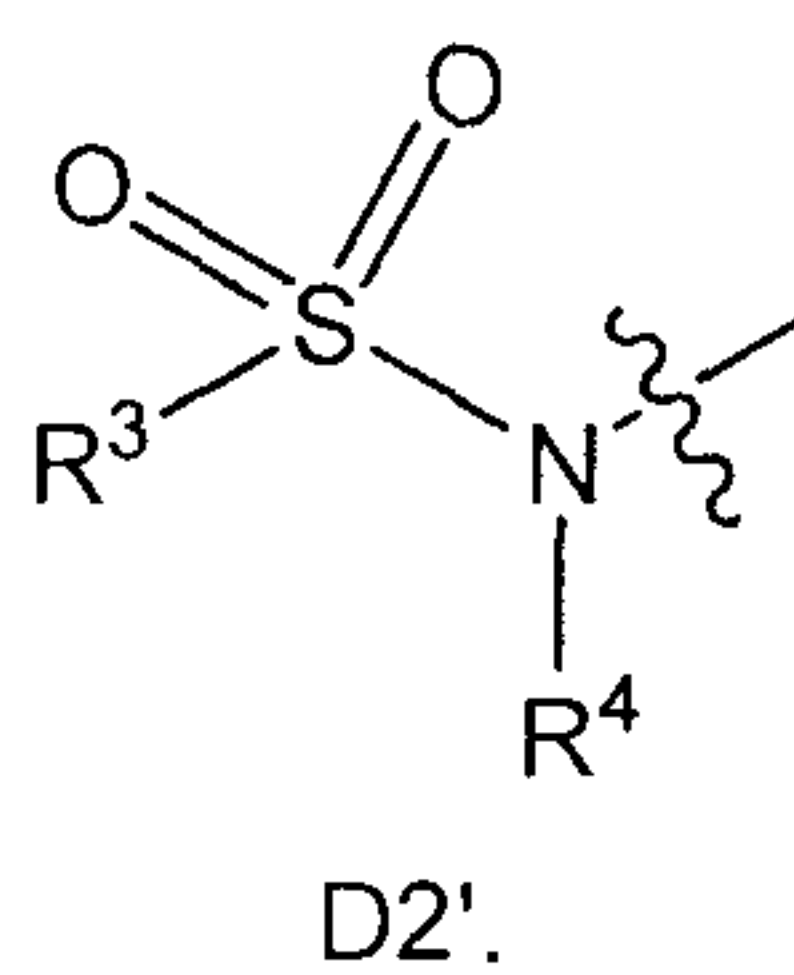
In further preferred embodiments of the compounds according to the invention

D stands for a radical selected from the group consisting of

GRA3454-WO
22nd December 2009



In likewise preferred embodiments of the compounds according to the invention y stands for 0, such that the radical D2 assumes the following form D2':



In the compounds according to the invention R^3 preferably stands for phenyl, naphthyl, chromanyl, indolyl, benzofuranyl, benzothiophenyl (benzothienyl); benzooxazolyl, benzooxadiazolyl, pyrrolyl, furanyl, thienyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazothiazolyl, carbazolyl, dibenzofuranyl, dibenzothiophenyl (dibenzothienyl) or for a phenyl or naphthyl bound by a C_{1-3} alkylene group, particularly preferably for phenyl, naphthyl, chromanyl, benzothiophenyl

GRA3454-WO
22nd December 2009

(benzothienyl), benzooxadiazolyl, thienyl, pyridinyl, imidazothiazolyl, dibenzofuranyl or for a phenyl bound by a C₁₋₃ alkylene group, most particularly preferably for phenyl, naphthyl, chromanyl, benzothiophenyl (benzothienyl) or for a phenyl bound by a C_{1 or 2} alkylene group, wherein the aforementioned aryl or heteroaryl radicals are each unsubstituted or mono- or polysubstituted, identically or differently, wherein the substituents are mutually independently selected in particular from the group consisting of -O-C₁₋₃ alkyl, C₁₋₆ alkyl, F, Cl, Br, I, CF₃, OCF₃, OH, SH, phenyl, phenoxy, naphthyl, furyl, thienyl and pyridinyl and wherein the aforementioned alkylene groups are each unsubstituted or mono- or polysubstituted, identically or differently, wherein the substituents are mutually independently selected in particular from the group consisting of -O-C₁₋₃ alkyl, F, Cl, Br, I, CF₃, OCF₃, OH, SH, phenyl, phenoxy, naphthyl, furyl, thienyl and pyridinyl.

The radical R³ can stand in particular for phenyl or naphthyl, wherein the phenyl or naphthyl is unsubstituted or mono- or polysubstituted, for example di-, tri-, tetra- or pentasubstituted, with identical or different radicals selected from methyl, methoxy, CF₃, OCF₃, F and Cl.

In likewise preferred embodiments of the compounds according to the invention the radical R³ is selected from the group consisting of 4-methoxy-2,3,6-trimethylphenyl, 4-methoxy-2,6-dimethylphenyl, 4-methoxy-2,3,5-trimethylphenyl, 2,4,6-trimethylphenyl, 2-chloro-6-methylphenyl, 2,4,6-trichlorophenyl, 1,3-dichloro-5-trifluoromethylphenyl, 2-chloro-6-(trifluoromethyl)phenyl, 2,6-dichloro-4-methoxyphenyl, 2,6-dichloro-4-trifluoromethyl, 2-methylnaphthyl, 2-chloronaphthyl, 2-fluoronaphthyl, 2-chloro-4-(trifluoromethoxy)phenyl, 4-chloro-2,5-dimethylphenyl, 2-chloro-6-methylphenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 2,4-dichlorophenyl, 2,4,5-trichlorophenyl, 2,4,6-trichlorophenyl, 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 1-naphthyl and 2-naphthyl.

In particular the radical R³ can stand for 4-methoxy-2,6-dimethylphenyl, 4-chloro-2,5-dimethylphenyl, 1-naphthyl or 2-(trifluoromethyl)phenyl.

In the compounds according to the invention the radical R⁴ can stand in particular for a substituent which is selected from the group consisting of H, methyl, ethyl, n-propyl,

GRA3454-WO
22nd December 2009

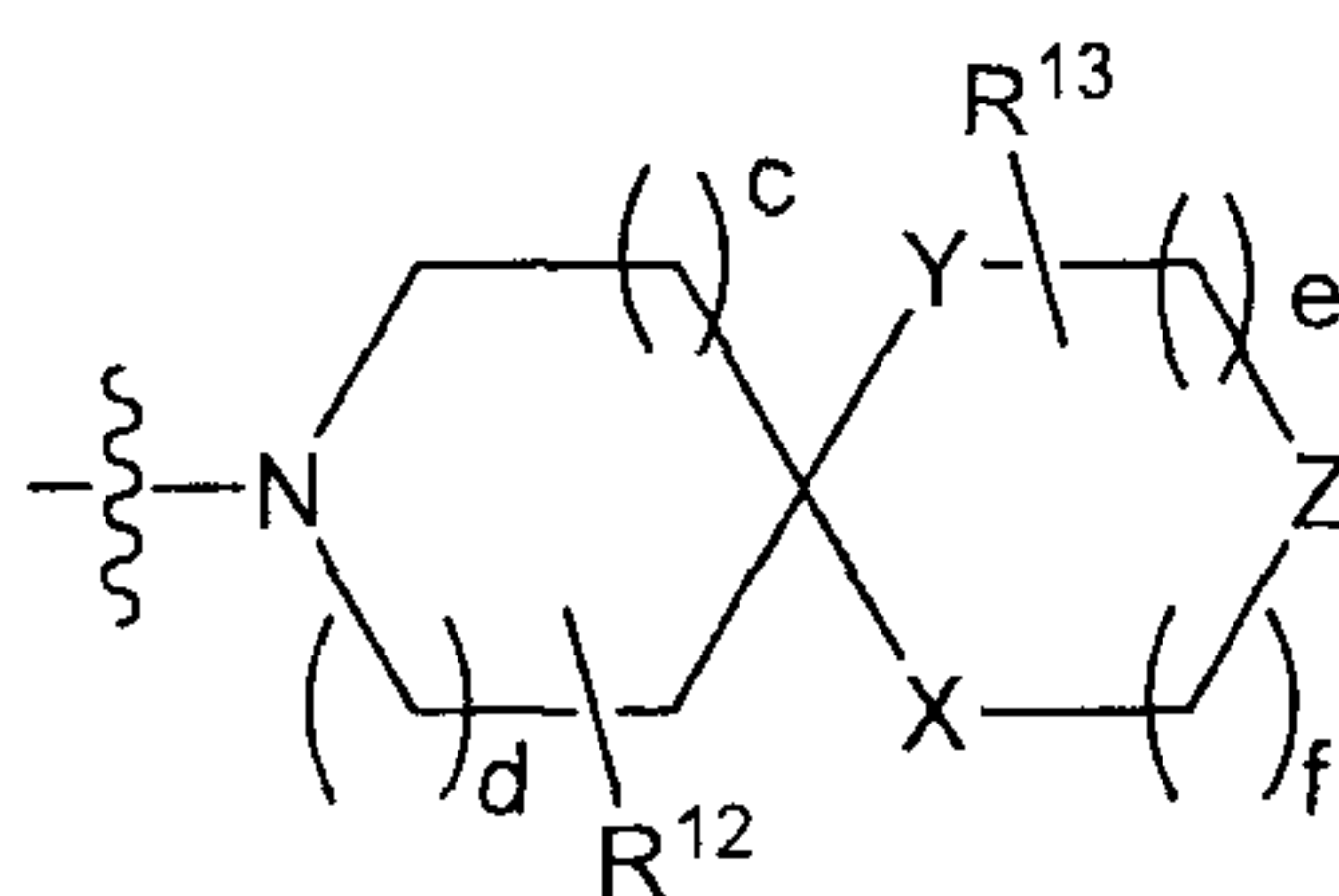
isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl and cyclopropyl. The radical R^4 particularly preferably stands for H.

In likewise preferred embodiments of the compounds according to the invention q stands for 1 or 2.

Likewise preferred embodiments of the compounds according to the invention are those in which R^8 stands for H; C_{1-6} alkyl, in particular methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl; cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2CF_3$, phenyl, benzyl, phenylethyl, phenylpropyl, or cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl bound by a C_{1-3} alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents. In particular R^8 can stand for H, methyl, ethyl, isopropyl or cyclopropyl.

Likewise preferred embodiments of the compounds according to the invention are those in which R^{9a} and R^{9b} each mutually independently stand for H; F; methyl; ethyl, isopropyl, CF_3 , methoxy; cyclopropyl; phenyl; benzyl, phenylethyl, C_{1-3} alkylene-cyclopropyl, C_{1-3} alkylene-cyclobutyl, C_{1-3} alkylene-cyclopentyl, C_{1-3} alkylene-cyclohexyl or C_{1-3} alkylene- CF_3 , each unsubstituted or mono- or polysubstituted with identical or different substituents. In particular R^{9a} and R^{9b} each stand for H.

Likewise preferred embodiments of the compounds according to the invention are those in which the aforementioned general formula (II) assumes the following substructure (IIa):

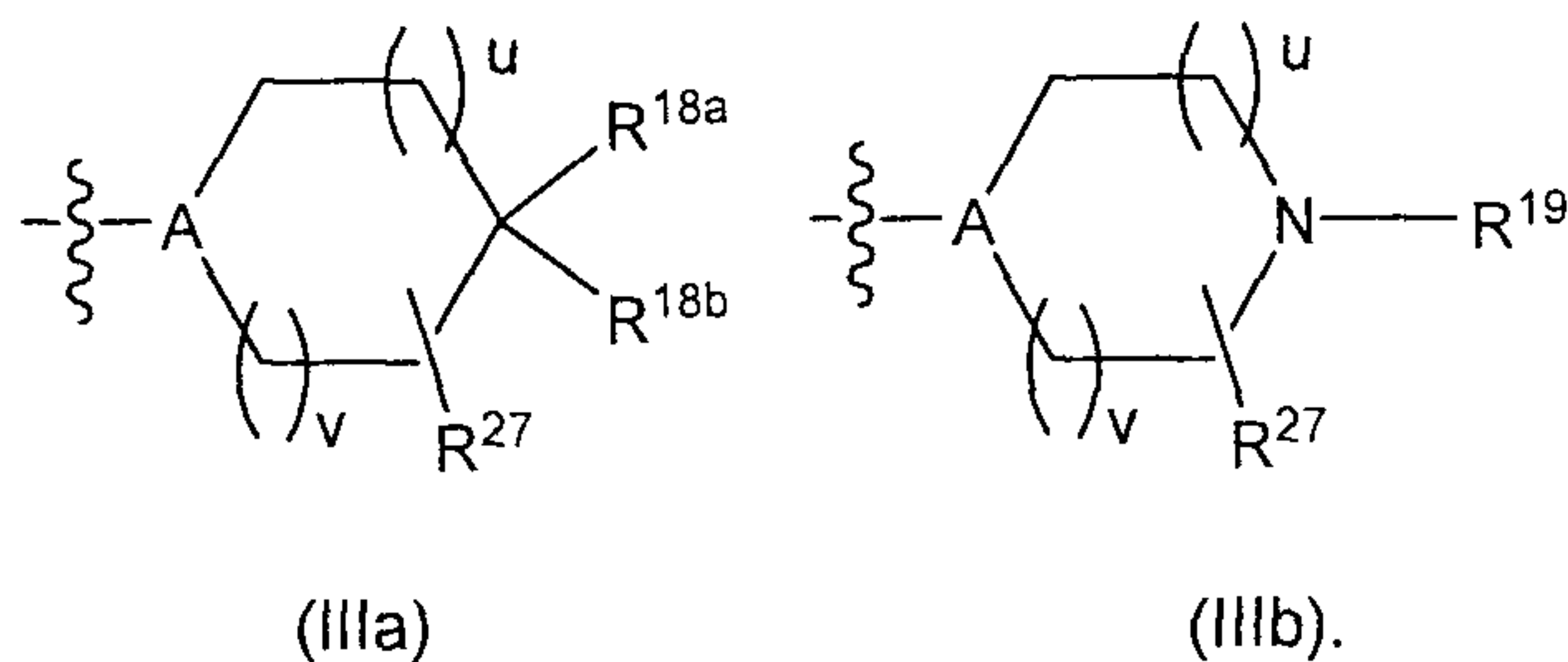


(IIa).

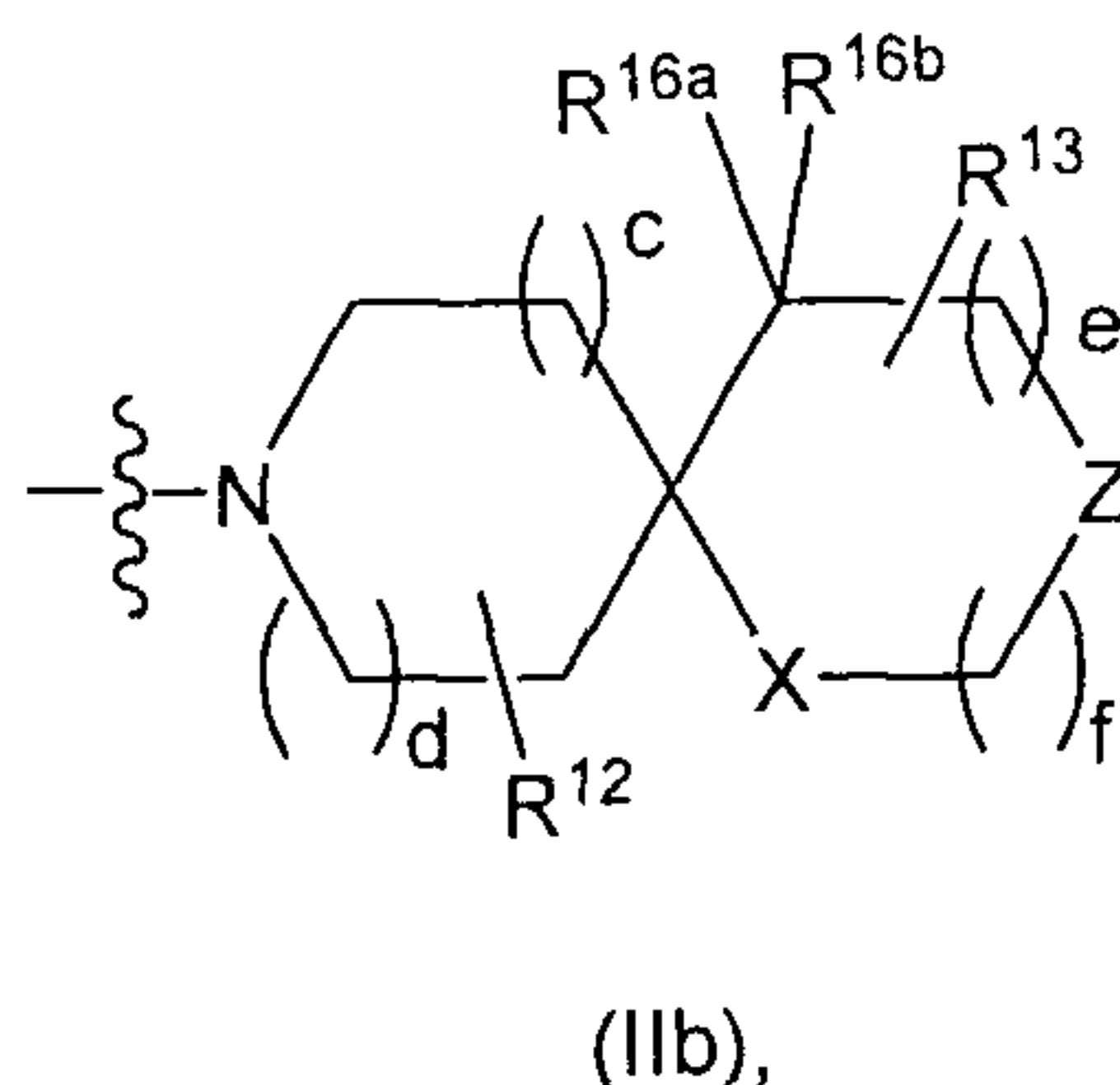
GRA3454-WO

22nd December 2009

Likewise preferred embodiments of the compounds according to the invention are those in which the aforementioned general formula (III) assumes one of the following substructures (IIIa) or (IIIb):



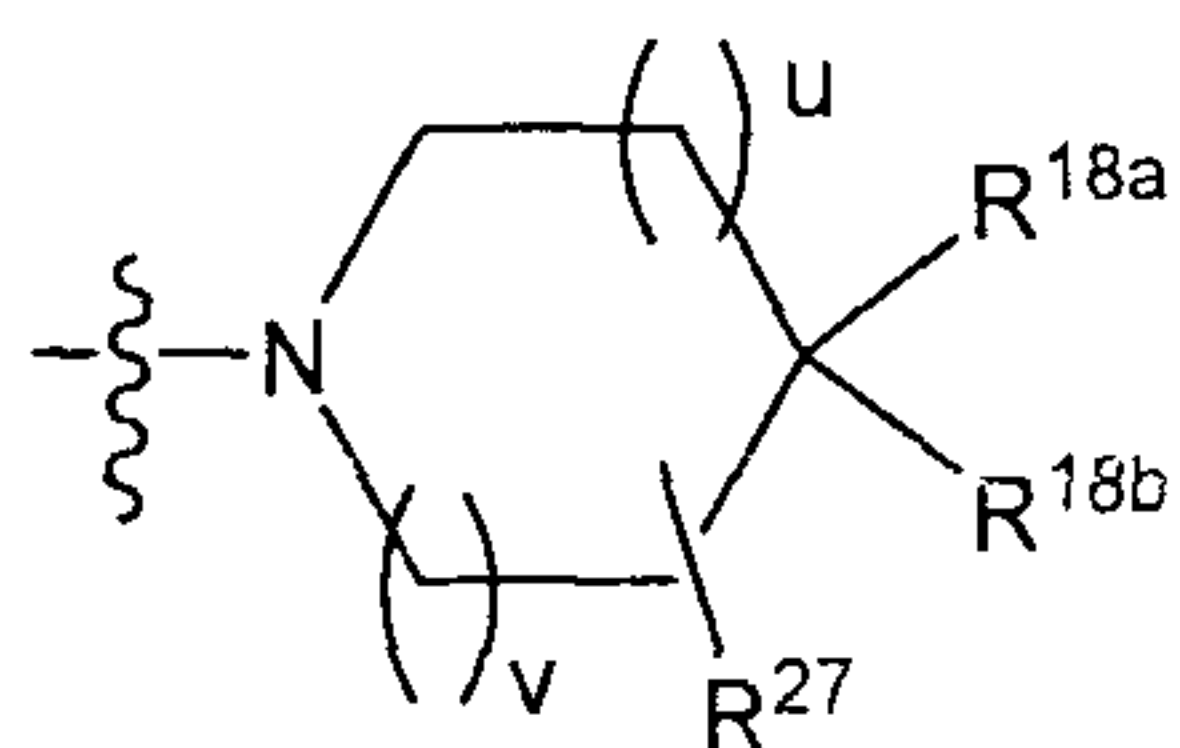
Likewise preferred embodiments of the compounds according to the invention are those in which the substructure according to the formula (IIa) shown above assumes the following substructure (IIb):



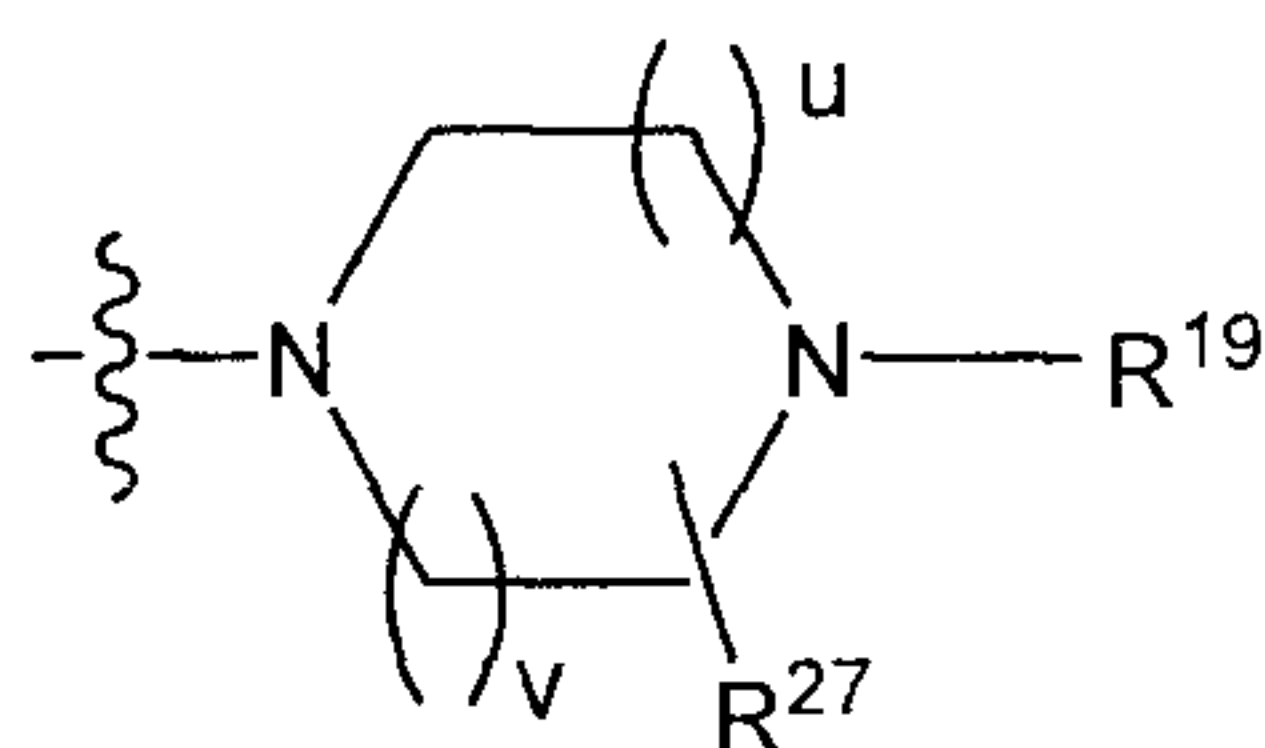
wherein in certain embodiments of these compounds according to the invention R^8 can stand for H or C_{1-6} alkyl, in each case unsubstituted or mono- or polysubstituted with identical or different radicals, and R^{9a} and R^{9b} each stand for H.

Likewise preferred embodiments of the compounds according to the invention are those compounds in which the substructures according to the formulae (IIIa) and (IIIb) shown above assume one of the following substructures (IIlc), (IIId), (IIle) or (IIIf):

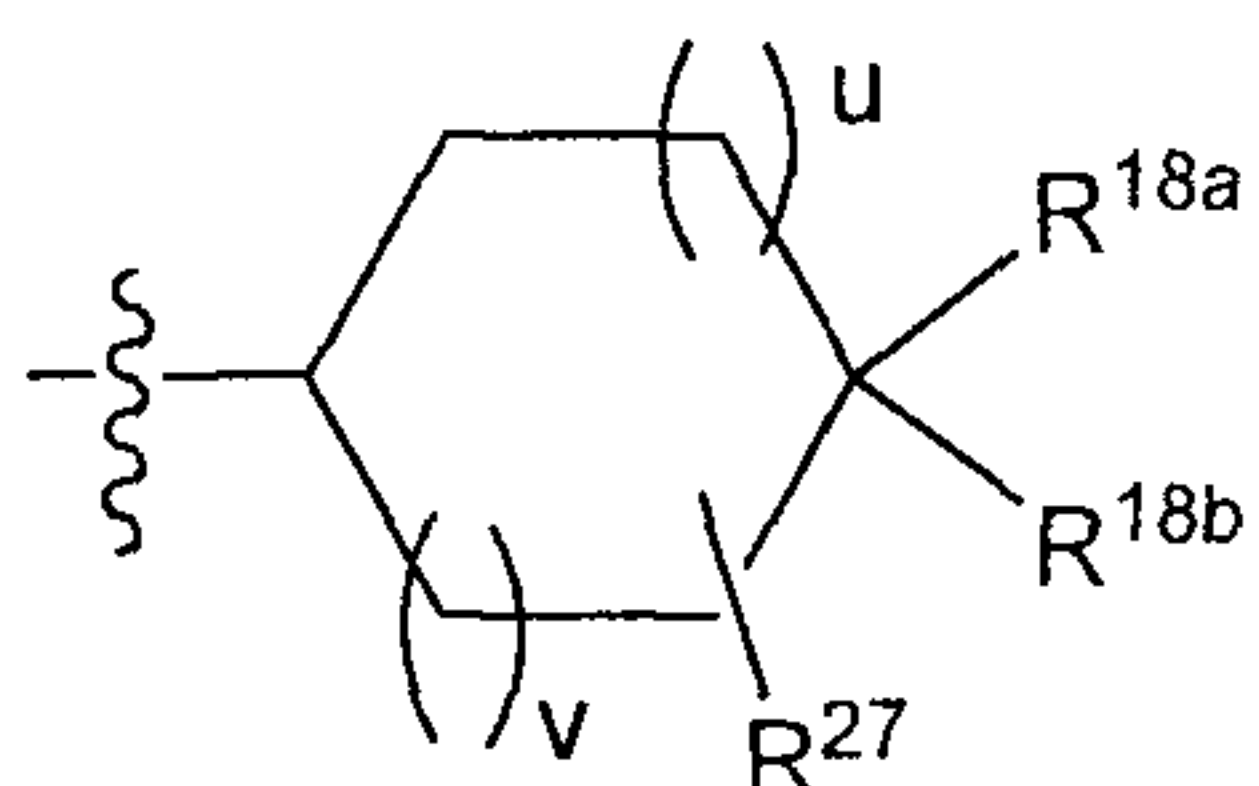
GRA3454-WO
22nd December 2009



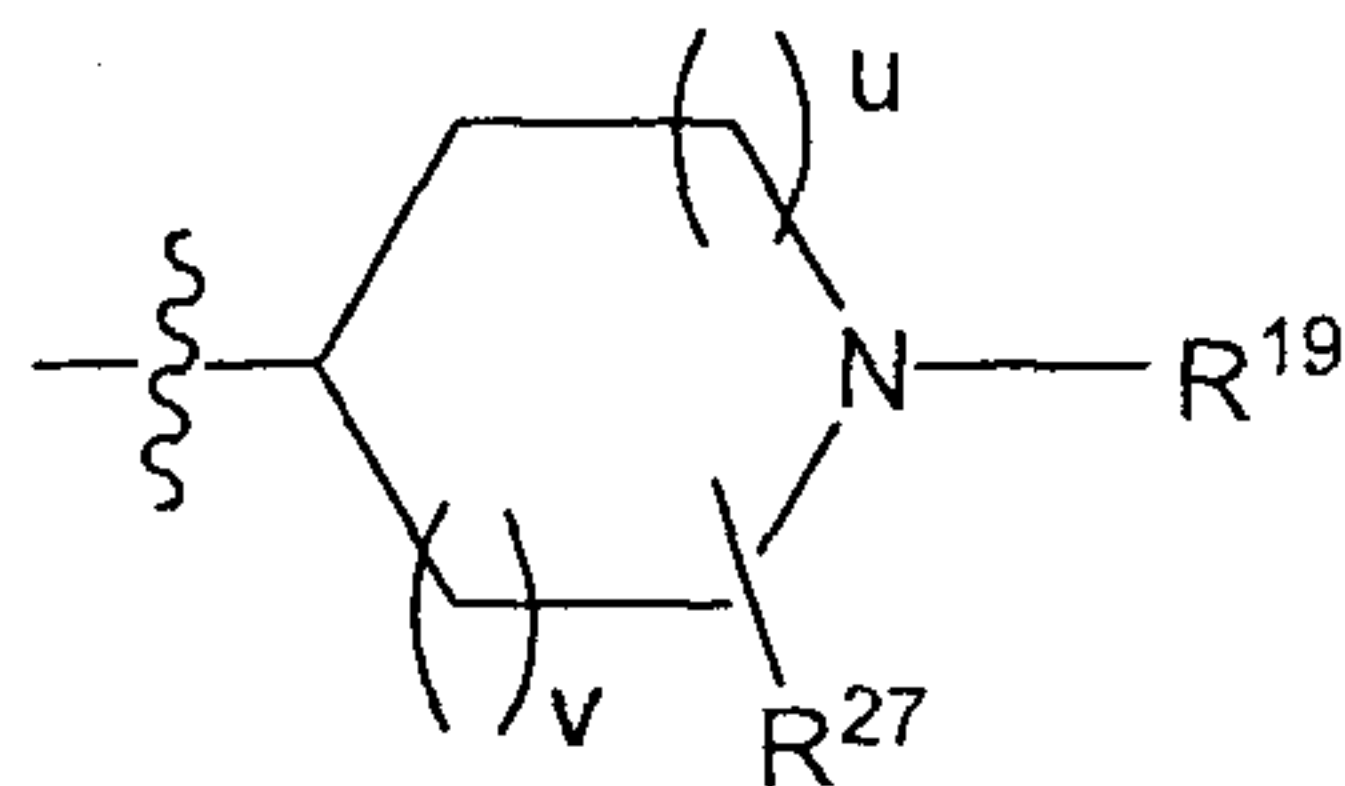
(IIIc)



(IIIId)



(IIIe)



(IIIIf)

In certain embodiments of these compounds according to the invention s and t each stand for 0.

Likewise preferred embodiments of the compounds according to the invention are those in which

(a1) the substructure having formula (IIa) assumes the substructure (IIb) and s and t each stand for 0;

or

(a2) the substructures having formulae (IIIa) and (IIIb) assume one of the substructures (IIIc) or (IIId) and s and t each stand for 0;

or

(a3) the substructures having formulae (IIIa) and (IIIb) assume one of the substructures (IIIc) or (IIId) and two of the substituents R^{27} together form a C_{1-3} alkylene bridge such that the cyclic compound represented in substructure (IIIc) or (IIId) assumes a bicyclically bridged form and s and t each stand for 0;

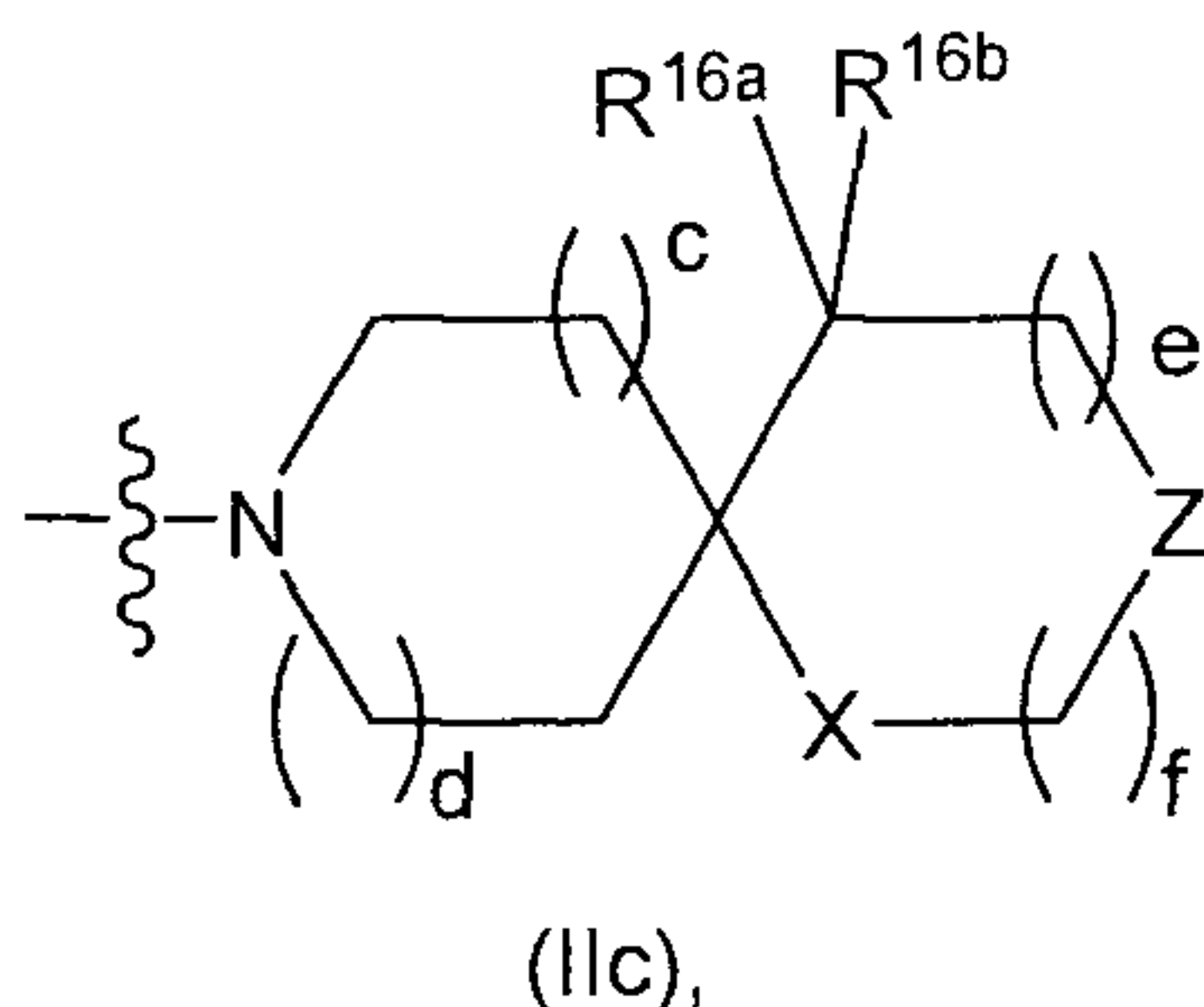
GRA3454-WO
22nd December 2009

or

(a4) the substructures having formulae (IIIa) and (IIIb) assume one of the substructures (IIIc), (IIId), (IIIe) or (IIIf), s stands for 1 and t stands for 0, 1, 2 or 3 and R^8 stands for H, C_{1-6} alkyl or C_{3-6} cycloalkyl, in each case unsubstituted or mono- or polysubstituted with identical or different substituents, and R^{9a} and R^{9b} mutually independently stand for H, C_{1-6} alkyl or C_{3-6} cycloalkyl.

Likewise preferred embodiments of the compounds according to the invention are those in which

s and t each stand for 0 and the general formula (II) assumes the following substructure (IIc)



wherein

c, d, e and f each mutually independently denote 0, 1 or 2;

X stands for $CR^{14a}R^{14b}$, NR^{15} or O,

Z stands for $CR^{18a}R^{18b}$ or NR^{19} ,

or

if X stands for O and f stands for 0, Z denotes $=N(CR^{126})-$, wherein the N atom is singly bound to the O atom,

GRA3454-WO
22nd December 2009

R^{126} stands for H, C_{1-4} alkyl or for an unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl optionally bound by a C_{1-3} alkylene group, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

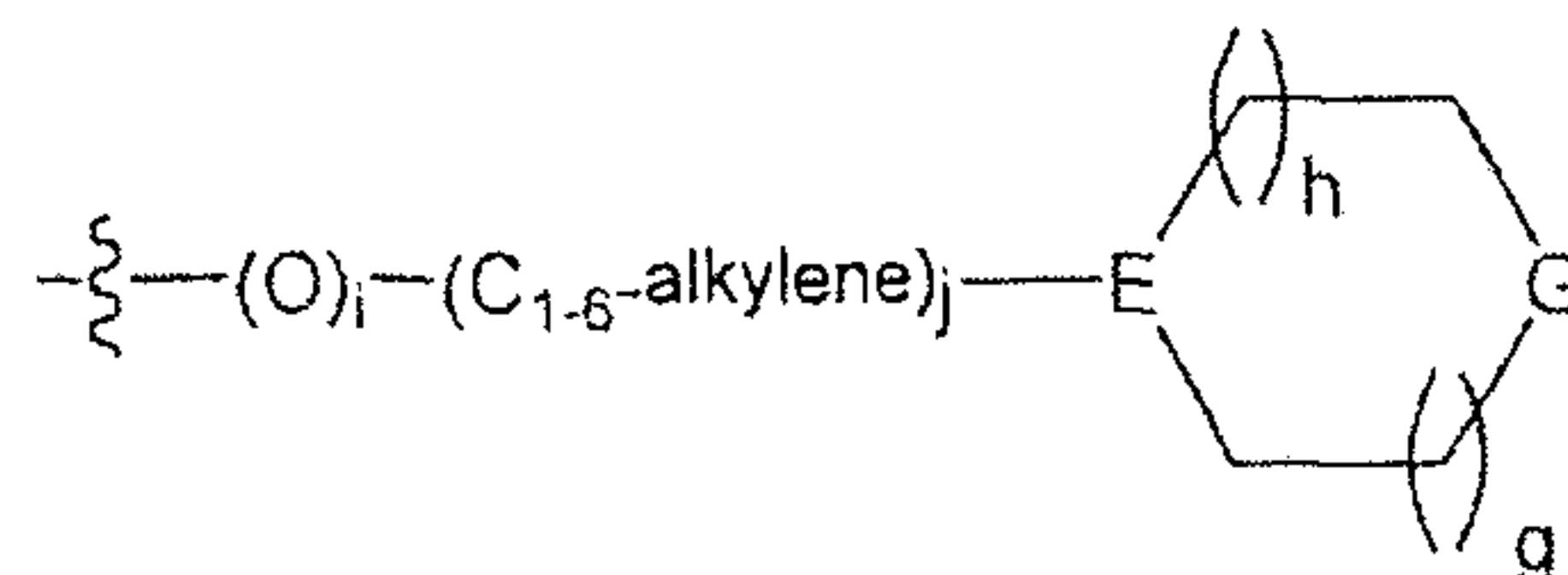
R^{14a} , R^{14b} , R^{16a} and R^{16b} mutually independently stand for H or for an unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl optionally bound by a C_{1-3} alkylene group, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl, and/or R^{16a} and R^{16b} together stand for =O;

R^{15} stands for H, C_{1-4} alkyl or for an unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl optionally bound by a C_{1-3} alkylene group, wherein the substituents are preferably selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

R^{18a} stands for H, C_{1-4} alkyl, C_{3-6} cycloalkyl, $-NH(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})_2$, unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, or for an unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by an $-(O)_{0-1}-C_{1-6}$ alkylene group; wherein the substituents are preferably each mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

or

R^{18a} stands for the radical according to the general formula (IVa)



(IVa)

GRA3454-WO
22nd December 2009

wherein

i stands for 0 or 1;

j stands for 0 or 1;

h and g, mutually independently, stand for 0 or 1,

E stands for N or CH; with the proviso that if i stands for 1 and j stands for 0 then E stands for CH,

G stands for $\text{CR}^{37a}\text{R}^{37b}$ or NR^{38} ;

wherein R^{37a} and R^{37b} mutually independently stand for H; F or C_{1-4} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents,

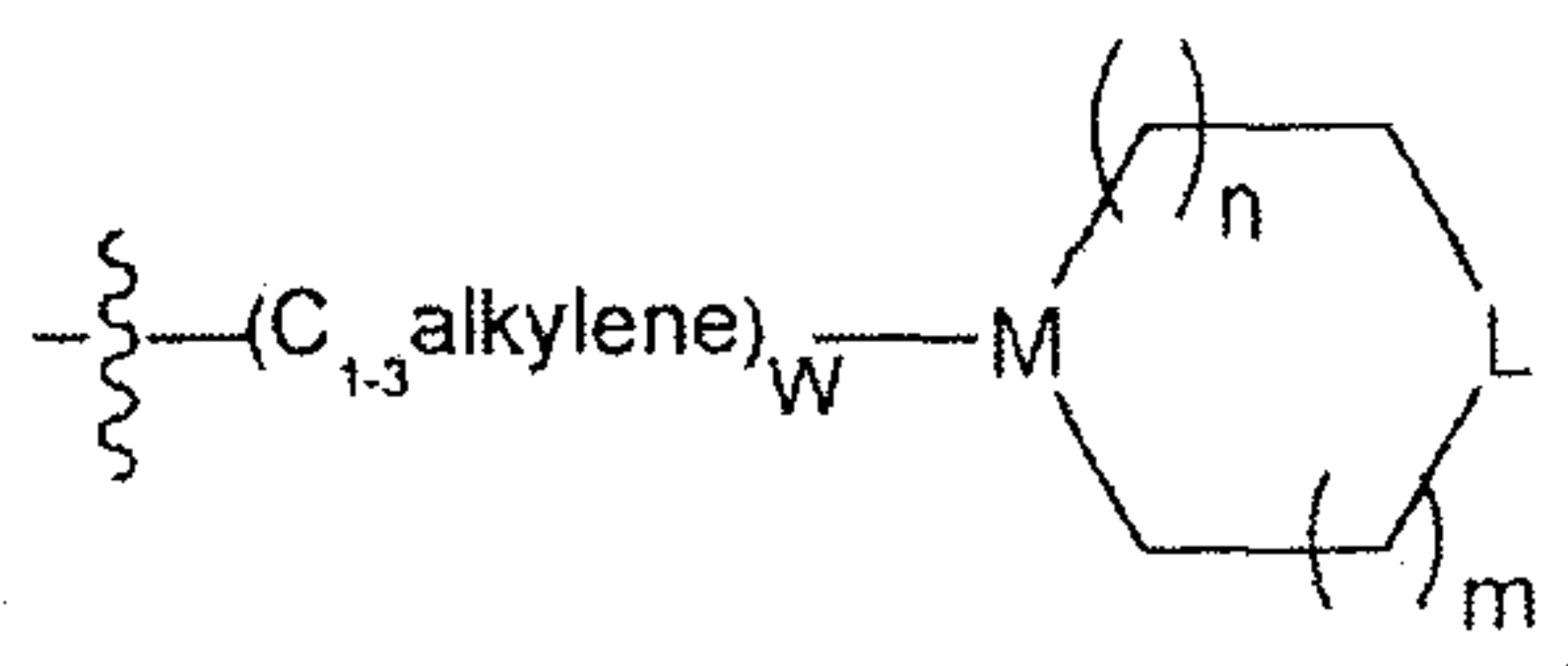
R^{38} stands for H; C_{1-6} alkyl, C_{3-6} cycloalkyl or pyridyl;

R^{18b} stands for H, OH, C_{1-6} alkyl, phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by a C_{1-6} alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents; O-phenyl or O-pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, phenyl, pyridyl or thienyl bridged by C_{1-6} alkylene-NH(C=O), each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

R^{19} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-(\text{C}=\text{O})-\text{C}_{1-6}$ alkyl; C_{1-6} alkylene-NH(C_{1-6} alkyl), C_{1-6} alkylene-N(C_{1-6} alkyl)₂ or for phenyl, pyridyl, thienyl, thiazolyl, triazolyl, pyrimidinyl or imidazolyl; each unsubstituted or mono- or polysubstituted with identical or different substituents; or for phenyl, pyridyl, thienyl, thiazolyl, pyrimidinyl, triazolyl or imidazolyl bound by a C_{1-6} alkylene group; each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are

GRA3454-WO
22nd December 2009

preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl, or for the radical according to the general formula (VIIIa)



(VIIIa)

wherein

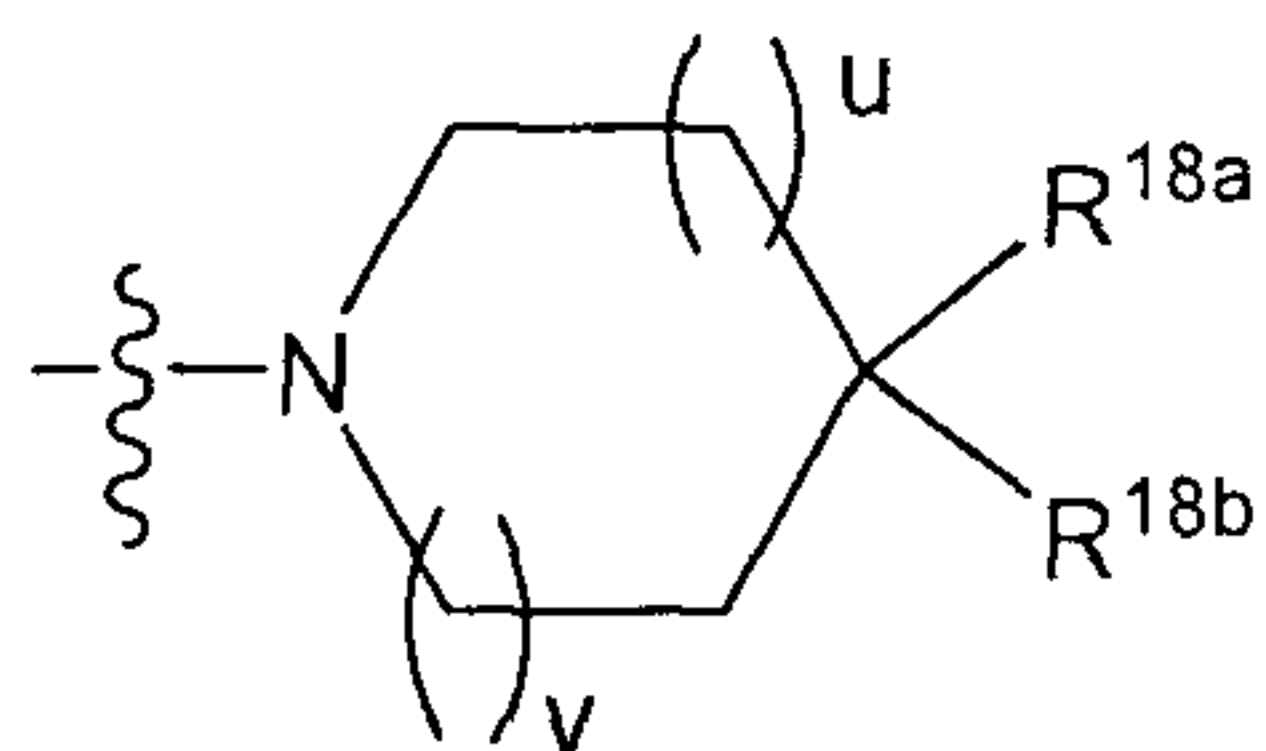
- w stands for 0 or 1;
- n stands for 0 or 1;
- m stands for 0 or 1;
- M stands for CH or N, with the proviso that if w stands for 0 then M stands for CH;
- L stands for CR^{44a}R^{44b} or NR⁴⁵;

wherein R^{44a} and R^{44b} mutually independently stand for H; F or C₁₋₆ alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; and

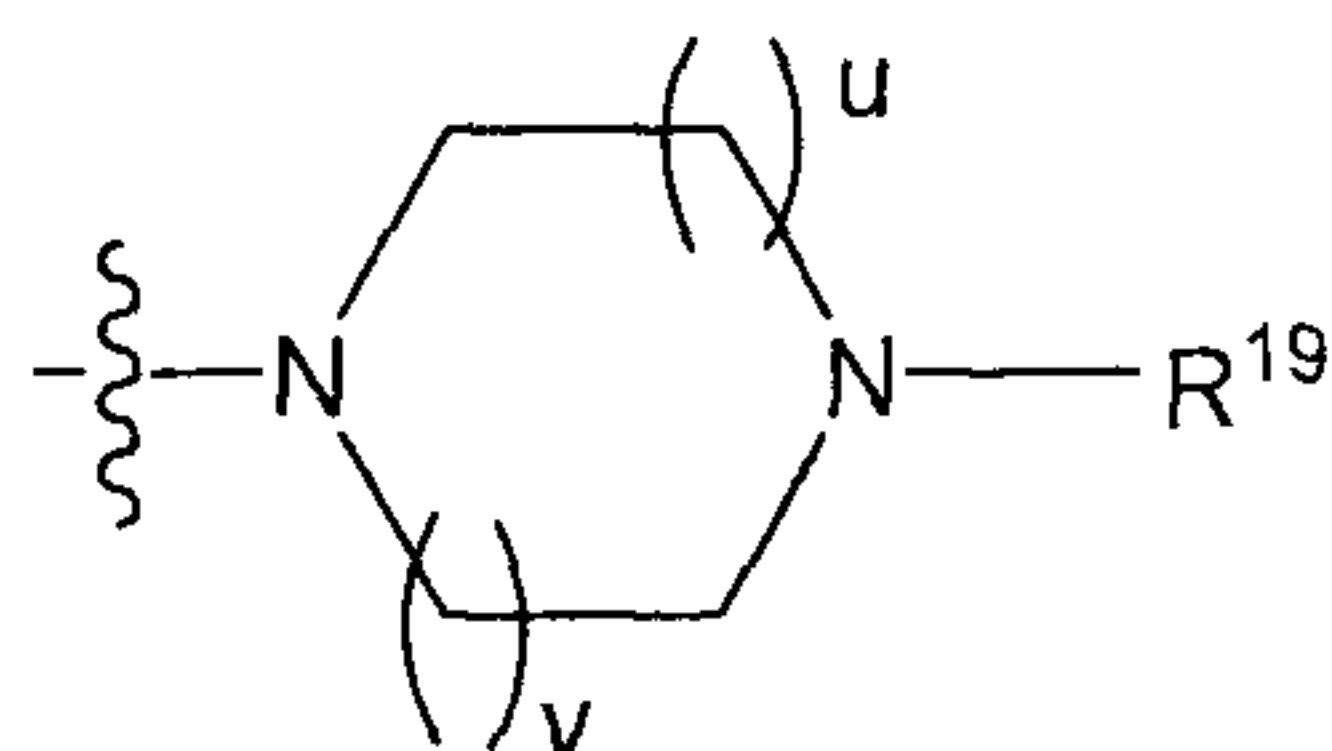
R⁴⁵ stands for H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or pyridyl.

Other preferred embodiments of the compounds according to the invention are those in which

s and t each stand for 0 and the general formula (III) assumes one of the substructures (IIIc') or (IIId')



(IIIc')



(IIId')

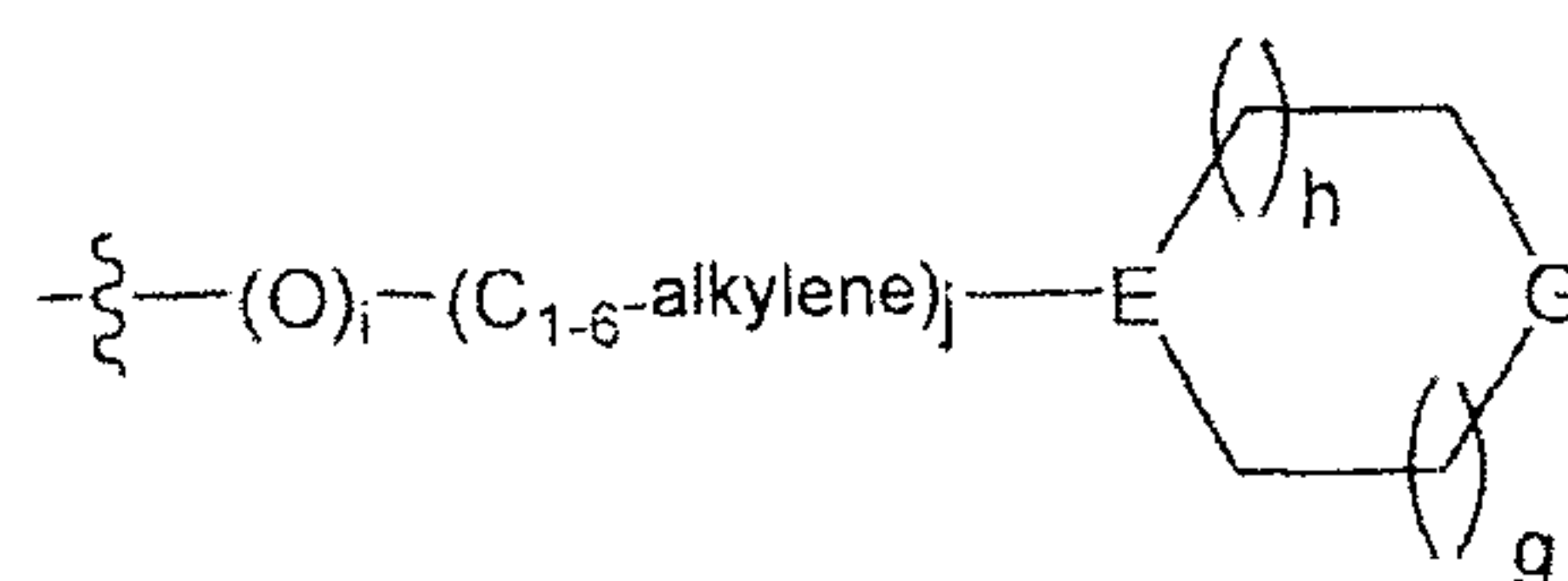
GRA3454-WO
22nd December 2009

wherein u and v mutually independently stand for 0, 1 or 2,

R^{18a} stands for H, C_{1-4} alkyl, C_{3-6} cycloalkyl, $-NH(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})_2$, unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, or for an unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by an $-(O)_{0-1}-C_{1-6}$ alkylene group; wherein the substituents are preferably each mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and $O-C_{1-4}$ alkyl,

or

R^{18a} stands for the radical according to the general formula (IVa)



(IVa)

wherein

i stands for 0 or 1;

j stands for 0 or 1;

h and g, mutually independently, stand for 0 or 1,

E stands for N or CH; with the proviso that if i stands for 1 and j stands for 0 then E stands for CH,

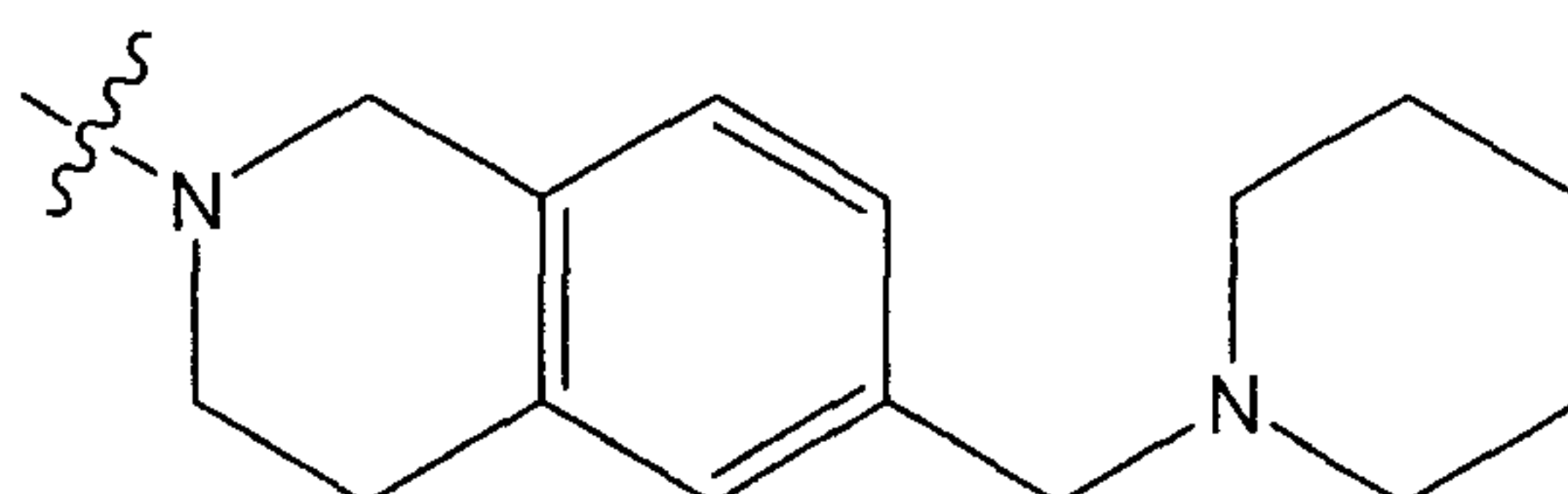
G stands for $CR^{37a}R^{37b}$ or NR^{38} ;

wherein R^{37a} and R^{37b} mutually independently stand for H; F or C_{1-4} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents,

GRA3454-WO
22nd December 2009

R^{38} stands for H; C_{1-6} alkyl, C_{3-6} cycloalkyl or pyridyl; or

R^{18a} stands for the following radical:

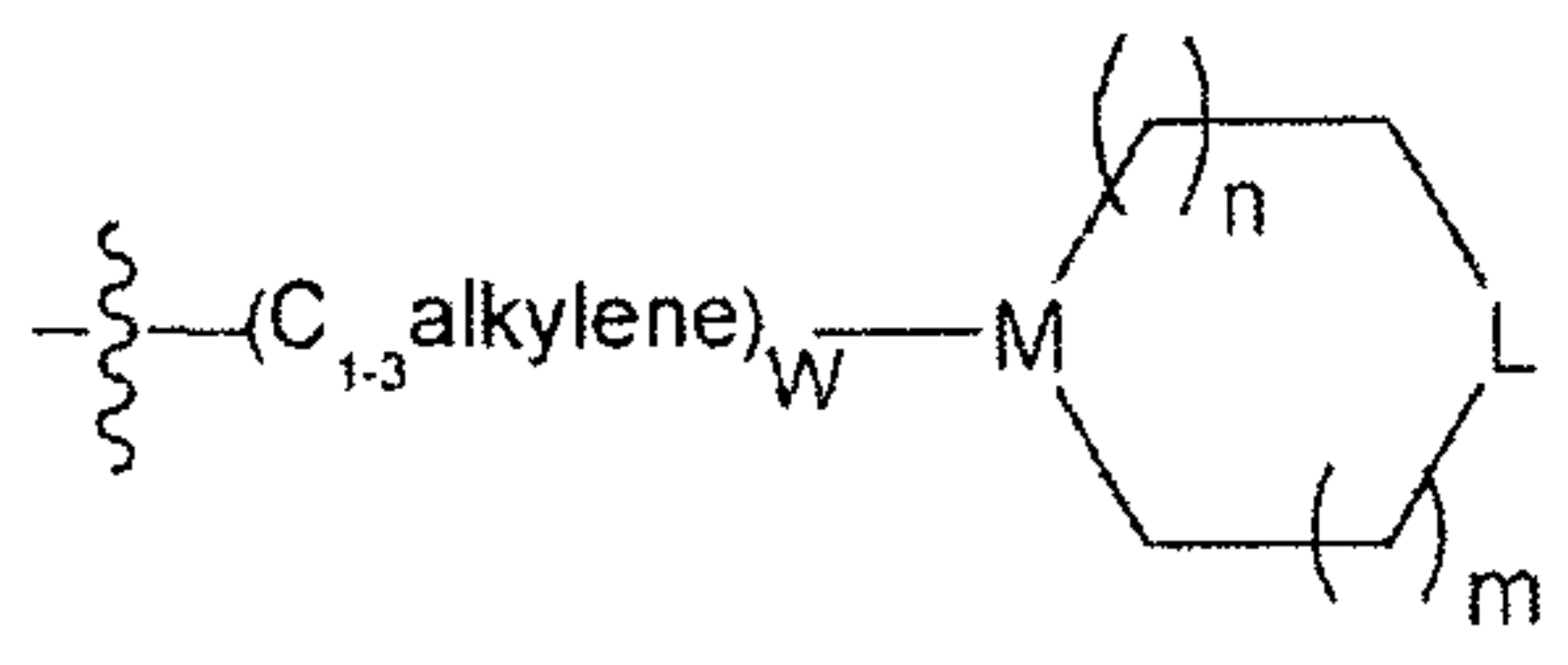


R^{18b} stands for H, OH, C_{1-6} alkyl, phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by a C_{1-6} alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents; O-phenyl or O-pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, phenyl, pyridyl or thienyl bridged by C_{1-6} alkylene-NH(C=O), each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

R^{19} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-(C=O)-C_{1-6}$ alkyl; C_{1-6} alkylene-NH(C_{1-6} alkyl), C_{1-6} alkylene-N(C_{1-6} alkyl) $_2$ or for phenyl, pyridyl, thienyl, thiazolyl, triazolyl, pyrimidinyl or imidazolyl; each unsubstituted or mono- or polysubstituted with identical or different substituents; or for phenyl, pyridyl, thienyl, thiazolyl, pyrimidinyl, triazolyl or imidazolyl bound by a C_{1-6} alkylene group; each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

GRA3454-WO
22nd December 2009

or for the radical according to the general formula (VIIIa)



(VIIIa)

wherein

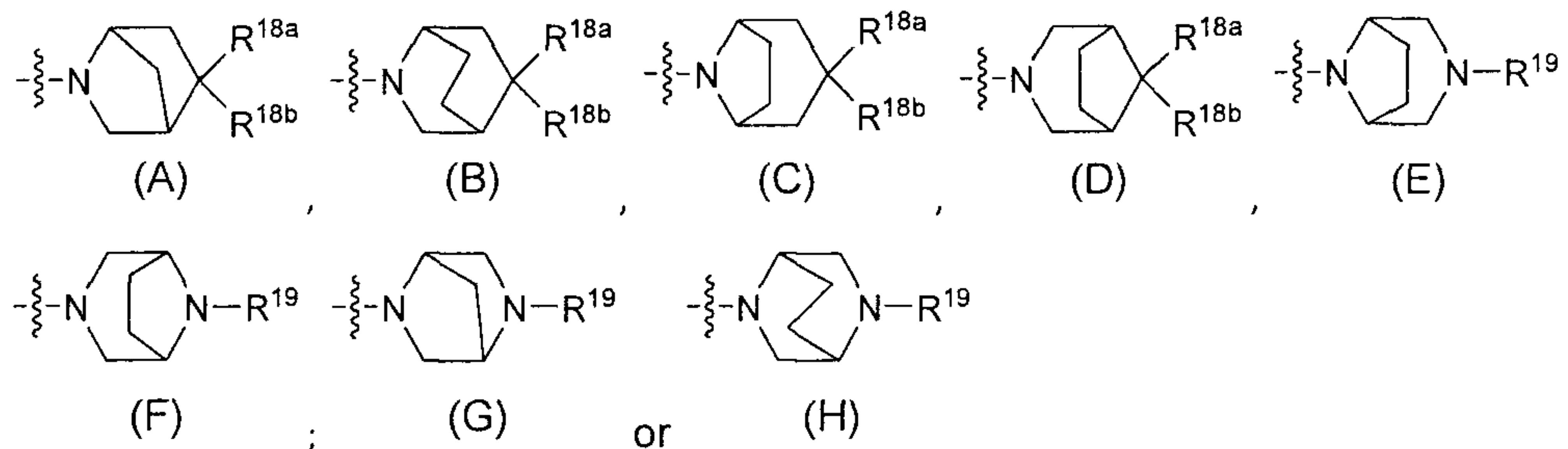
- w stands for 0 or 1;
- n stands for 0 or 1;
- m stands for 0 or 1;
- M stands for CH or N, with the proviso that if w stands for 0 then M stands for CH;
- L stands for CR^{44a}R^{44b} or NR⁴⁵;

wherein R^{44a} and R^{44b} mutually independently stand for H; F or C₁₋₆ alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; and

R⁴⁵ stands for H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or pyridyl.

Preferred embodiments of the compounds according to the invention are also those in which

s and t each stand for 0 and the general formula (III) assumes one of the following substructures (A) to (H)



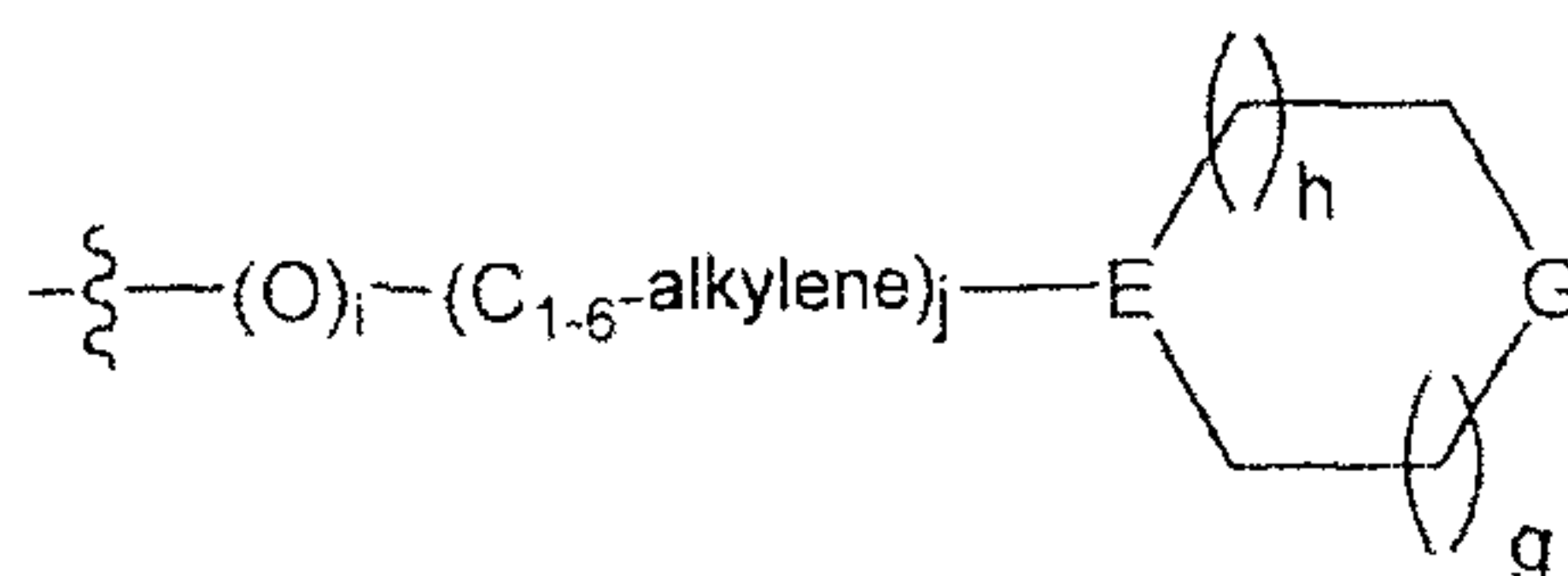
GRA3454-WO
22nd December 2009

and wherein

R^{18a} stands for H, C_{1-4} alkyl, C_{3-6} cycloalkyl, $-NH(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})_2$, unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, or for an unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by an $-(O)_{0-1}-C_{1-6}$ alkylene group; wherein the substituents are preferably each mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and $O-C_{1-4}$ alkyl,

or

R^{18a} stands for the radical according to the general formula (IVa)



(IVa)

wherein

i stands for 0 or 1;

j stands for 0 or 1;

h and g, mutually independently, stand for 0 or 1,

E stands for N or CH; with the proviso that if i stands for 1 and j stands for 0 then E stands for CH,

G stands for $CR^{37a}R^{37b}$ or NR^{38} ;

wherein R^{37a} and R^{37b} mutually independently stand for H; F or C_{1-4} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents,

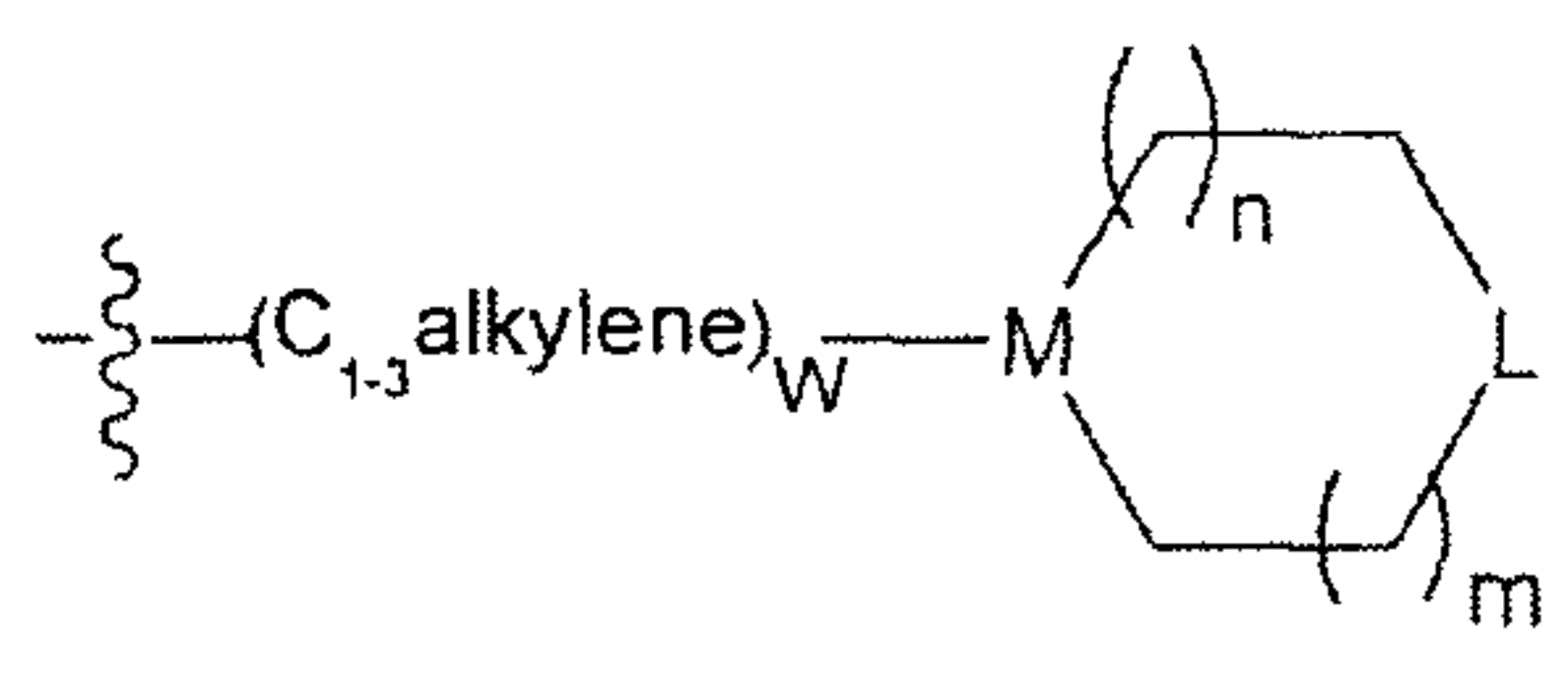
GRA3454-WO
22nd December 2009

R^{38} stands for H; C_{1-6} alkyl, C_{3-6} cycloalkyl or pyridyl;

R^{18b} stands for H, OH, C_{1-6} alkyl, phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by a C_{1-6} alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents; O-phenyl or O-pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, phenyl, pyridyl or thienyl bridged by C_{1-6} alkylene-NH(C=O), each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

R^{19} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-(C=O)-C_{1-6}$ alkyl; C_{1-6} alkylene-NH(C_{1-6} alkyl), C_{1-6} alkylene-N(C_{1-6} alkyl) $_2$ or for phenyl, pyridyl, thienyl, thiazolyl, triazolyl, pyrimidinyl or imidazolyl; each unsubstituted or mono- or polysubstituted with identical or different substituents; or for phenyl, pyridyl, thienyl, thiazolyl, pyrimidinyl, triazolyl or imidazolyl bound by a C_{1-6} alkylene group; each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

or for the radical according to the general formula (VIIIa)



(VIIIa)

wherein

w stands for 0 or 1;
 n stands for 0 or 1;
 m stands for 0 or 1;

GRA3454-WO
22nd December 2009

- M stands for CH or N, with the proviso that if w stands for 0 then M stands for CH;
L stands for $\text{CR}^{44a}\text{R}^{44b}$ or NR^{45} ;

wherein R^{44a} and R^{44b} mutually independently stand for H; F or C_{1-6} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; and

R^{45} stands for H, C_{1-6} alkyl, C_{3-6} cycloalkyl or pyridyl.

Preferred embodiments of the compounds according to the invention are also those in which

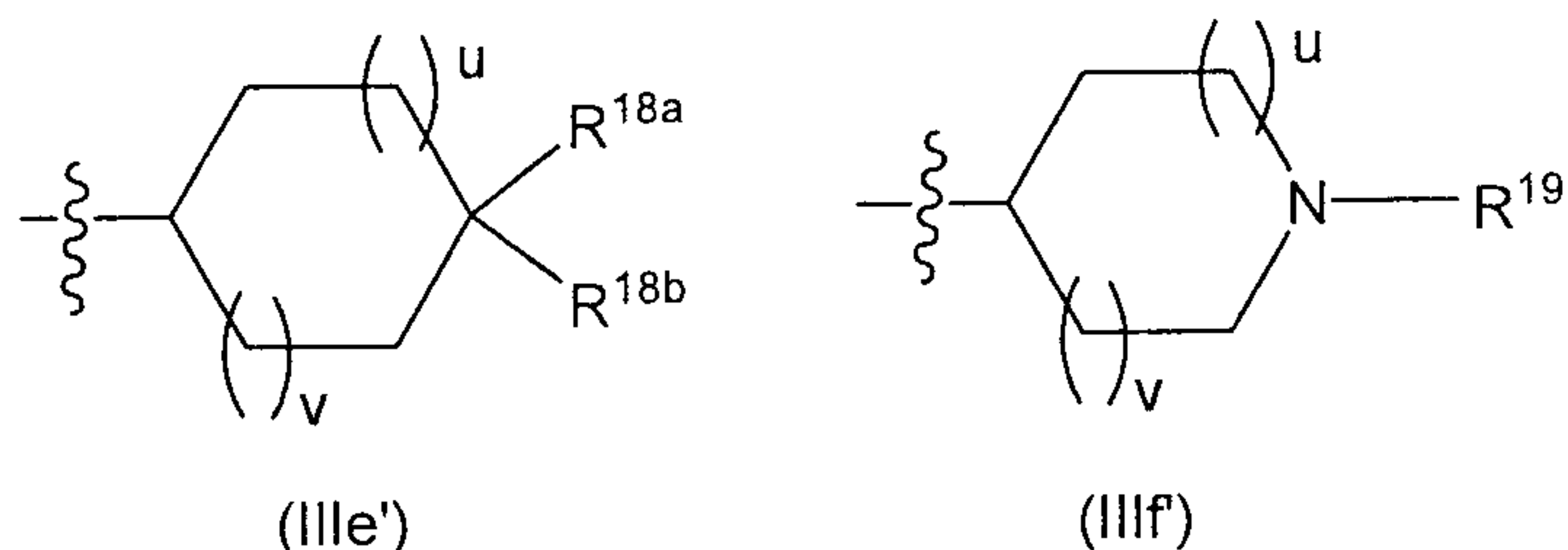
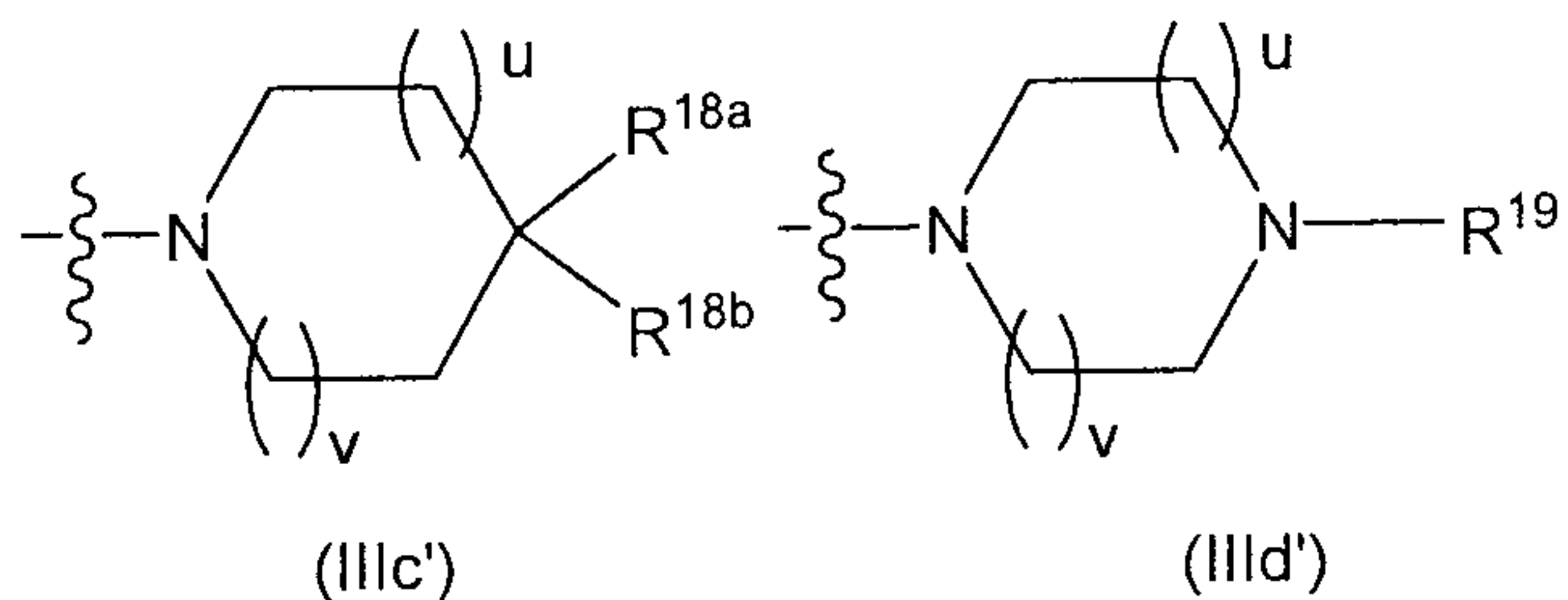
s stands for 1,

t stands for 0, 1, 2 or 3,

R^8 stands for H, C_{1-4} alkyl or C_{3-6} cycloalkyl

R^{9a} and R^{9b} mutually independently stand for H, C_{1-4} alkyl or C_{3-6} cycloalkyl, preferably both stand for H;

the general formula (III) assumes one of the following substructures (IIIc'), (IIId'), (IIIe') or (IIIf')



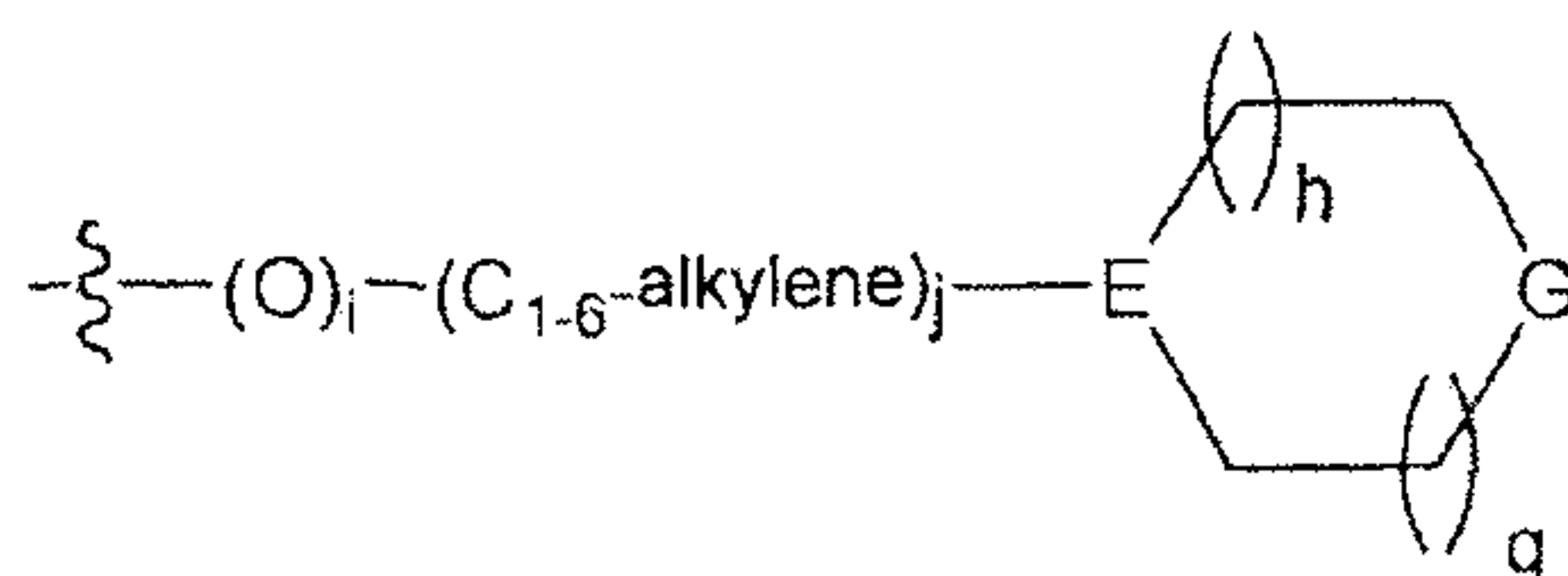
GRA3454-WO
22nd December 2009

wherein u and v mutually independently stand for 0, 1 or 2,

R^{18a} stands for H, C_{1-4} alkyl, C_{3-6} cycloalkyl, $-NH(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})_2$, unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, or for unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by an $-(O)_{0-1}-C_{1-6}$ alkylene group; wherein the substituents are preferably each mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and $O-C_{1-4}$ alkyl,

or

R^{18a} stands for the radical according to the general formula (IVa)



(IVa)

wherein

i stands for 0 or 1;

j stands for 0 or 1;

h and g, mutually independently, stand for 0 or 1,

E stands for N or CH; with the proviso that if i stands for 1 and j stands for 0 then E stands for CH,

G stands for $CR^{37a}R^{37b}$ or NR^{38} ;

GRA3454-WO
22nd December 2009

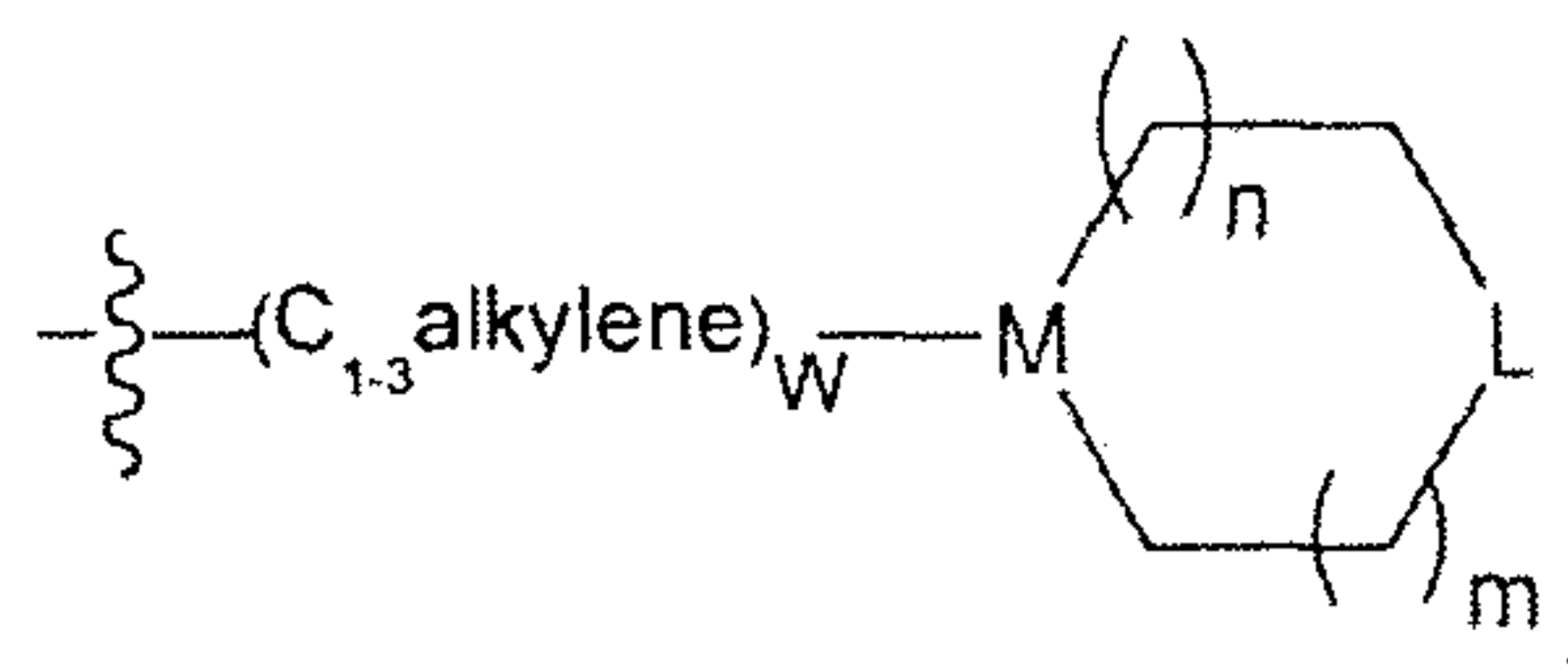
wherein R^{37a} and R^{37b} mutually independently stand for H; F or C_{1-4} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents,

R^{38} stands for H; C_{1-6} alkyl, C_{3-6} cycloalkyl or pyridyl;

R^{18b} stands for H, OH, C_{1-6} alkyl, phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by a C_{1-6} alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents; O-phenyl or O-pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, phenyl, pyridyl or thienyl bridged by C_{1-6} alkylene-NH(C=O), each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

R^{19} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-(C=O)-C_{1-6}$ alkyl; C_{1-6} alkylene-NH(C_{1-6} alkyl), C_{1-6} alkylene-N(C_{1-6} alkyl)₂ or for phenyl, pyridyl, thienyl, thiazolyl, triazolyl, pyrimidinyl or imidazolyl; each unsubstituted or mono- or polysubstituted with identical or different substituents; or for phenyl, pyridyl, thienyl, thiazolyl, pyrimidinyl, triazolyl or imidazolyl bound by a C_{1-6} alkylene group; each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

or for the radical according to the general formula (VIIIa)



(VIIIa)

GRA3454-WO
22nd December 2009

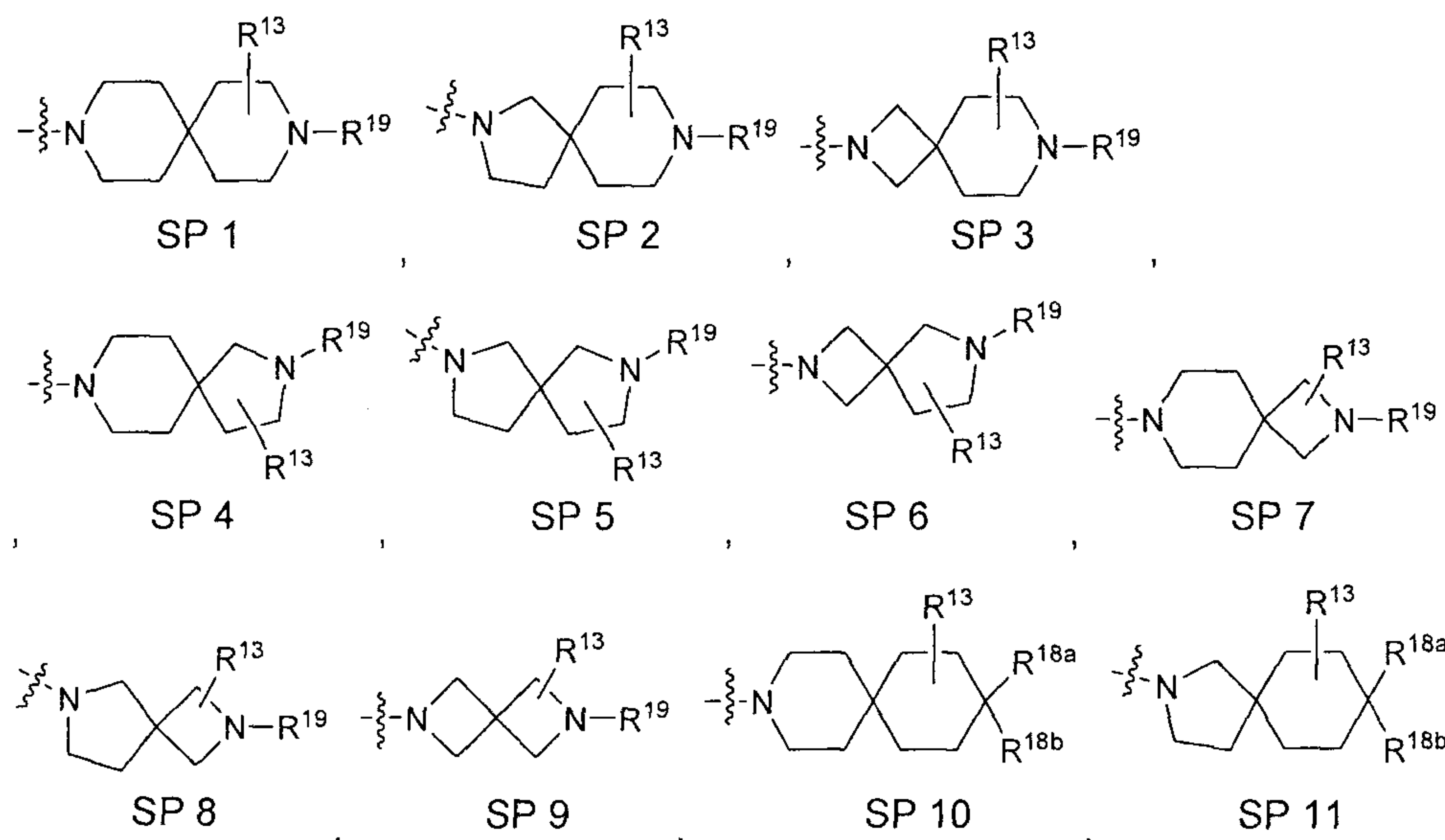
wherein

- w stands for 0 or 1;
 n stands for 0 or 1;
 m stands for 0 or 1;
 M stands for CH or N, with the proviso that if w stands for 0 then M stands for CH;
 L stands for CR^{44a}R^{44b} or NR⁴⁵;

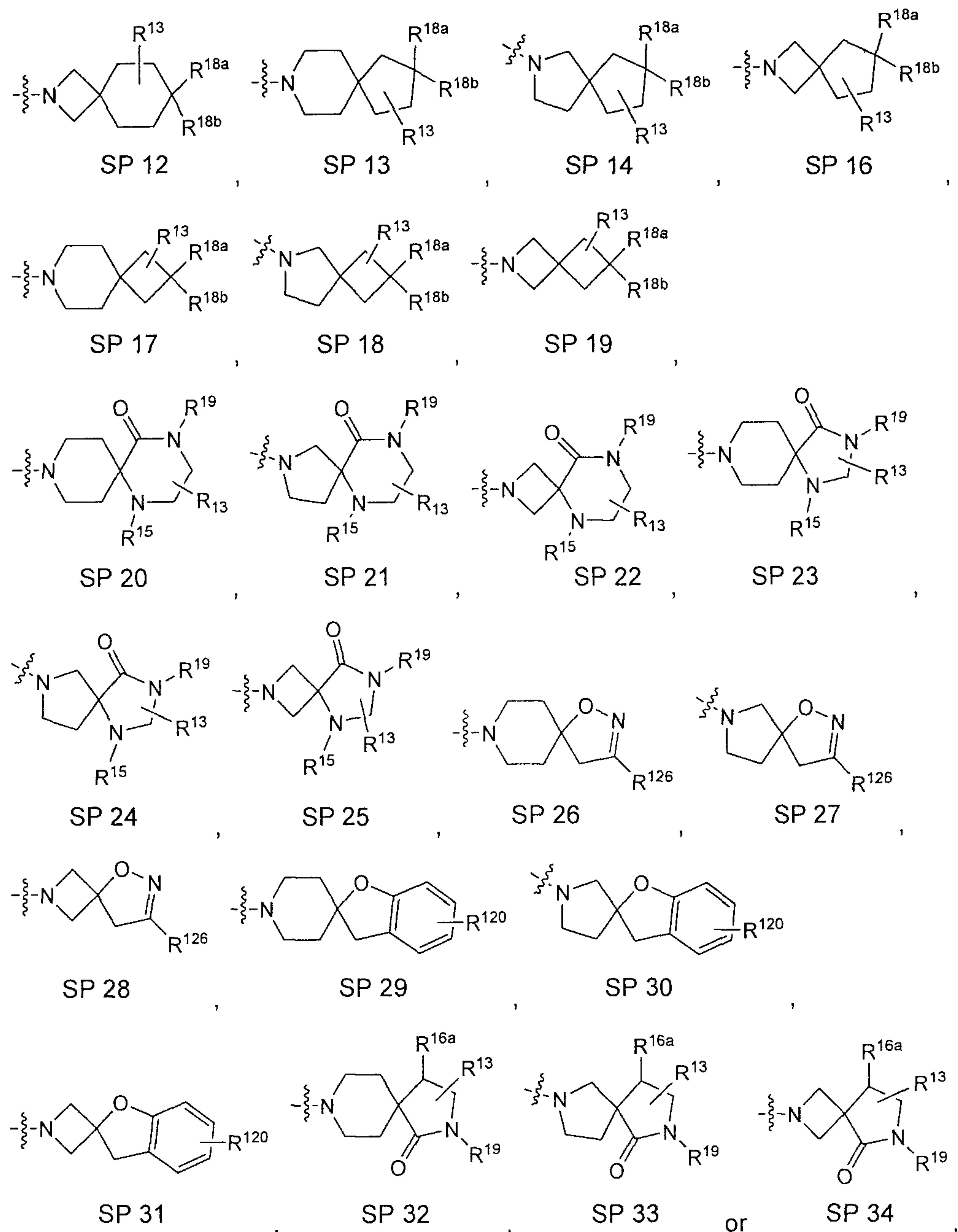
wherein R^{44a} and R^{44b} mutually independently stand for H; F or C₁₋₆ alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents;

R⁴⁵ stands for H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or pyridyl.

Other preferred embodiments of the compounds according to the invention are compounds in which the substructure according to formula II shown above assumes one of the following substructures SP:



GRA3454-WO
22nd December 2009



wherein

R^{13} stands for 1 or 2 radicals selected from H and phenyl, unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are

GRA3454-WO
22nd December 2009

preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

and/or two of the substituents R¹³ together form =O;

and/or two adjacent substituents R¹³ together form an anellated aryl or heteroaryl, in particular a benzo group, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

R¹⁵ stands for H; C₁₋₆ alkyl; C₃₋₈ cycloalkyl or for unsubstituted or identically or differently mono- or polysubstituted phenyl or pyridyl or for a phenyl or pyridyl bound by a C₁₋₆ alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

R^{16a} stands for H, C₁₋₆ alkyl or for phenyl or pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

R^{18a} stands for H; C₁₋₆ alkyl; C₃₋₈ cycloalkyl, N(C₁₋₆ alkyl)₂; NH(C₁₋₆ alkyl), azetidiny; pyrrolidiny, piperidiny, 4-(C₁₋₆ alkyl)-piperaziny; phenyl or pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; or for N(C₁₋₆ alkyl)₂; NH(C₁₋₆ alkyl), azetidiny; pyrrolidiny, piperidiny, 4-(C₁₋₆ alkyl)-piperaziny; phenyl, imidazolyl, triazolyl or pyridyl bound by an -(O)_{0/1}-C₁₋₆ alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents of C₁₋₆ alkyl; C₃₋₈ cycloalkyl, azetidiny; pyrrolidiny, piperidiny and 4-(C₁₋₆ alkyl)-piperaziny are preferably mutually independently selected from the group consisting of F, Cl, CF₃, =O, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl and wherein the substituents of phenyl, imidazolyl, triazolyl or

GRA3454-WO
22nd December 2009

pyridyl are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

R^{18b} stands for H; OH; C₁₋₆ alkyl; phenyl or pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, or for phenyl or pyridyl bound by a C₁₋₆ alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents; wherein the substituents of phenyl and pyridyl are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

R¹⁹ stands for H; C₁₋₆ alkyl; C₃₋₈ cycloalkyl, phenyl, pyridyl, thienyl, imidazolyl, thiazolyl or triazolyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, or for phenyl or pyridyl bound by a C₁₋₆ alkylene group or (C=O) group, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents of phenyl, pyridyl, thienyl, imidazolyl, thiazolyl and triazolyl are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

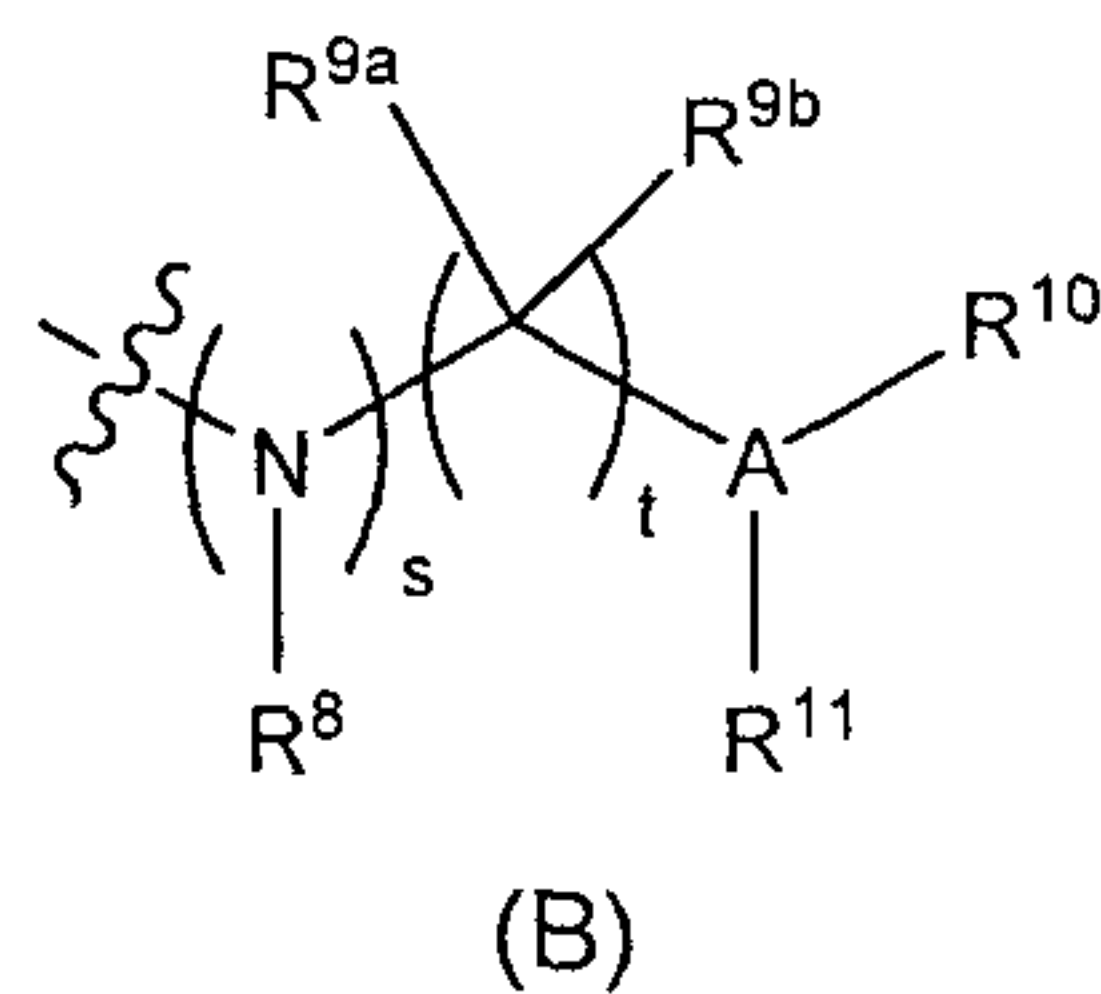
R¹²⁰ stands for H; F; Cl; OH; OCH₃, O-CF₃, C₁₋₆ alkyl; CF₃, phenyl, unsubstituted or mono- or polysubstituted, wherein the substituents of phenyl are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

R¹²⁶ stands for H; C₁₋₆ alkyl; C₃₋₆ cycloalkyl; phenyl or pyridyl; or for C₃₋₆ cycloalkyl, phenyl or pyridyl bound by a C₁₋₃ alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents of phenyl and pyridyl are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl.

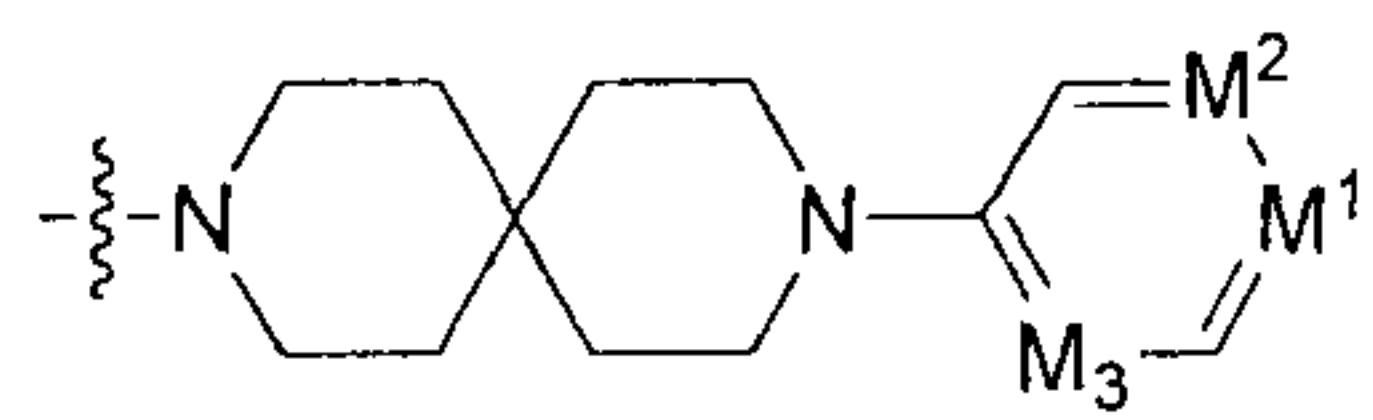
Of the substructures SP, substructures SP1, SP2, SP5, SP10, SP23, SP32 and SP26 can preferably be present in the compounds according to the invention.

GRA3454-WO
22nd December 2009

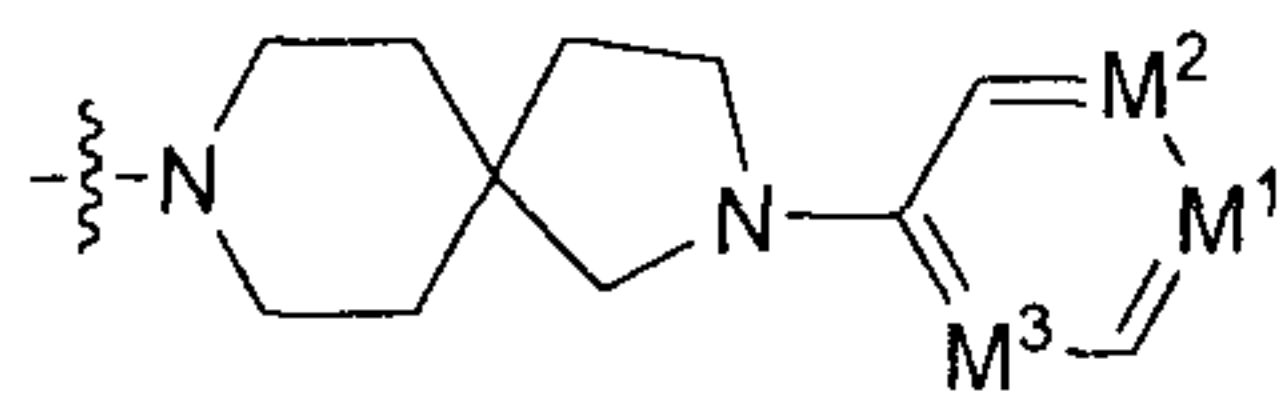
Other preferred embodiments of the compounds according to the invention are compounds in which the substructure (B) shown below in the general formula I shown above



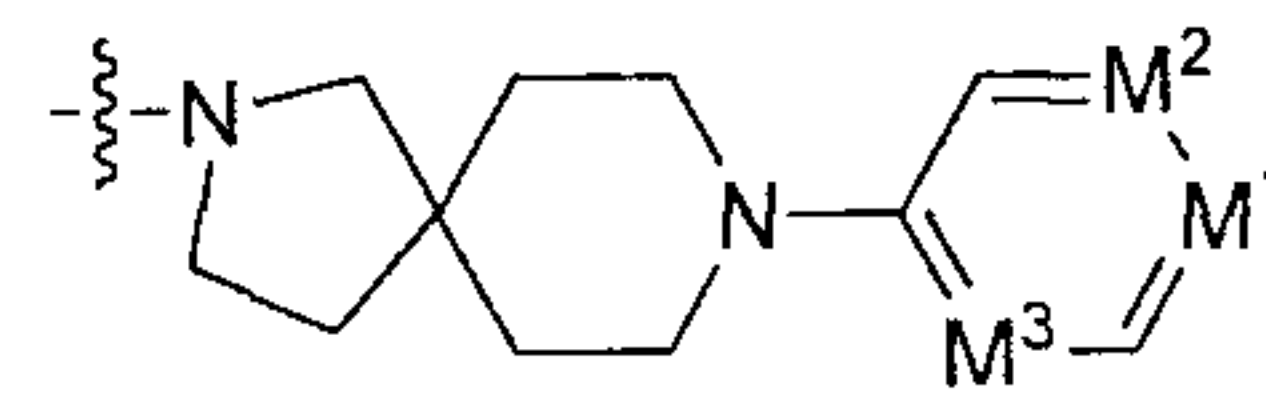
is selected from one of the following substructures B.1. to B.57.



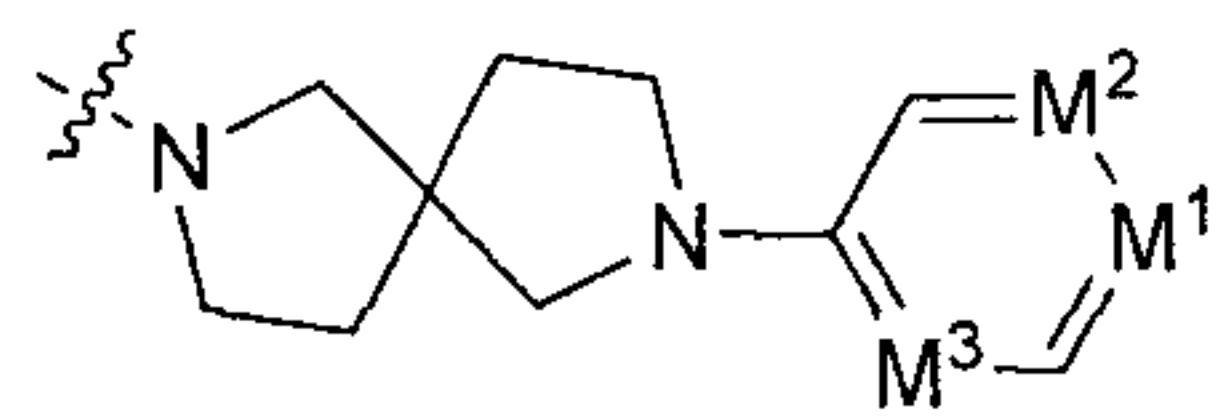
(B.1.)



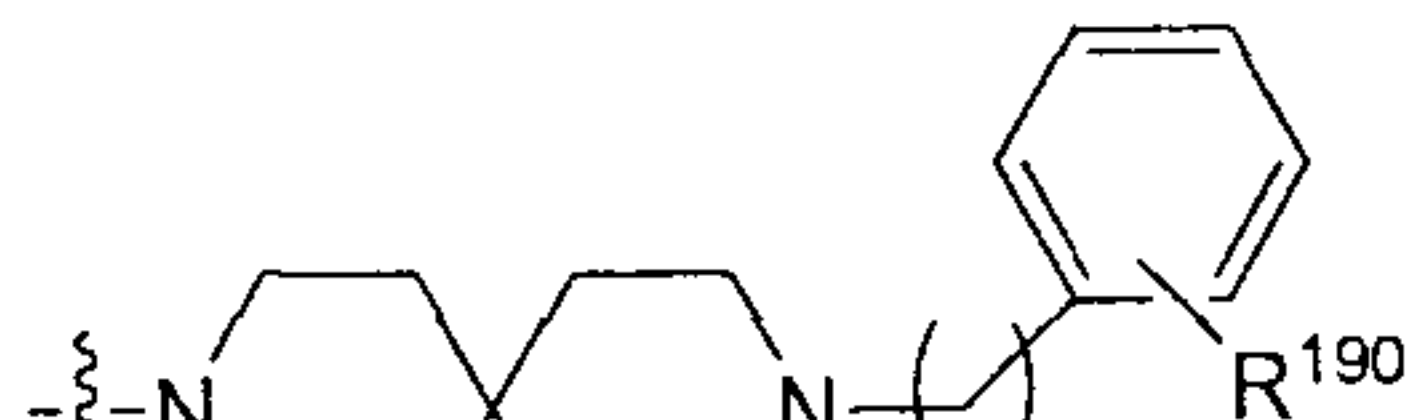
(B.2.)



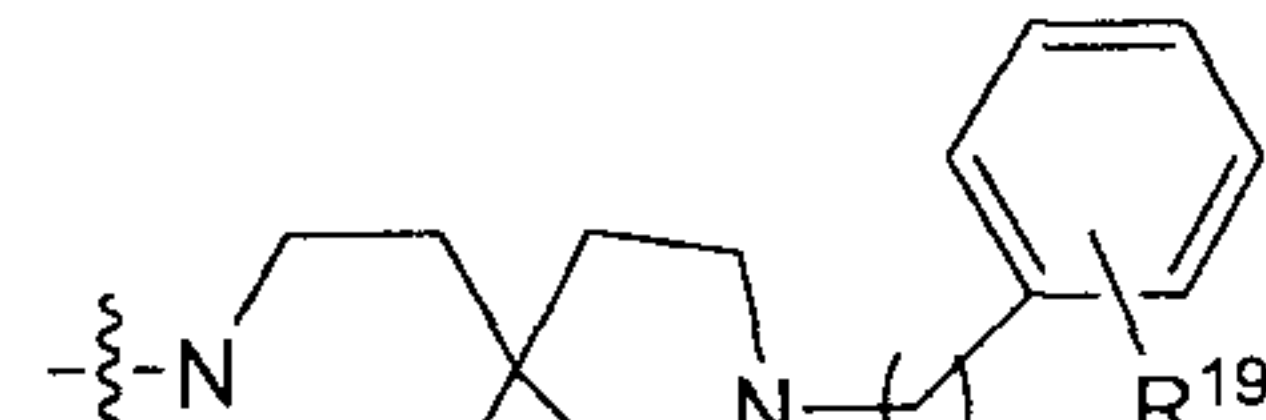
(B.3.)



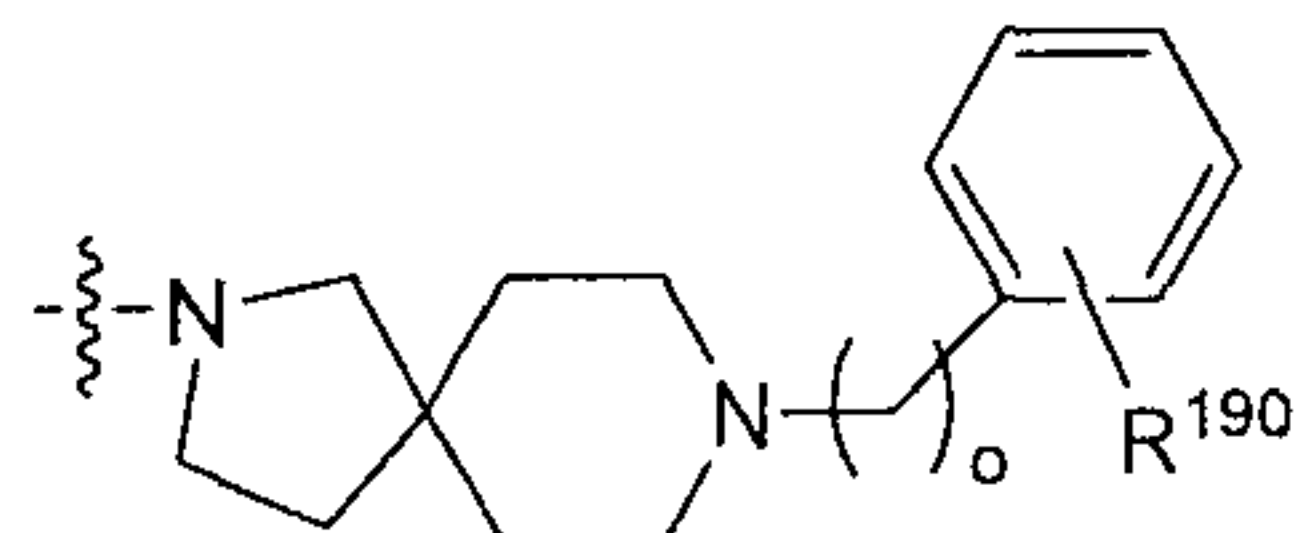
(B.4.)



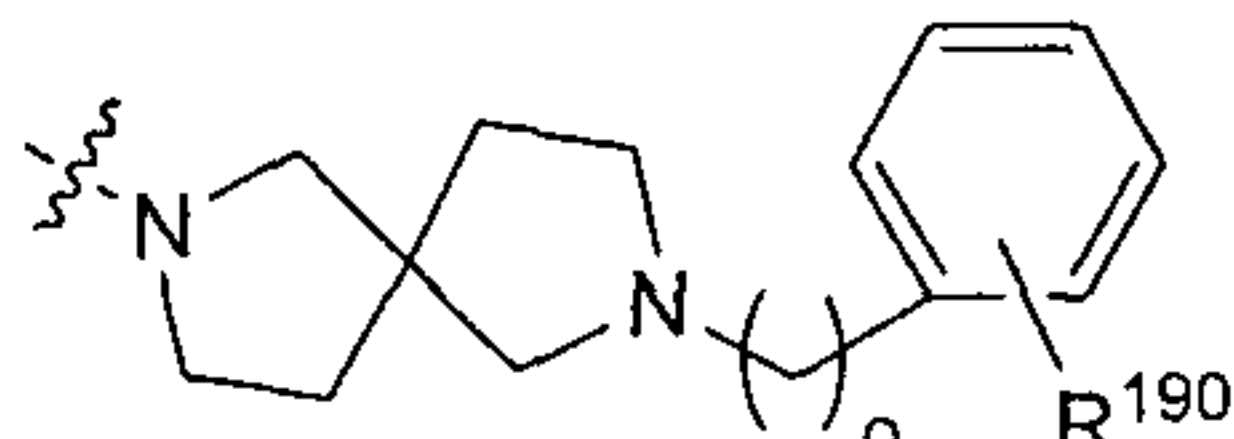
(B.5.)



(B.6.)



(B.7.)



(B.8.)



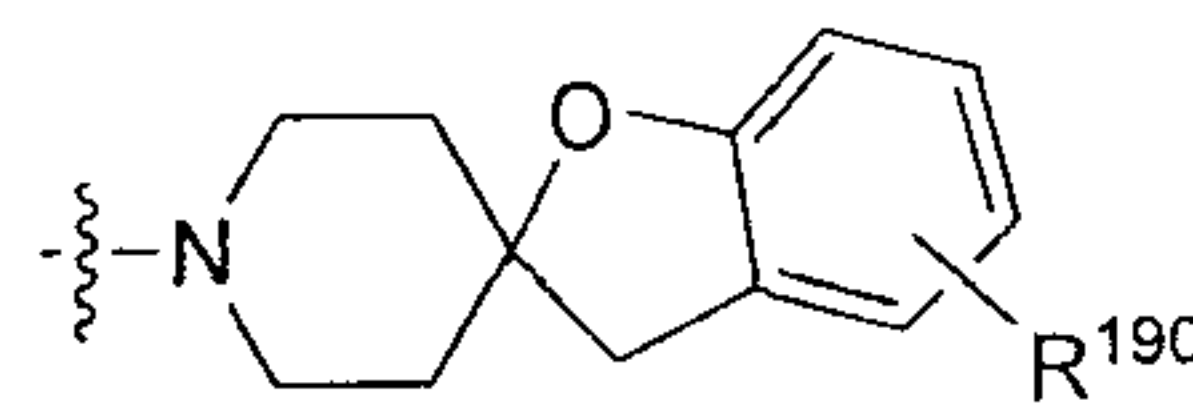
(B.9.)



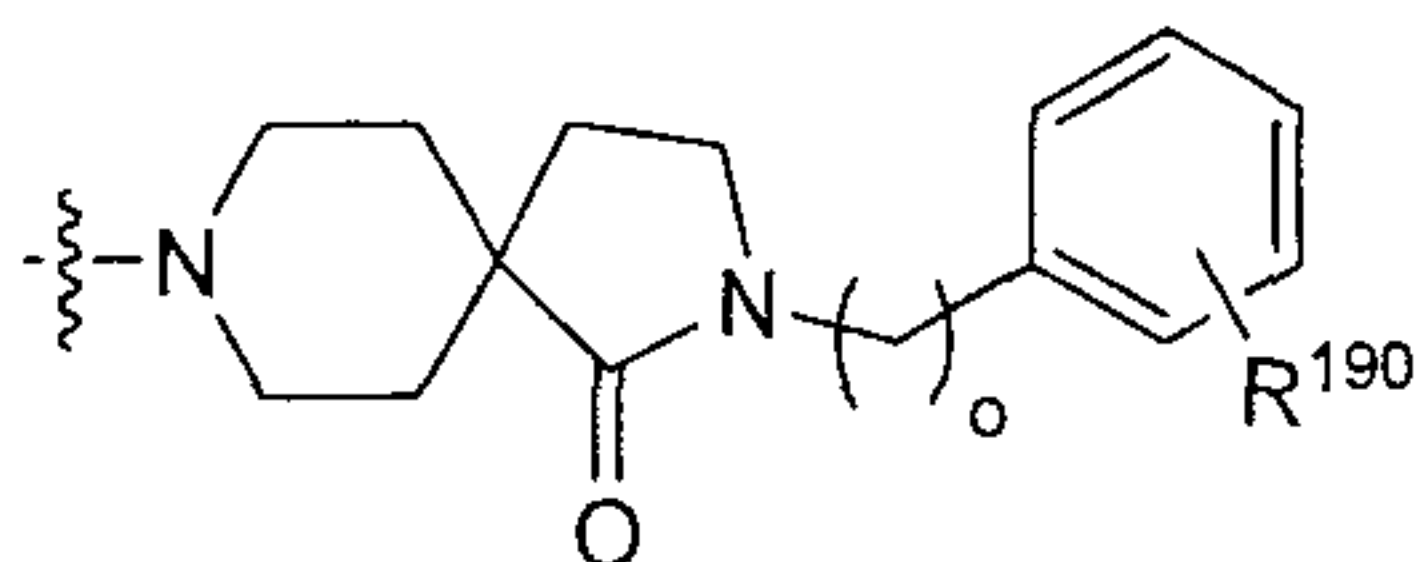
(B.10.)



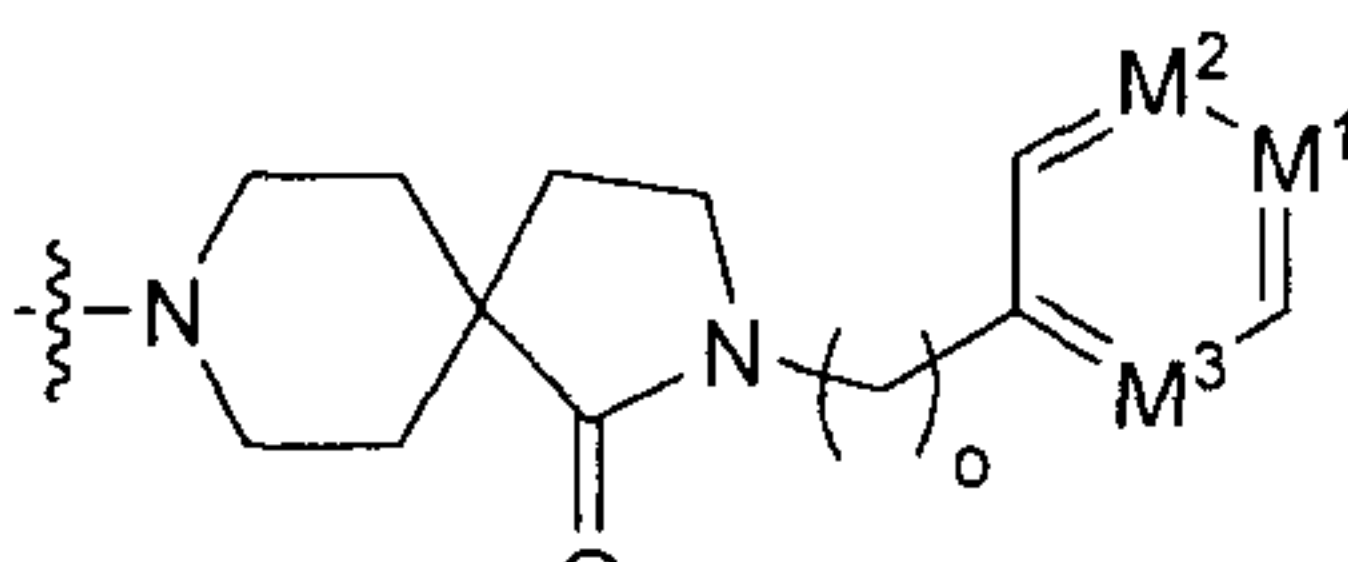
(B.11.)



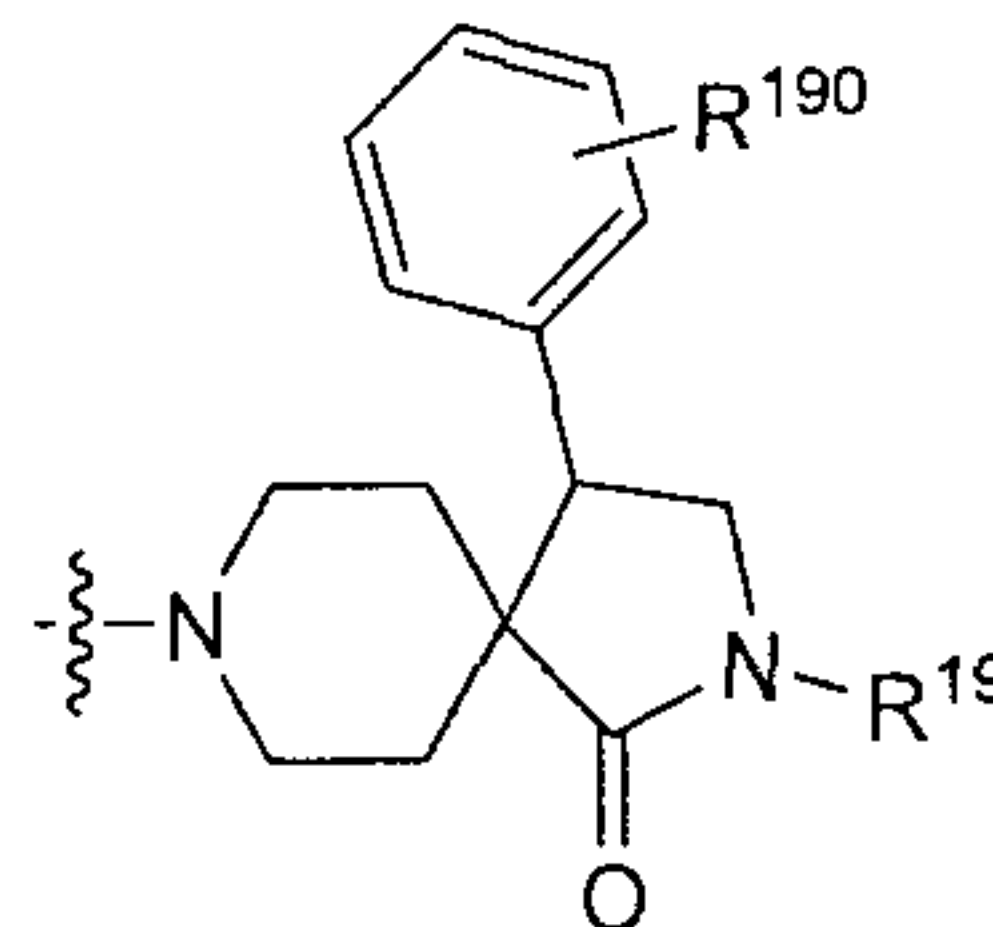
(B.12.)



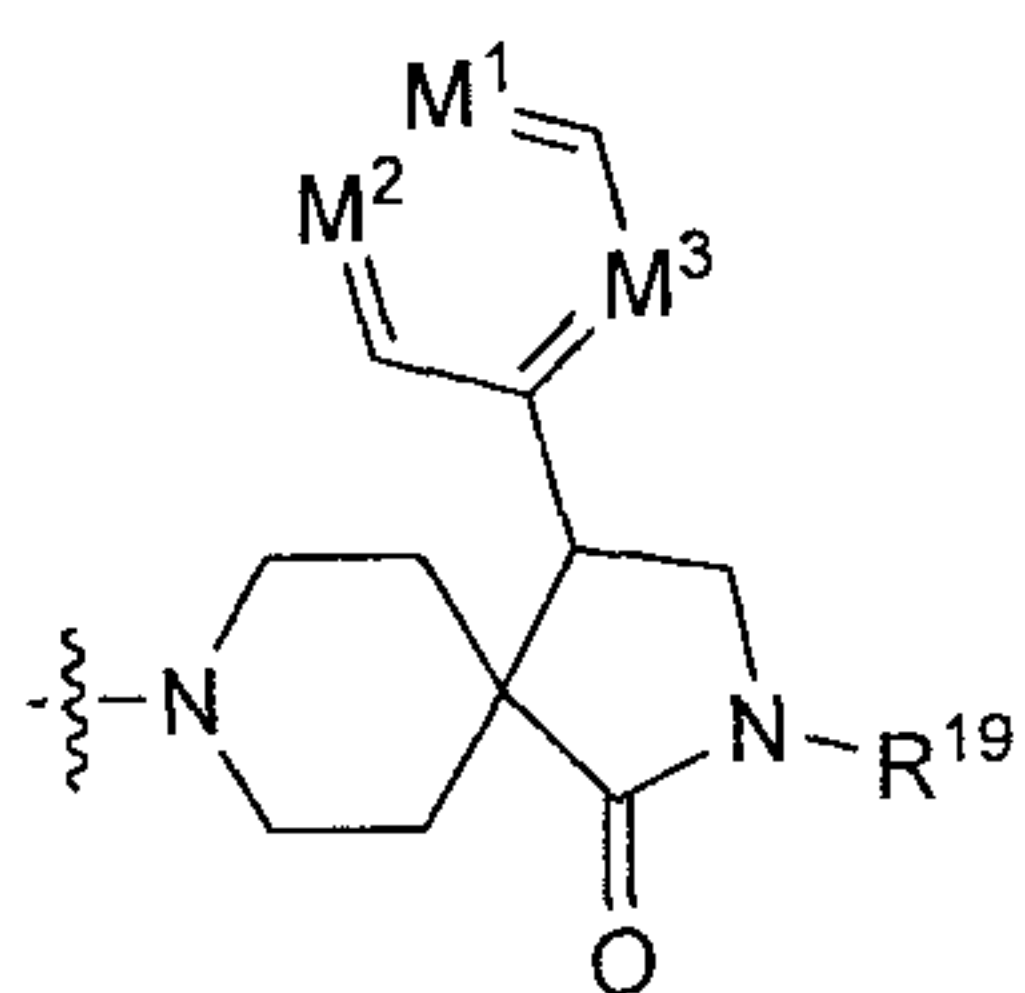
(B.13.)



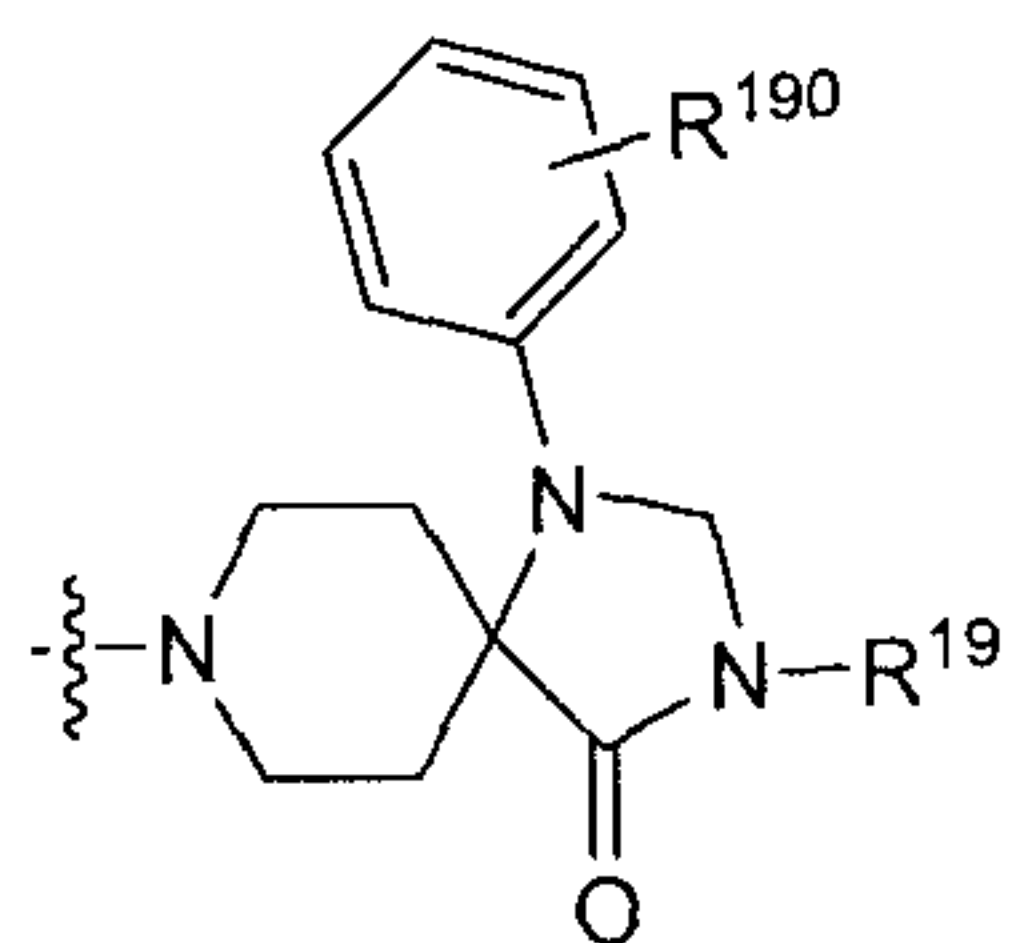
(B.14.)



GRA3454-WO
22nd December 2009

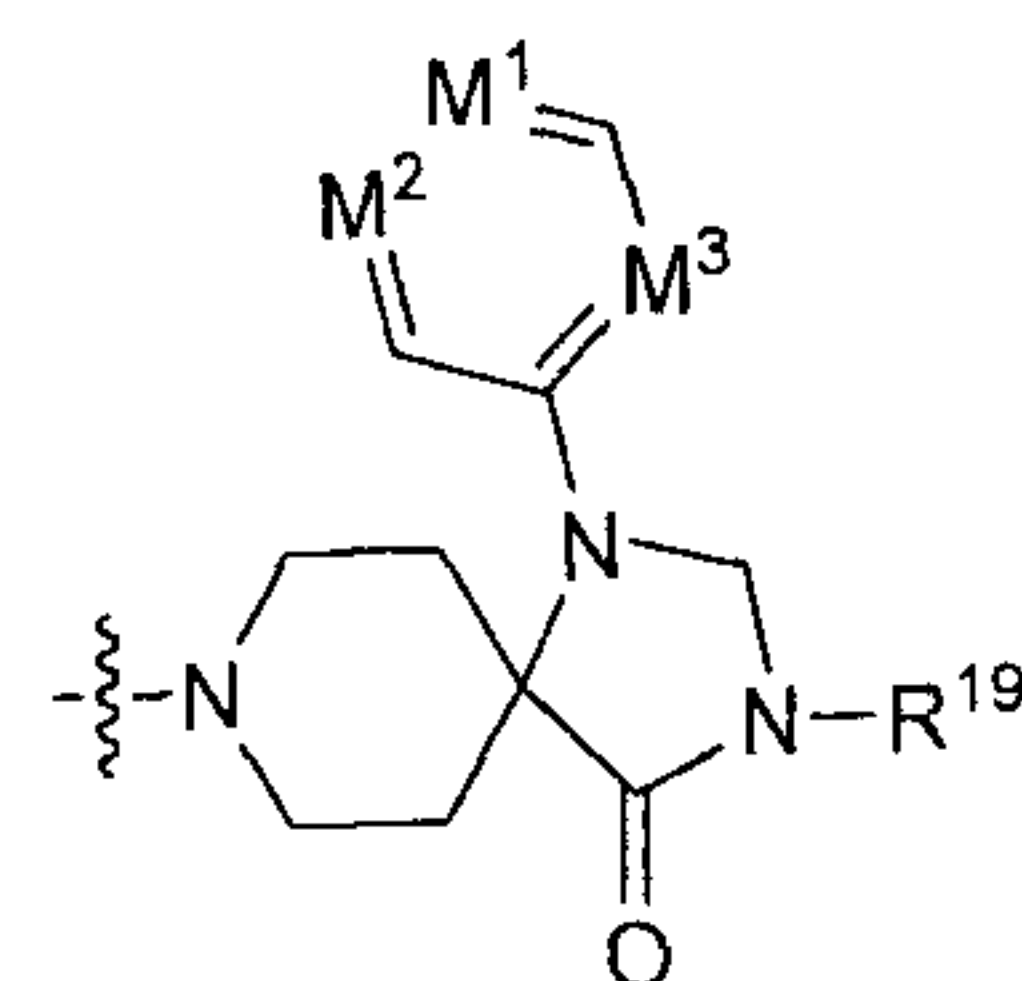


(B.16.)

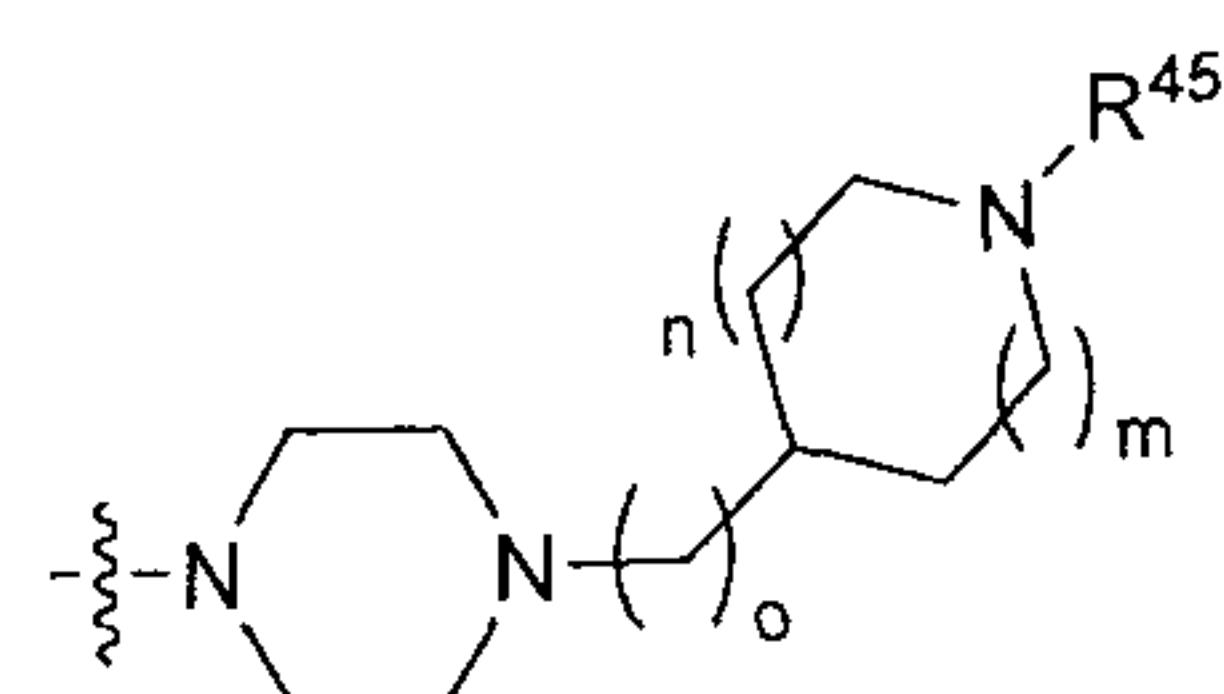


(B.17.)

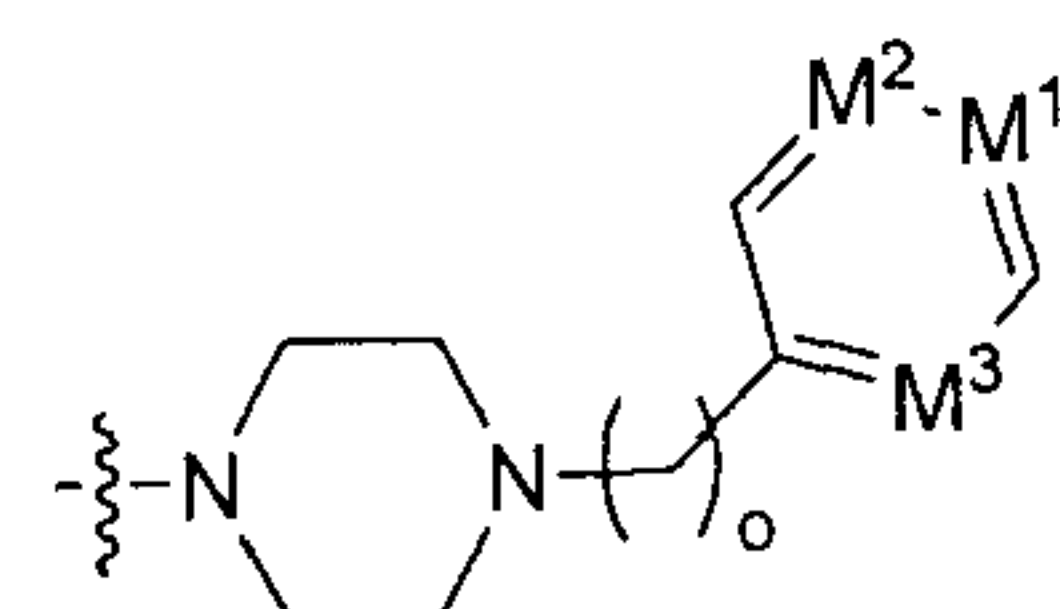
(B.15.)



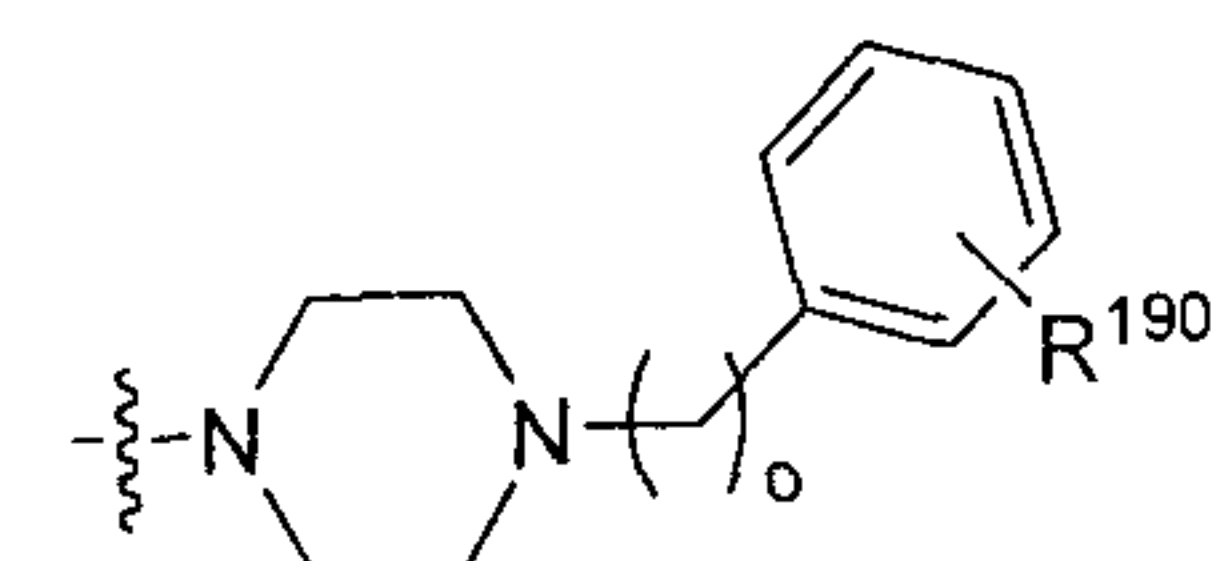
(B.18.)



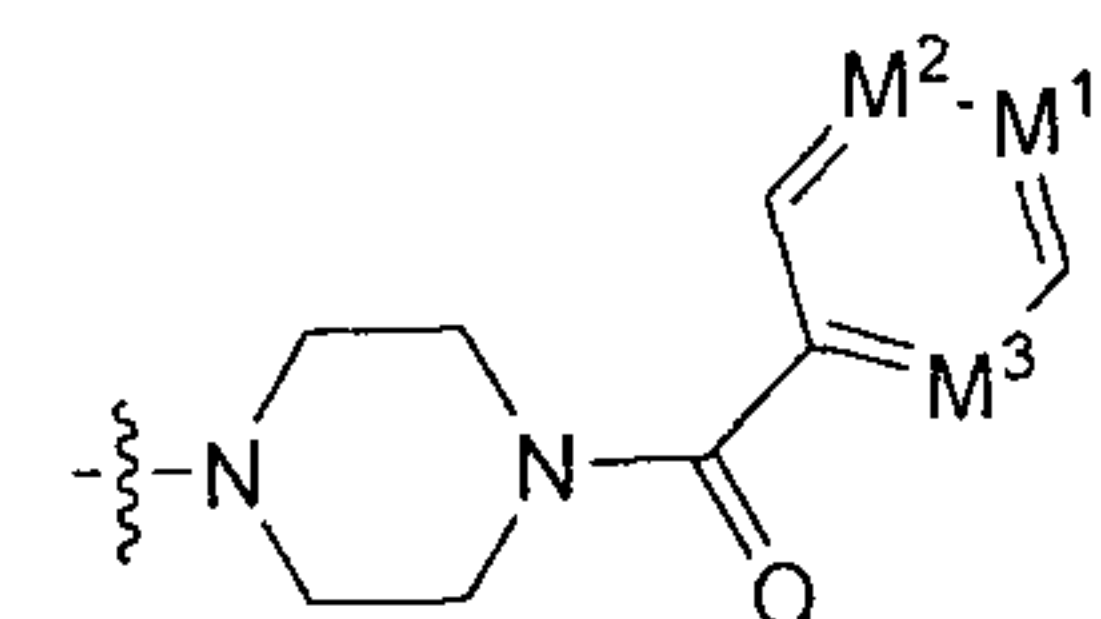
(B.19.)



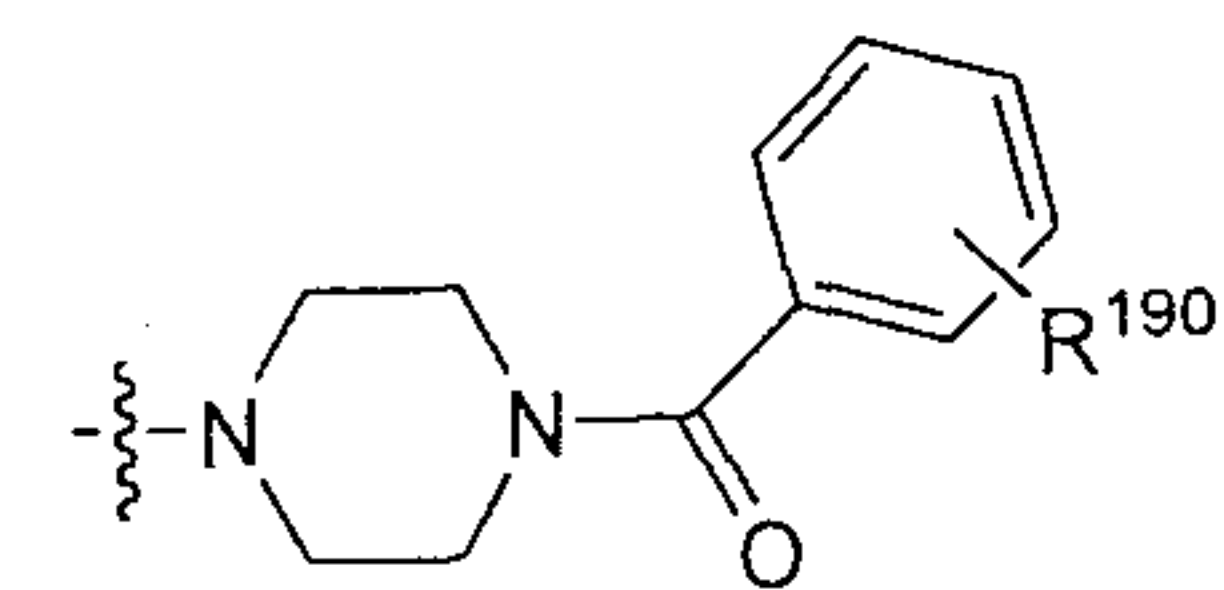
(B.20.)



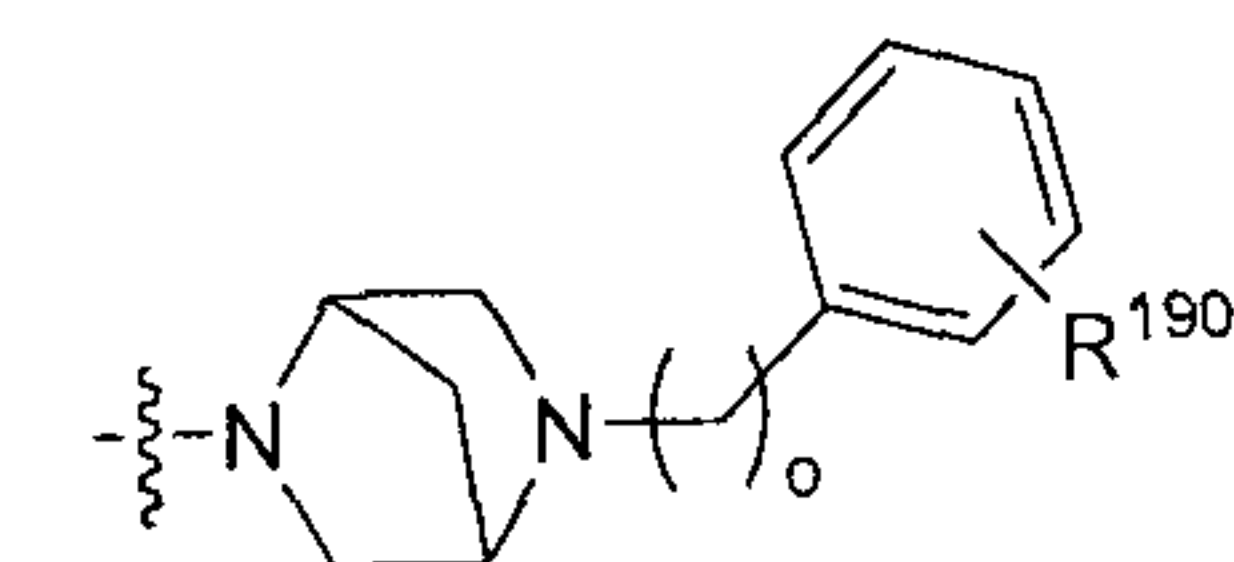
(B.21.)



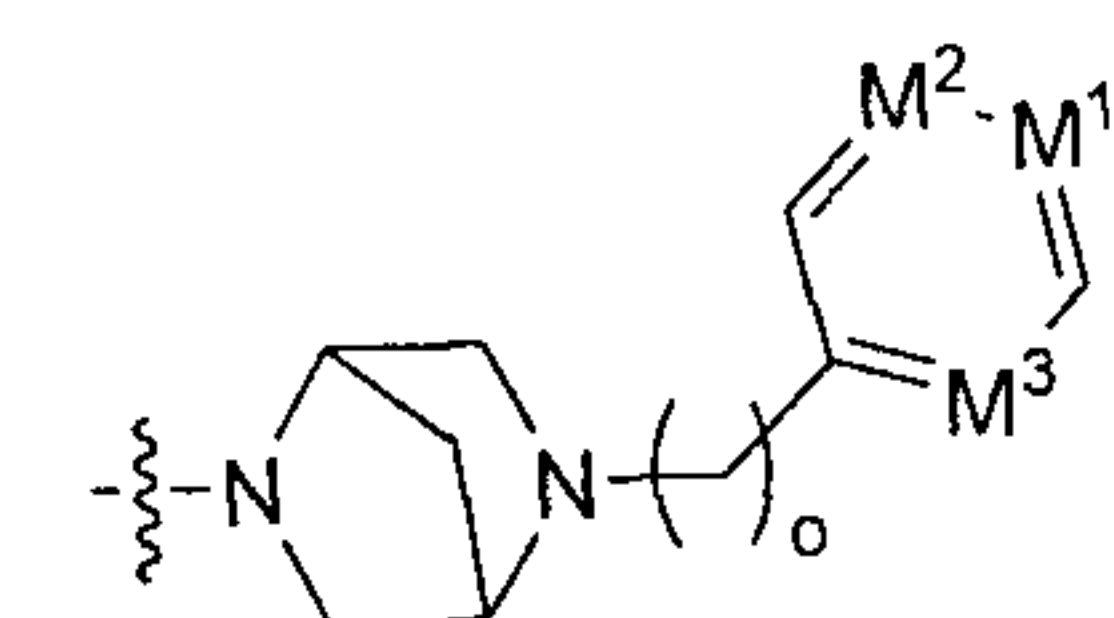
(B.22.)



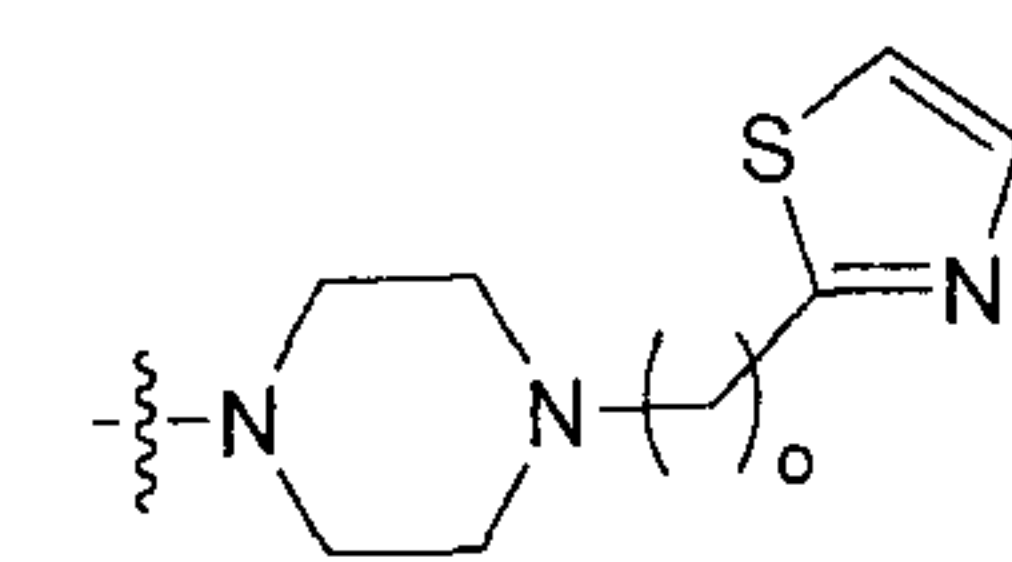
(B.23.)



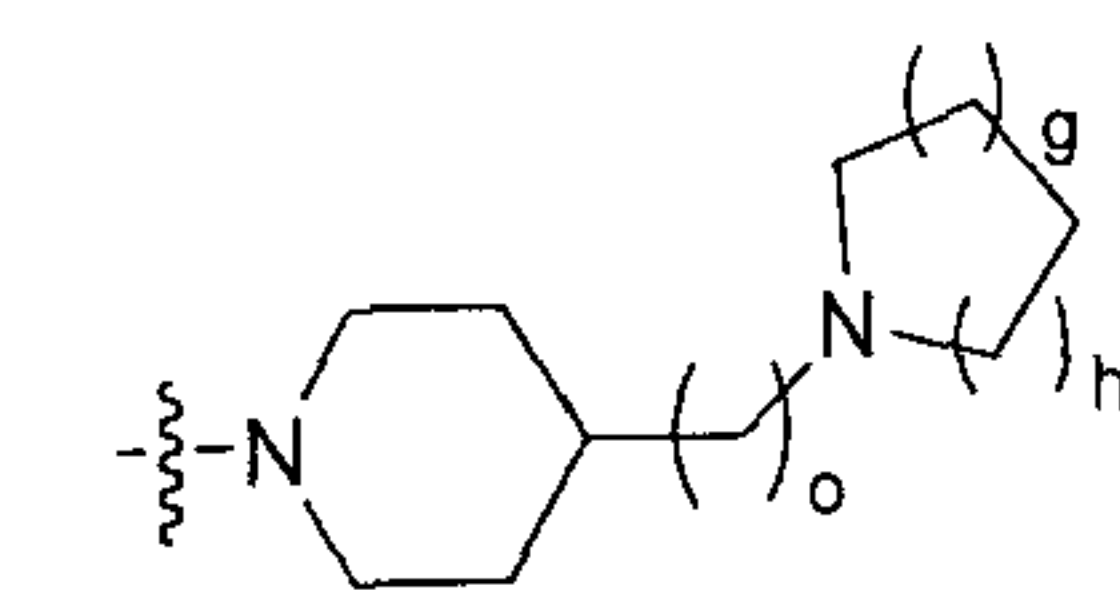
(B.24.)



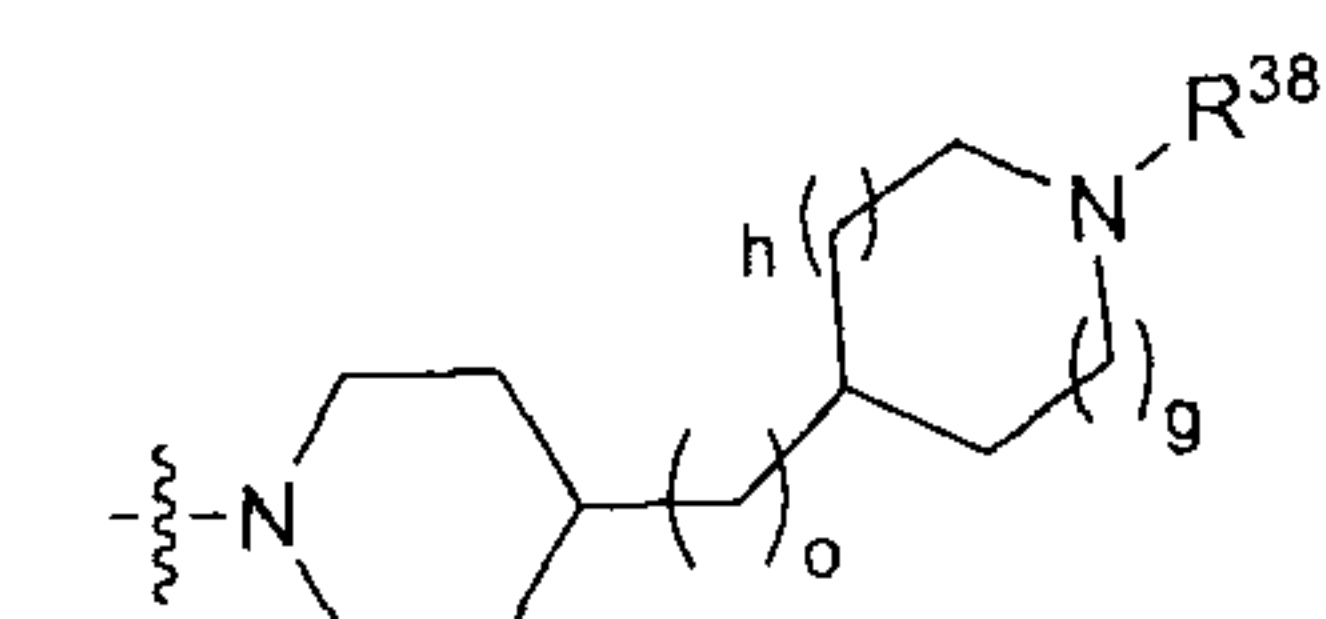
(B.25.)



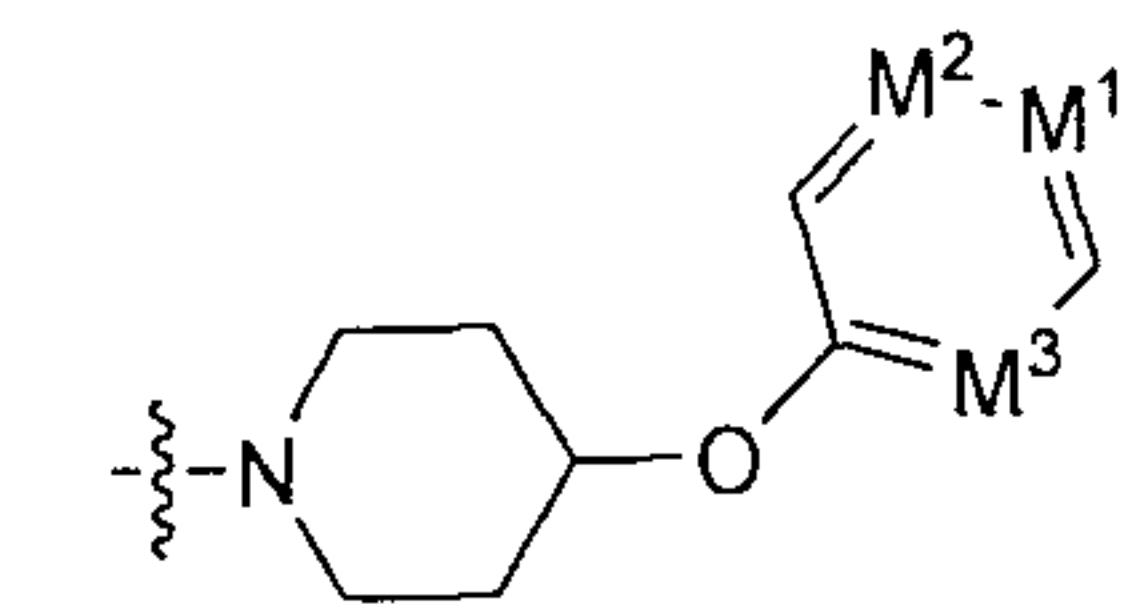
(B.26.)



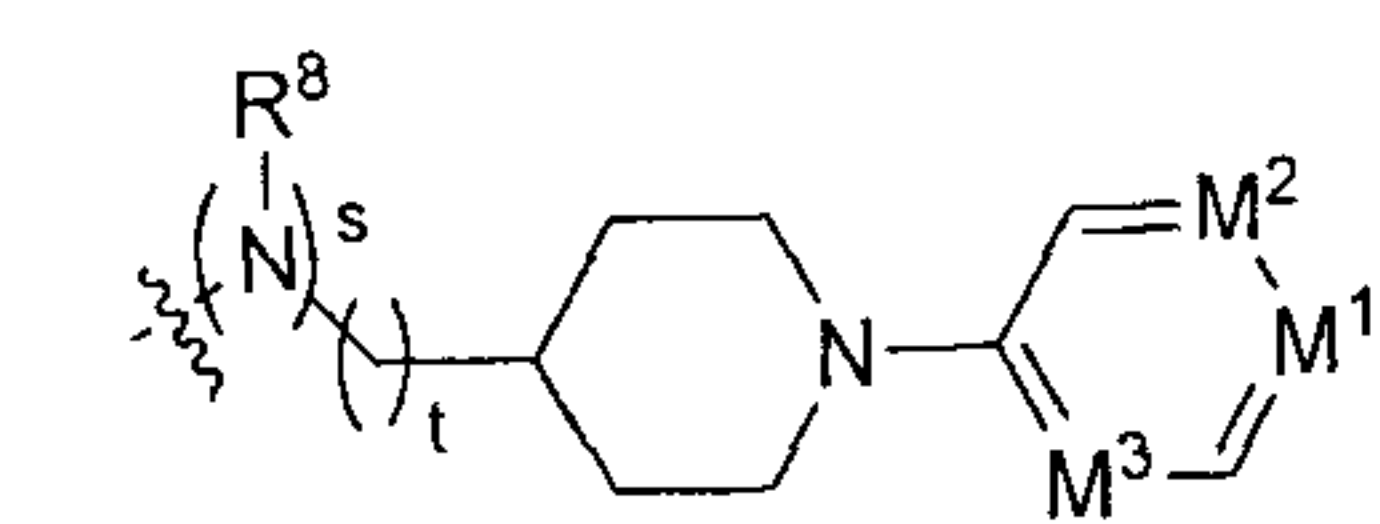
(B.27.)



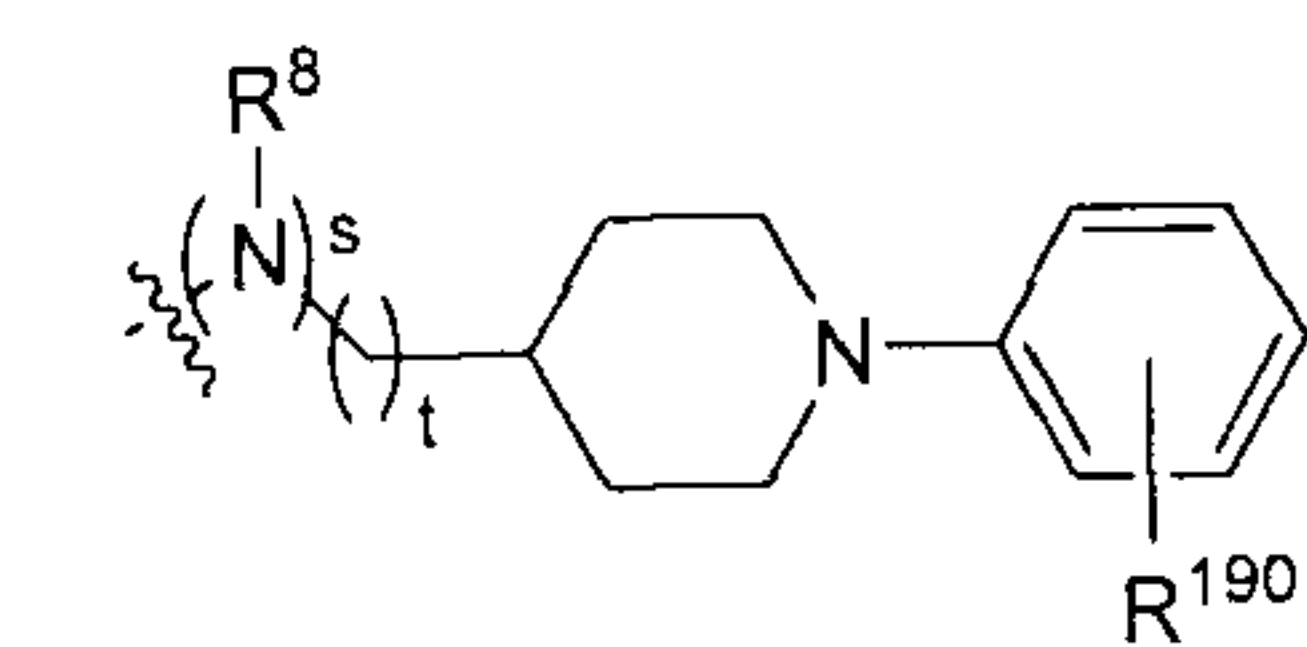
(B.28.)



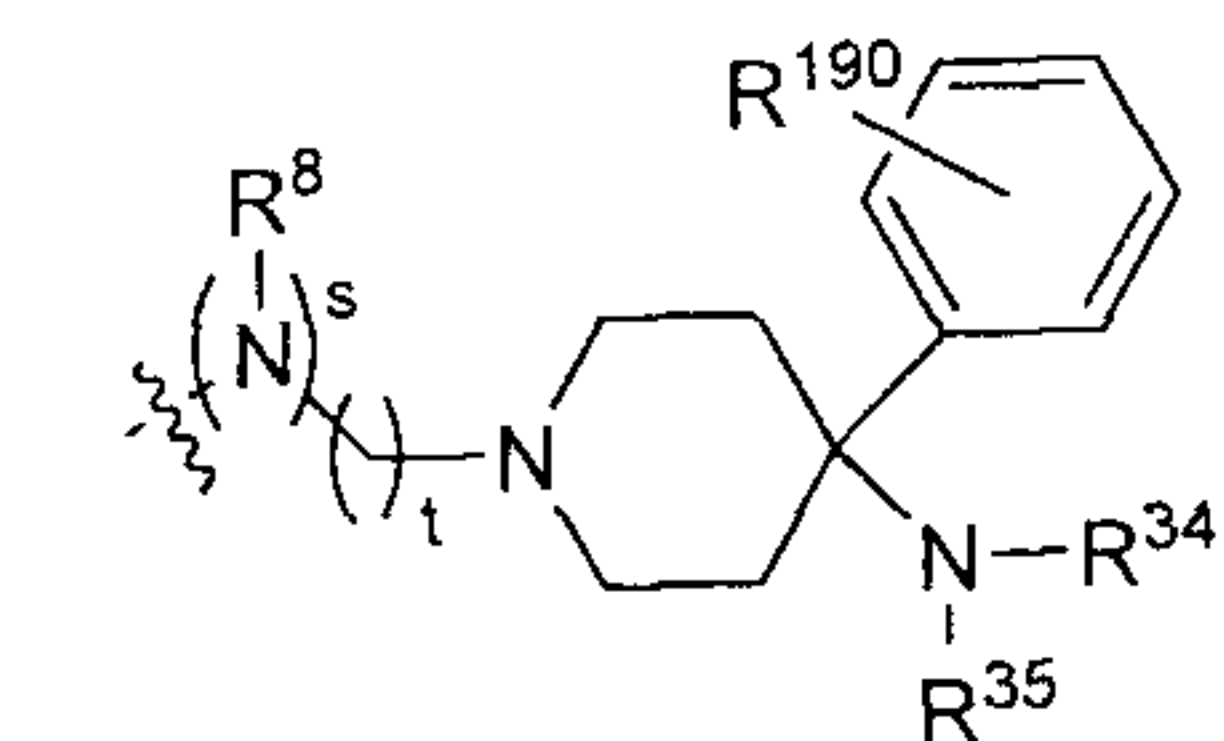
(B.29.)



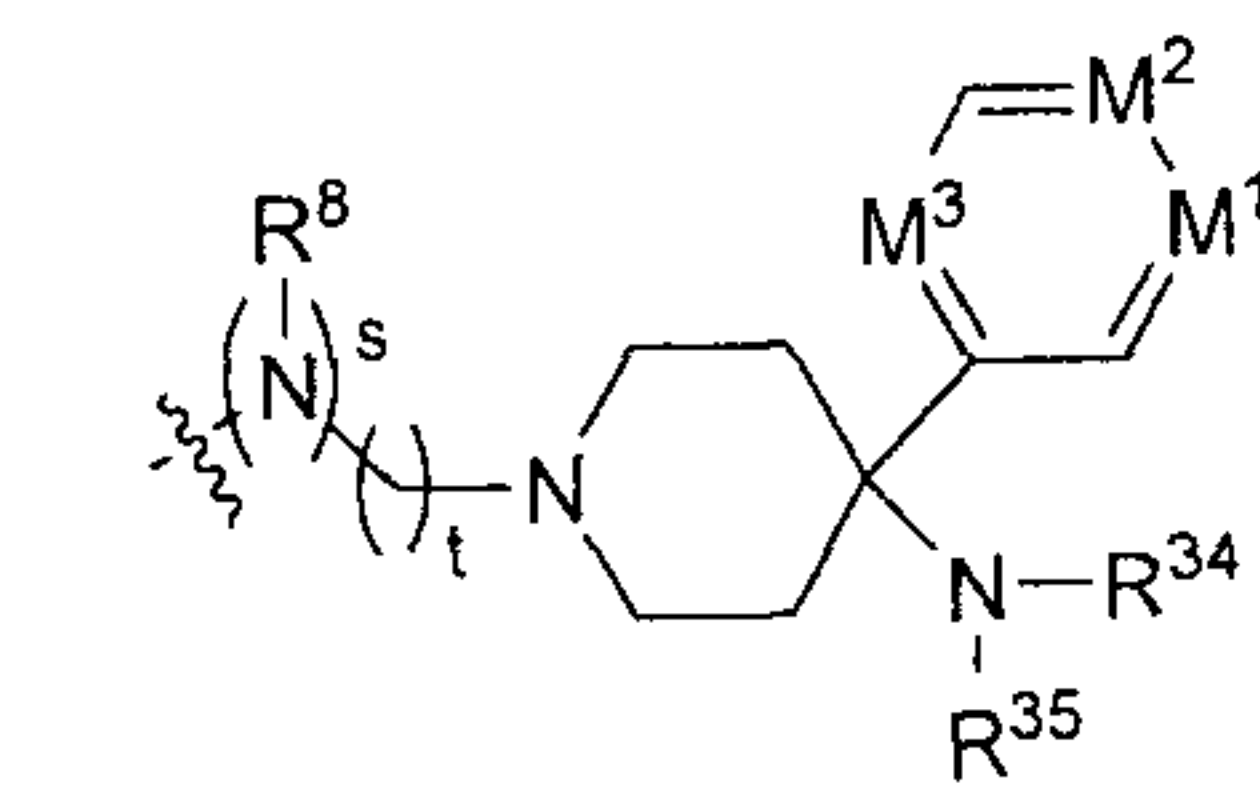
(B.30.)



(B.31.)

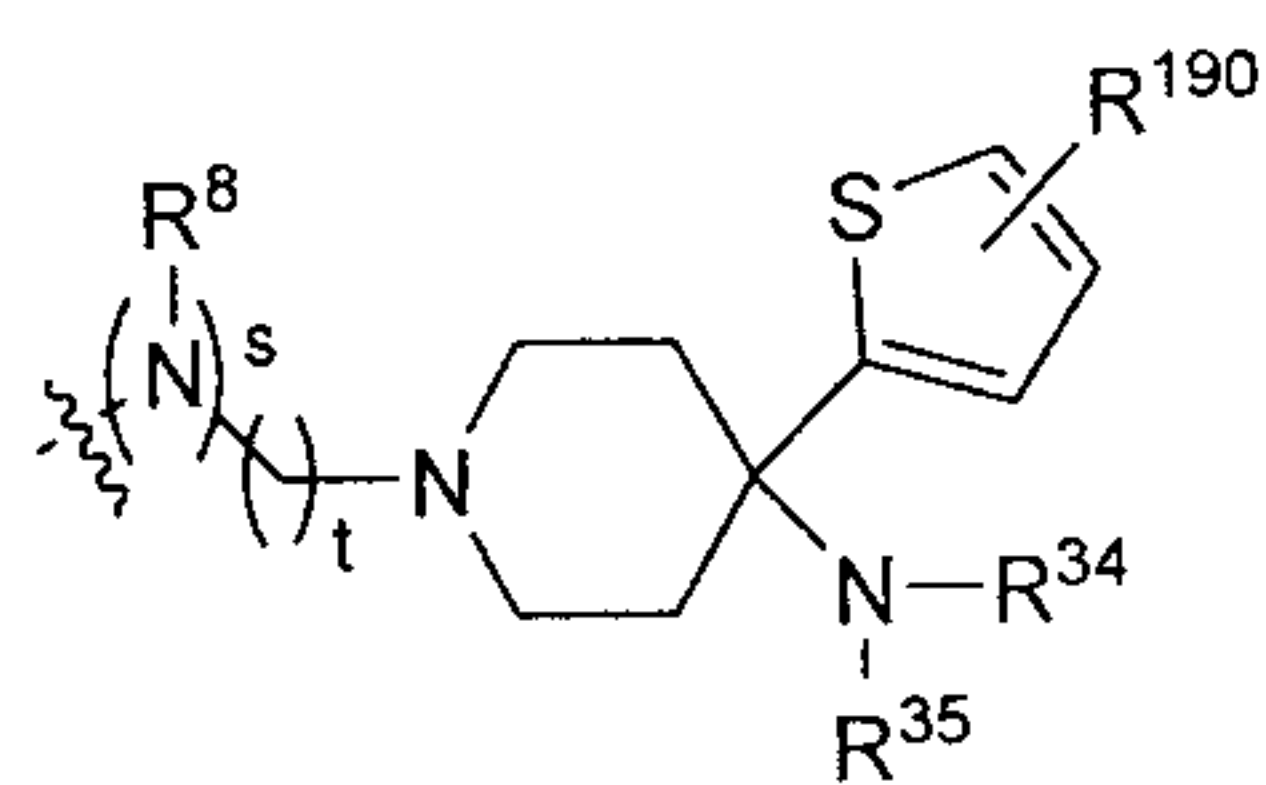


(B.32.)

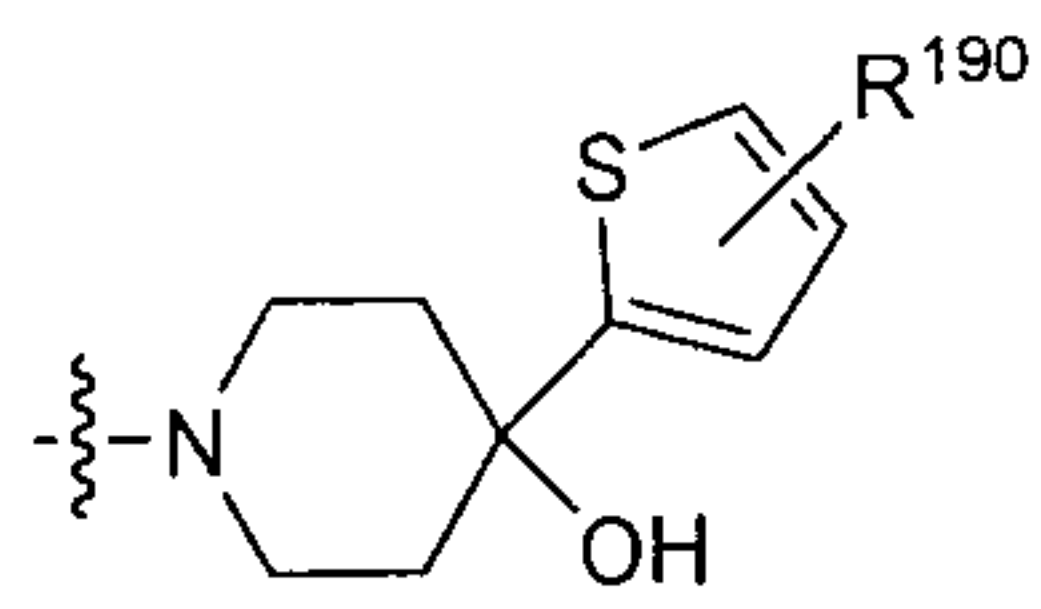


(B.33.)

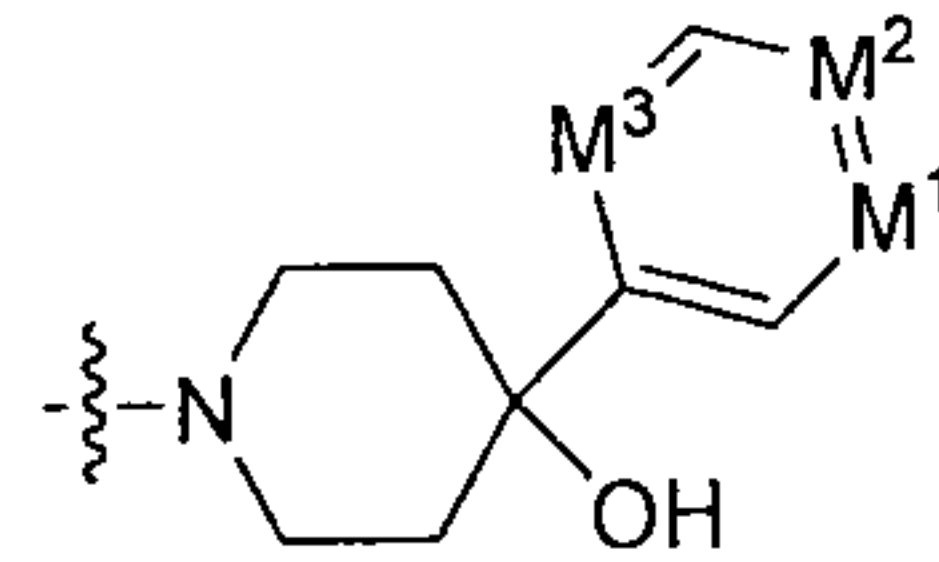
GRA3454-WO
22nd December 2009



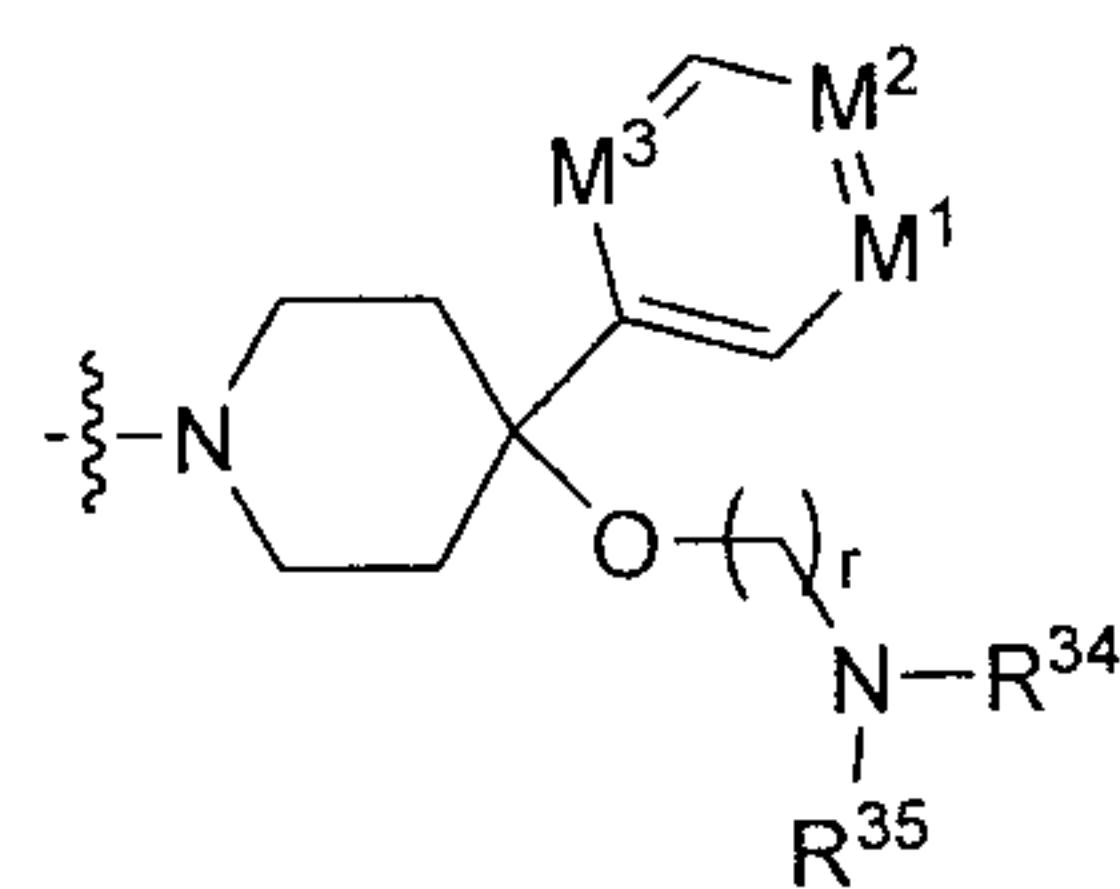
(B.34.)



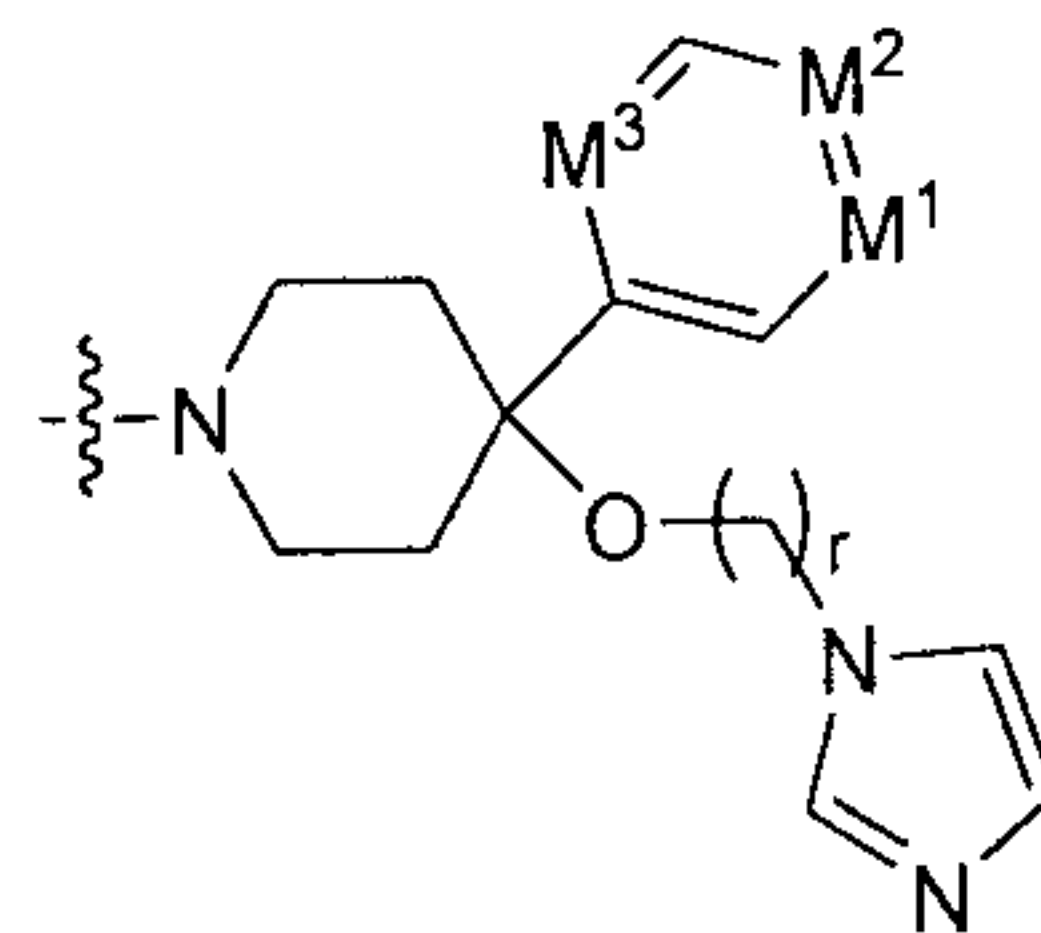
(B.35.)



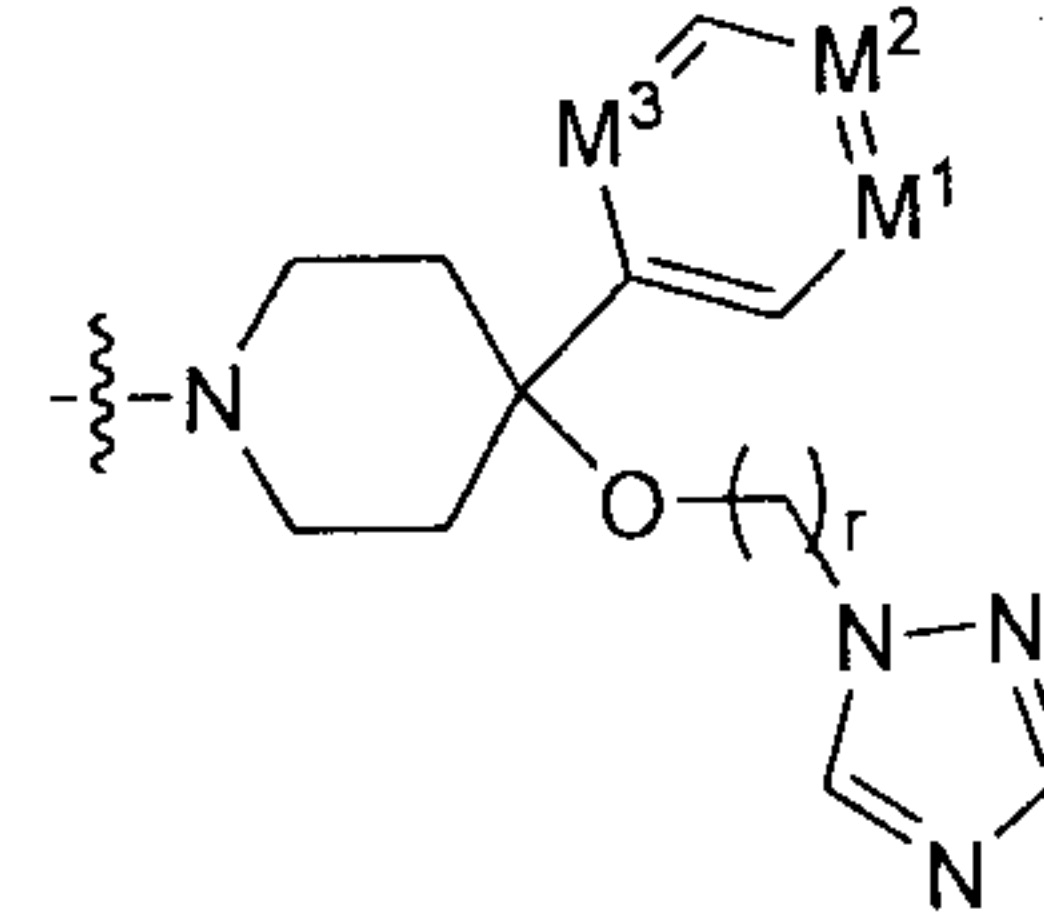
(B.36.)



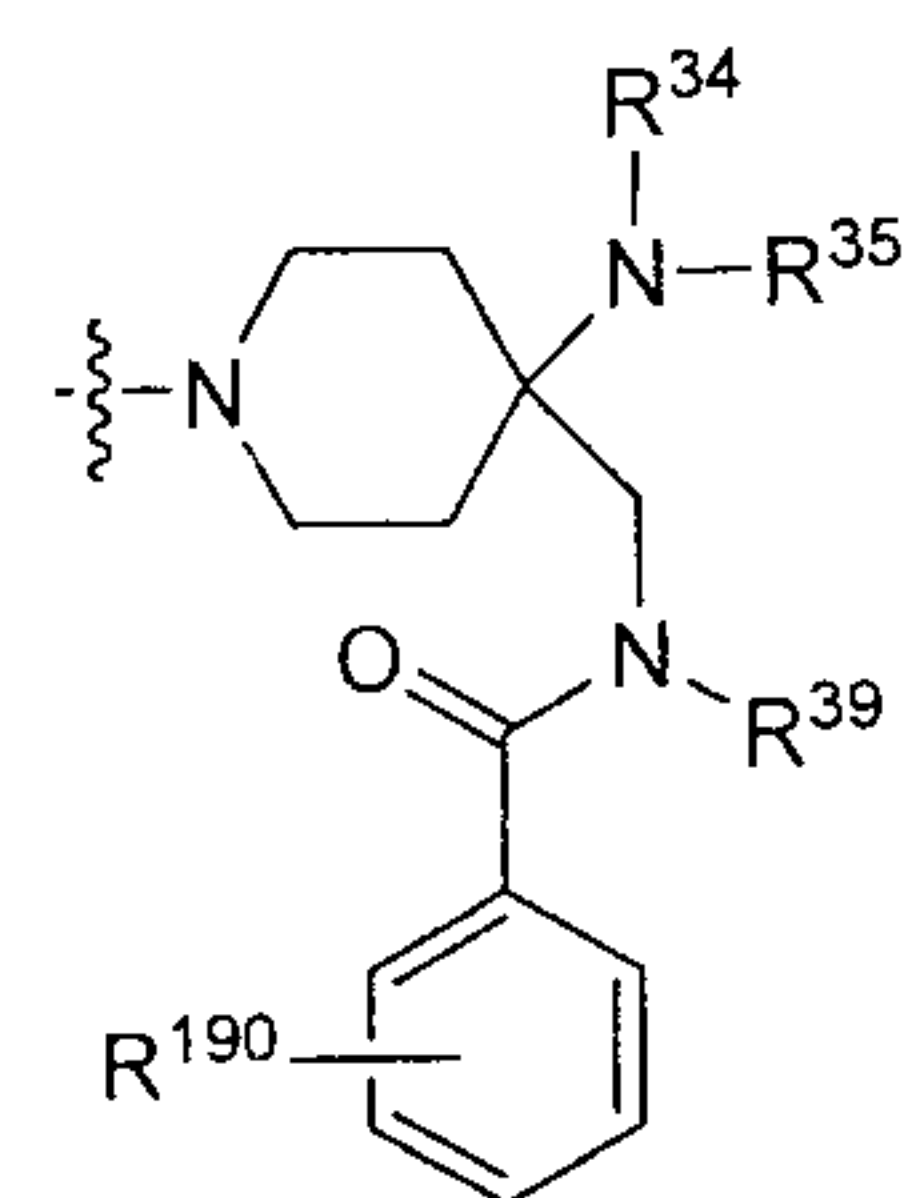
(B.37.)



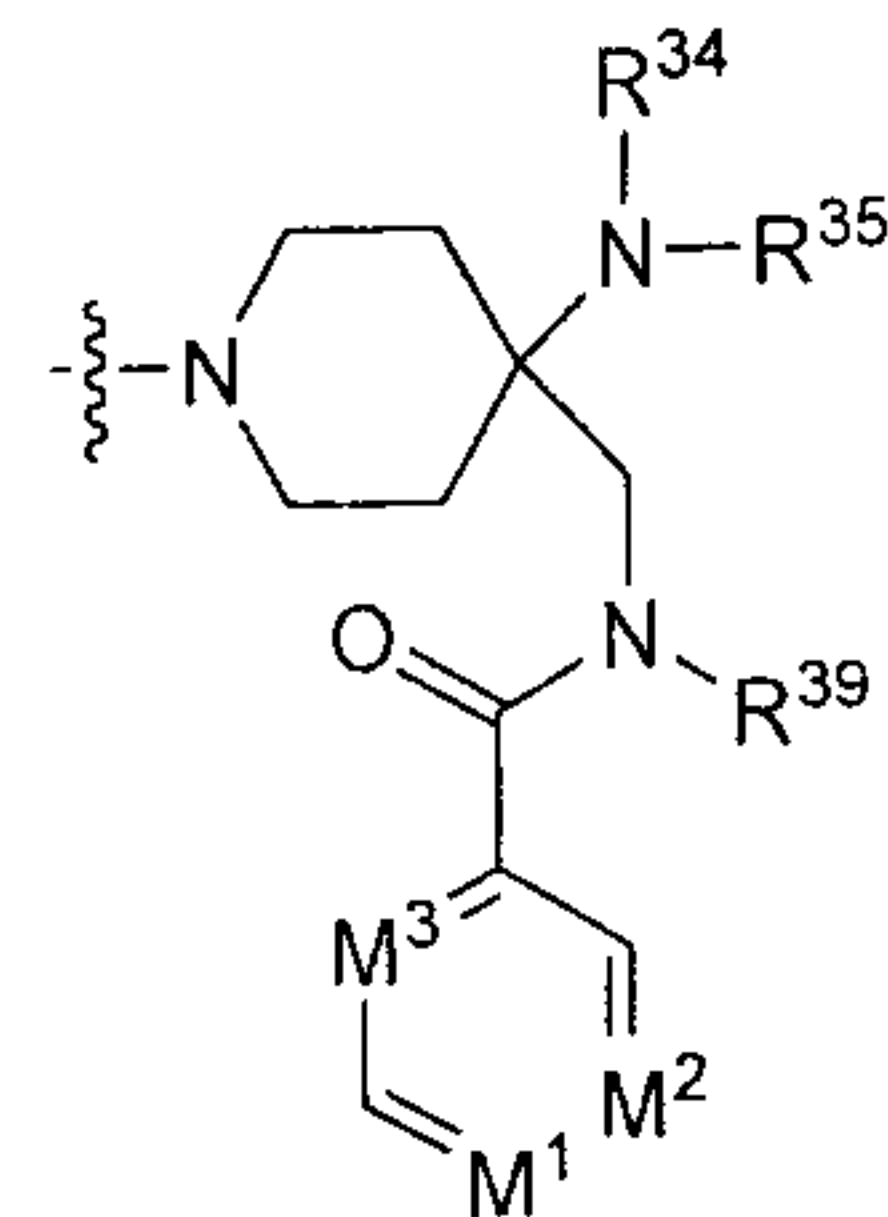
(B.38.)



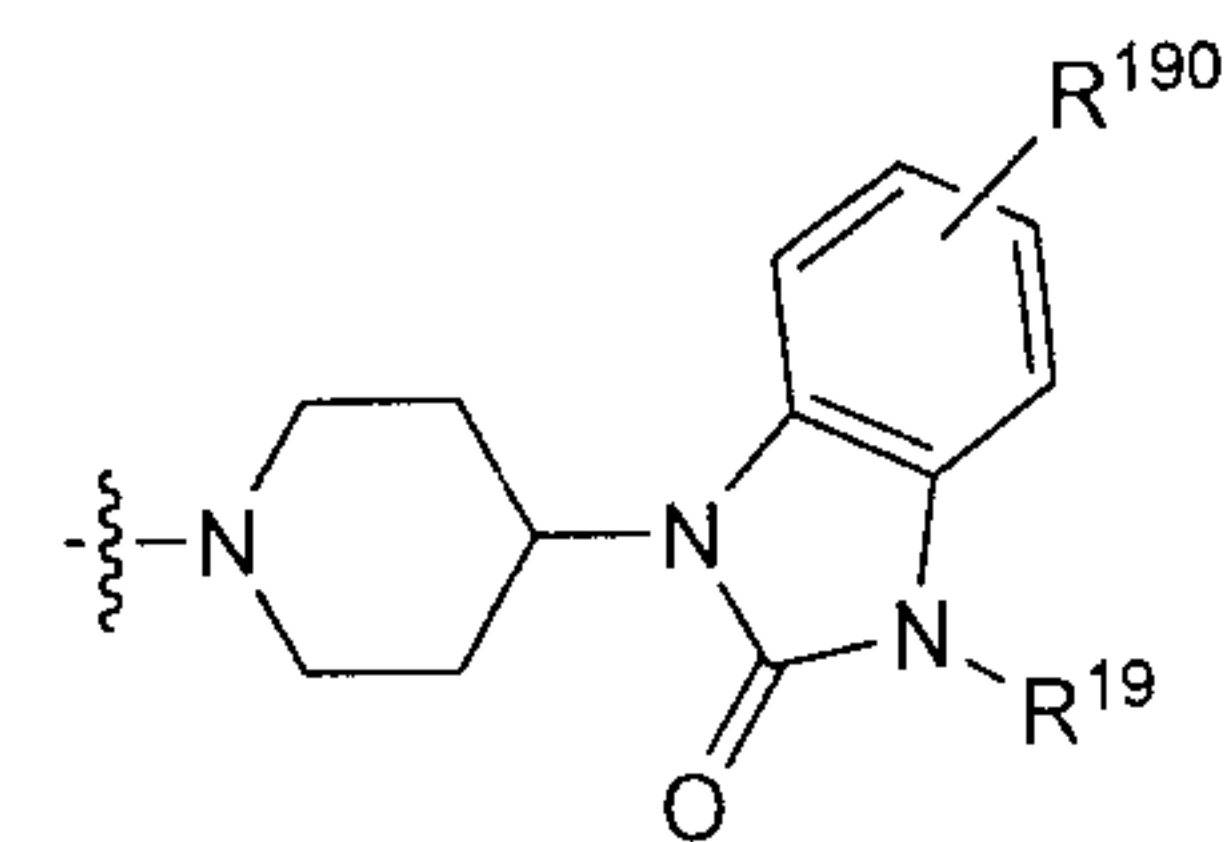
(B.39.)



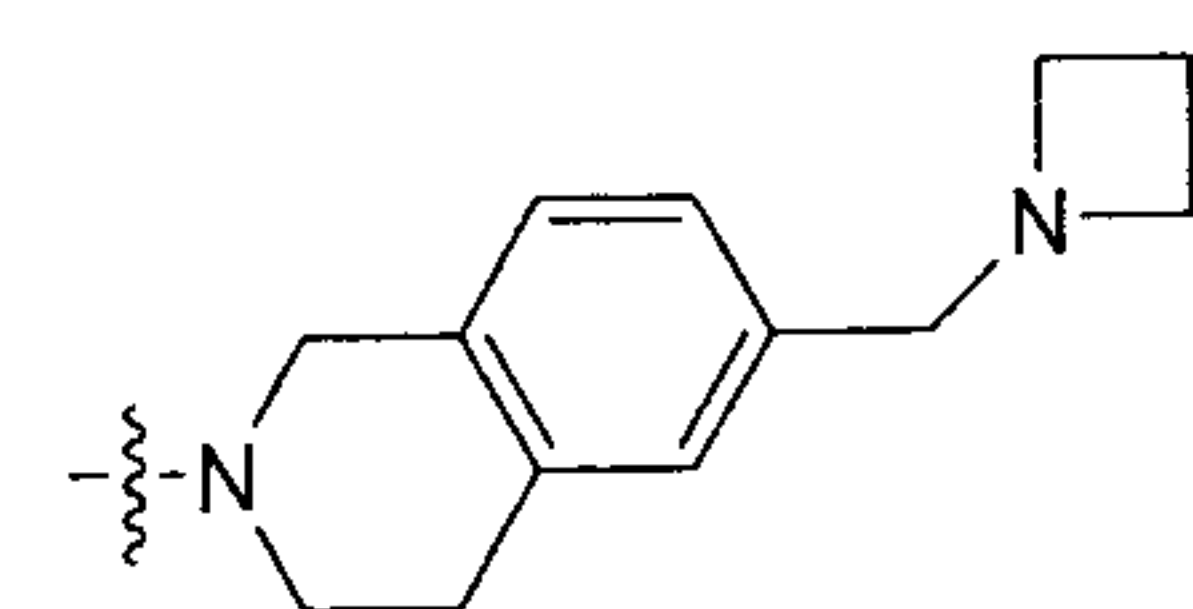
(B.40.)



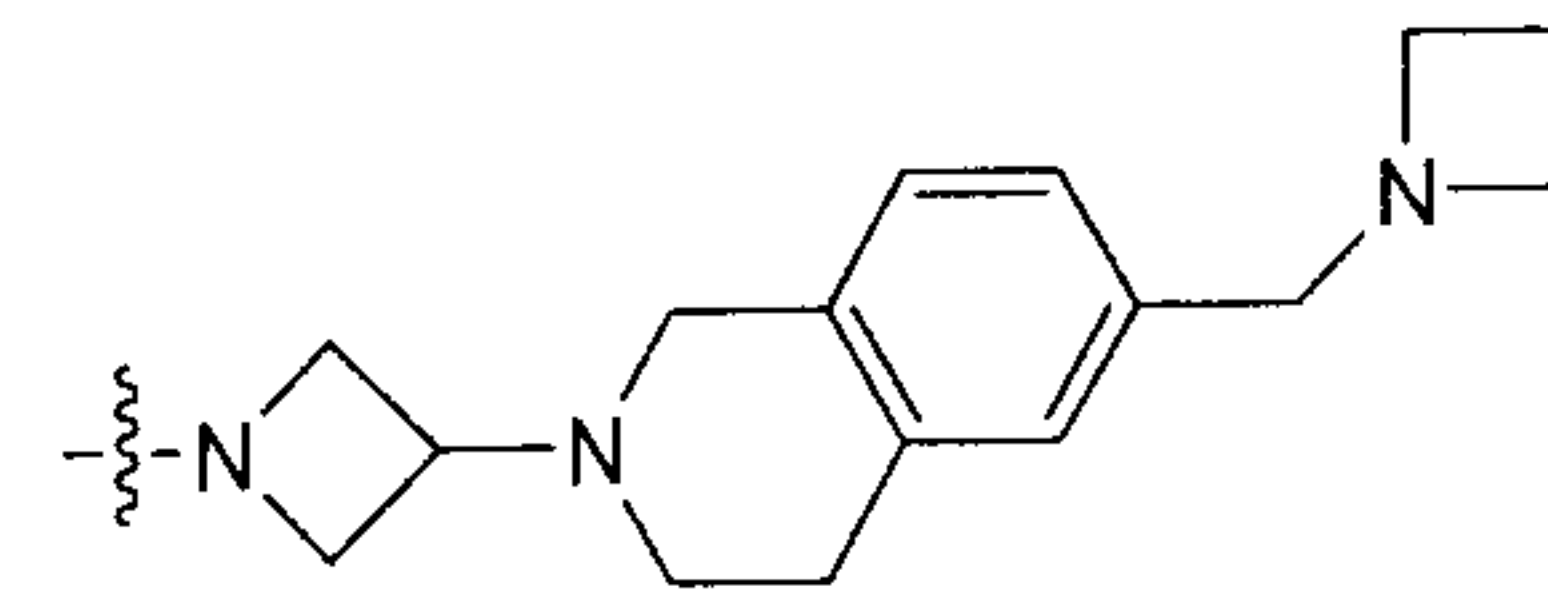
(B.40.)



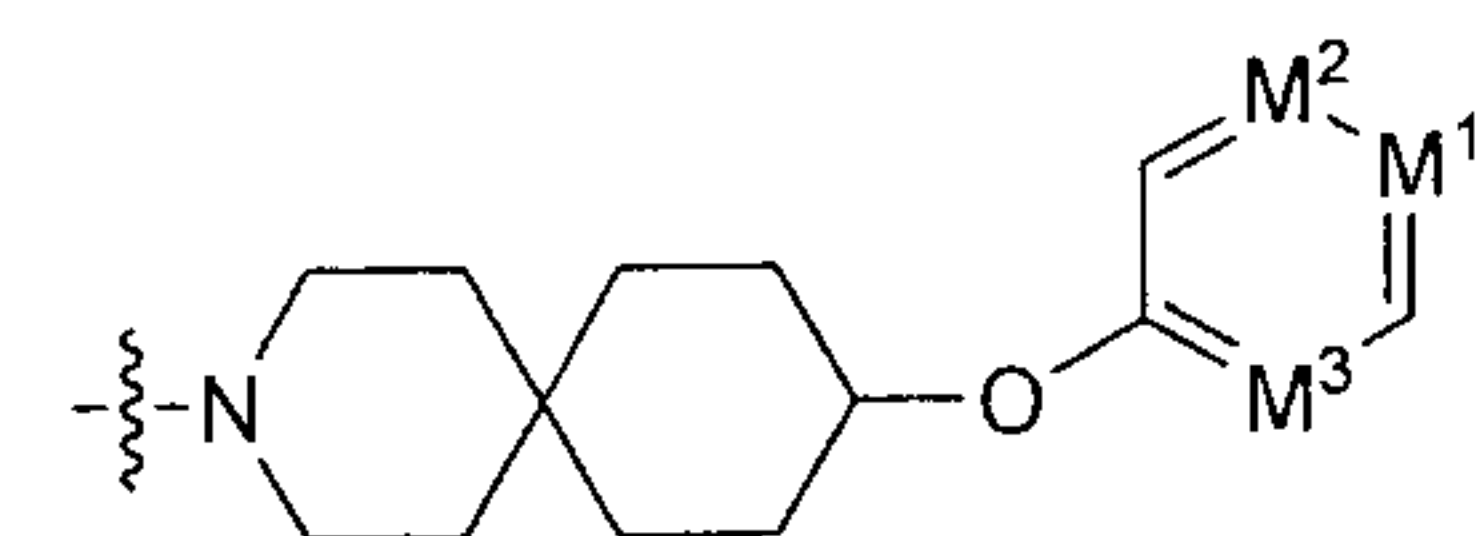
(B.41.)



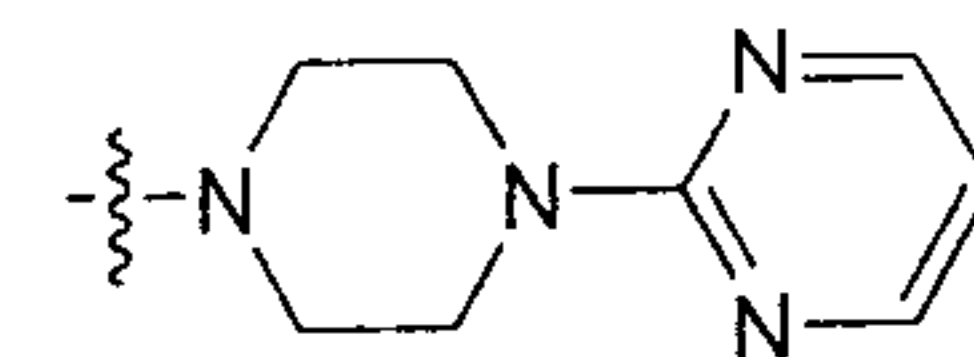
(B.42.) oder



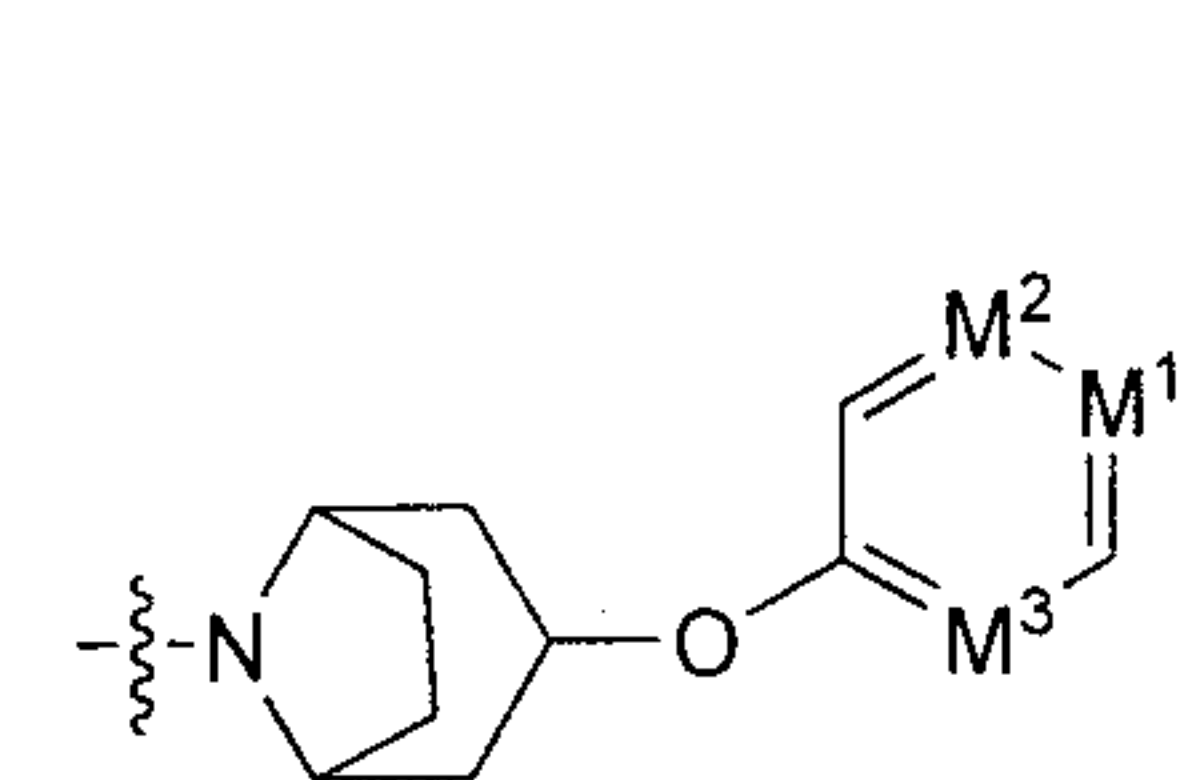
(B.43.)



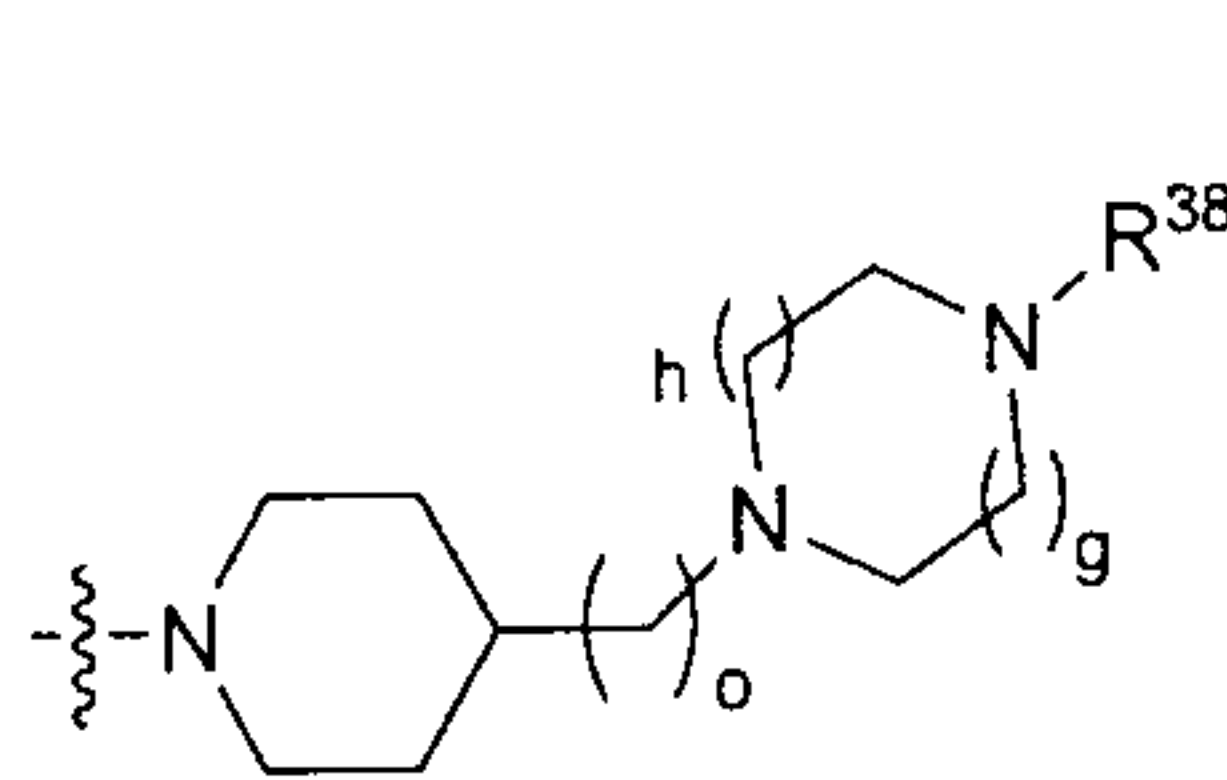
(B.44.)



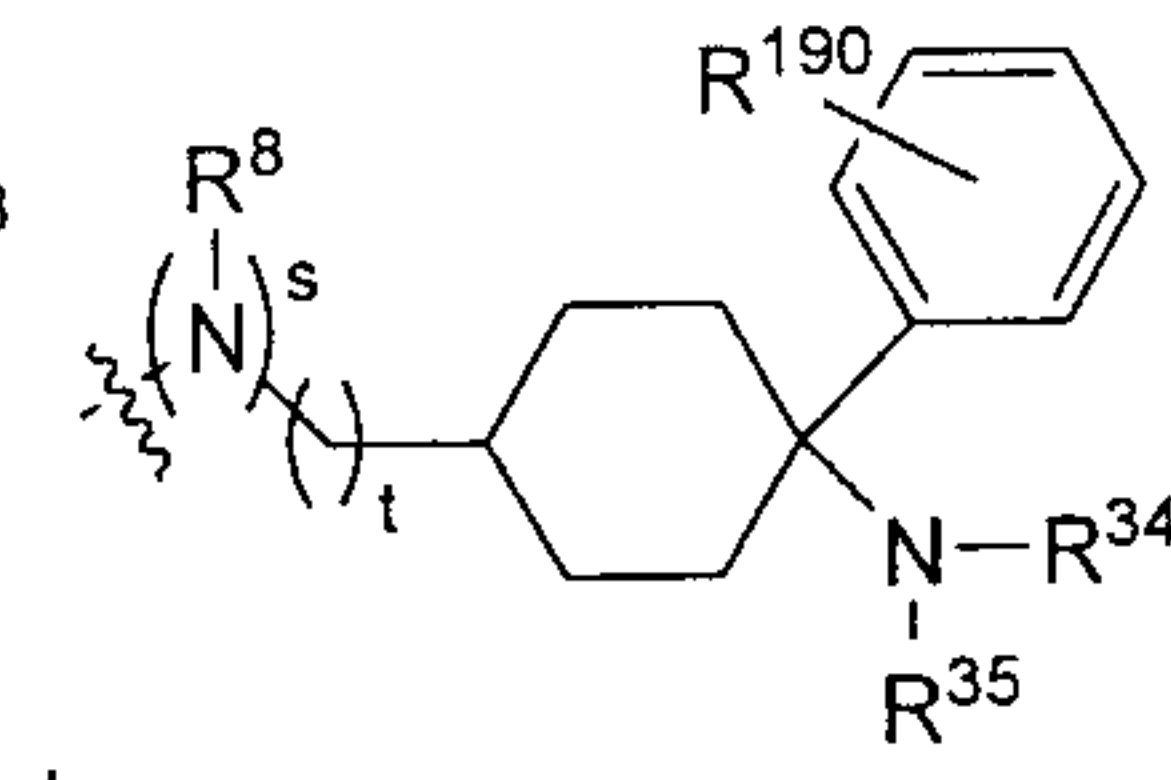
(B.45.)



(B.46.)

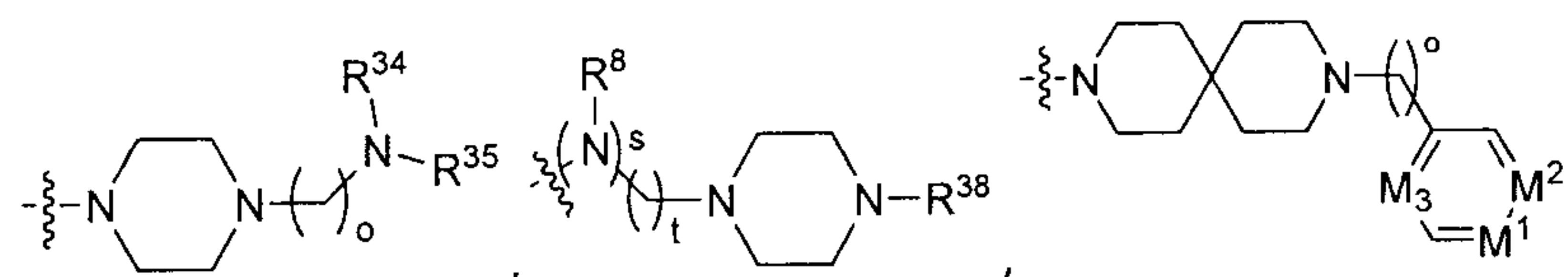


(B.47.)



(B.48.)

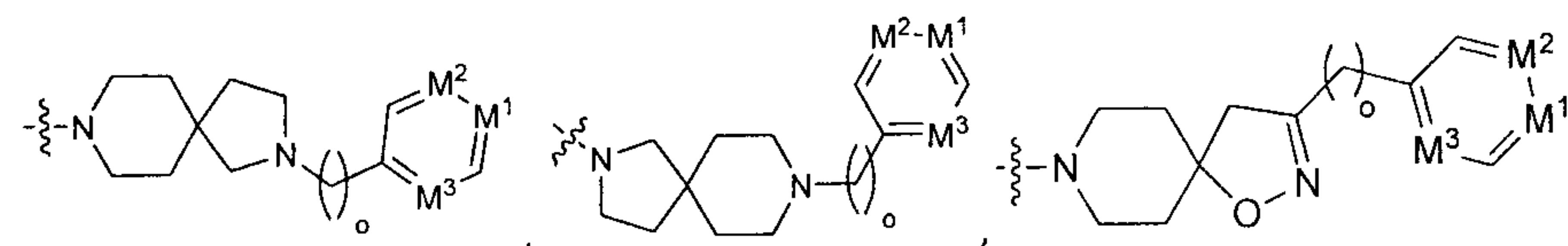
GRA3454-WO
22nd December 2009



(B.49.)

(B.50.)

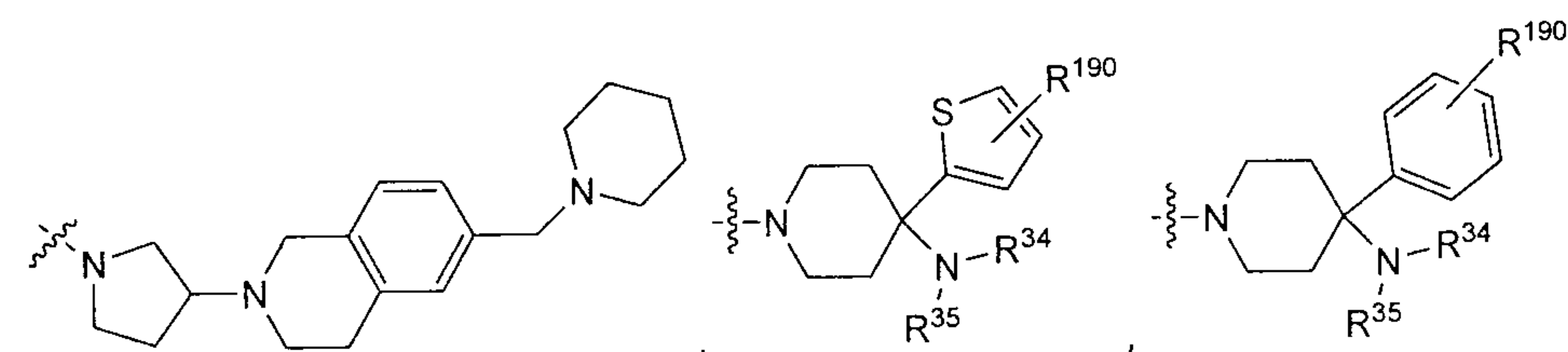
(B.51.)



(B. 52.)

(B. 53.)

(B.54.)



(B.55.)

(B.56)

(B.57)

wherein

h = 0 or 1;

g = 0 or 1;

m = 0 or 1;

n = 0 or 1;

o = 0, 1, 2 or 3;

r = 1, 2 or 3, in particular 1 or 2;

s = 0 or 1;

t = 0, 1, 2 or 3, in particular 0, 1 or 2, with the proviso that if s stands for 0 then t likewise stands for 0;

M¹, M² and M³ can mutually independently stand for N or CH, wherein one variable out of M¹, M² and M³ stands for N and the other two each stand for CH;

GRA3454-WO
22nd December 2009

R⁸ stands for H; C₁₋₆ alkyl, in particular methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl; C₃₋₆ cycloalkyl, in particular cyclopropyl, each unsubstituted or mono- or polysubstituted with identical or different substituents;

R¹⁹ stands for H; C₁₋₆ alkyl, in particular methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl; C₃₋₆ cycloalkyl, in particular cyclopropyl; each unsubstituted or mono- or polysubstituted with identical or different substituents;

R³⁴ and R³⁵ are preferably mutually independently methyl or ethyl or together with the N-atom linking them they form an azetidiny; pyrrolidiny, piperidiny, 4-(C₁₋₆ alkyl)-piperaziny group, each unsubstituted or mono- or polysubstituted with identical or different substituents;

R³⁸ stands for H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or pyridyl;

R³⁹ stands for H; C₁₋₆ alkyl, in particular methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl; C₃₋₆ cycloalkyl, in particular cyclopropyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; and

R⁴⁵ stands for H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or pyridyl; and

R¹⁹⁰ represents 0 to 4 substituents, which are mutually independently selected from F, Cl, O-CF₃, CF₃ or CN.

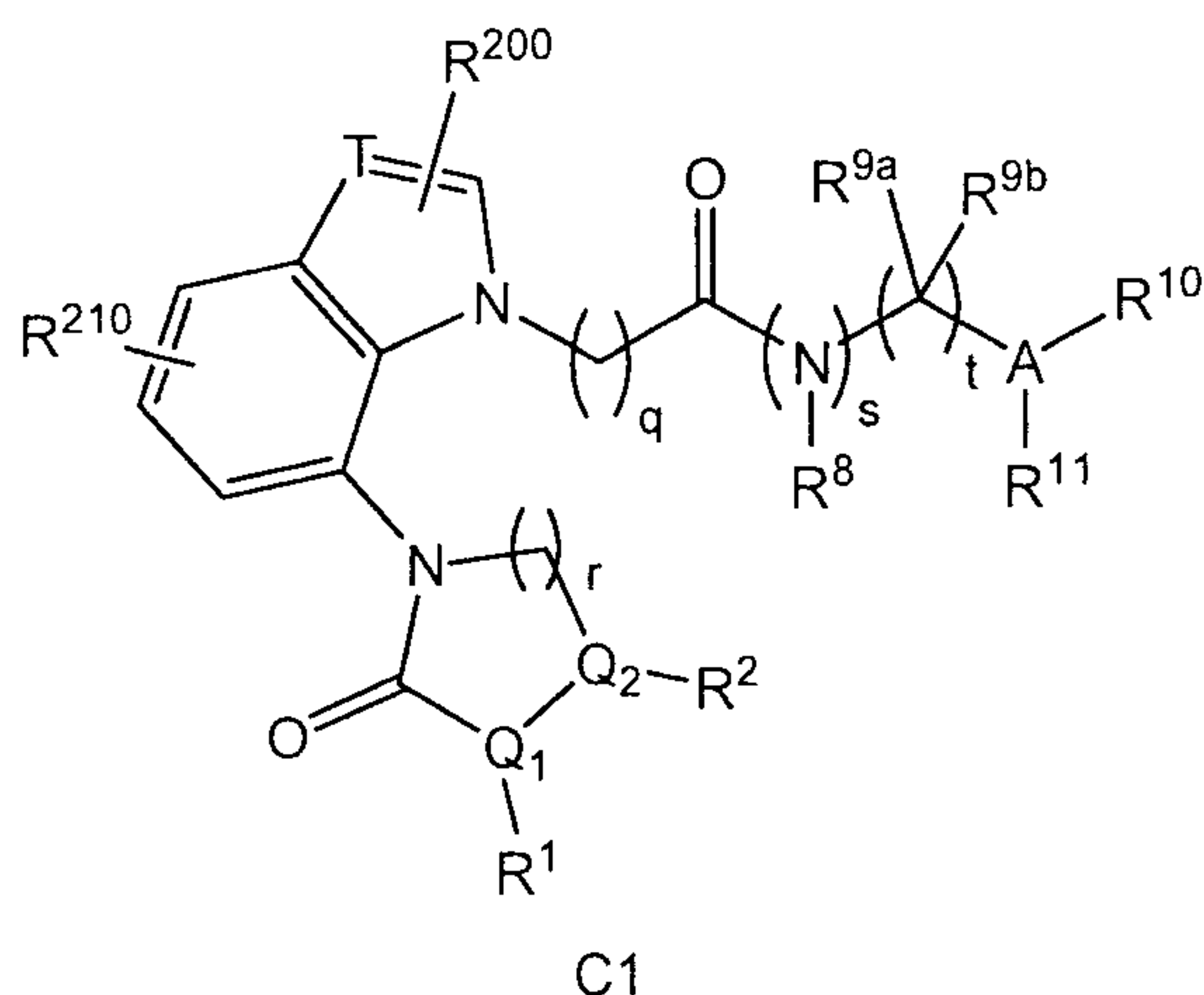
Of the substructures B, substructures B.1., B.3., B.4., B.10., B.11., B.44., B.8., B.17., B.15., B.54., B.13., B.19., B.20., B.45., B.21., B.49., B.24., B.25., B.27., B.29., B.47., B.55., B.37., B.36., B.57., B.30., B.32., B.34., B.48. and B.50. can preferably be present in the compounds according to the invention.

In substructures B.1., B.3., B.4., B.29., B.44., B.54. M¹ can preferably stand for N and M² and M³ each for CH. In substructure B.8. o can preferably stand for 1 and R¹⁹⁰ for H. In substructure B.17. R¹⁹ can preferably stand for H. In substructure B.15. R¹⁹ can preferably stand for CH₃ and R¹⁹⁰ for F in the 4-position. In substructure B.13. o can preferably stand for 0 or 1 and R¹⁹⁰ for H or F in the 4-position. In substructure B.30.

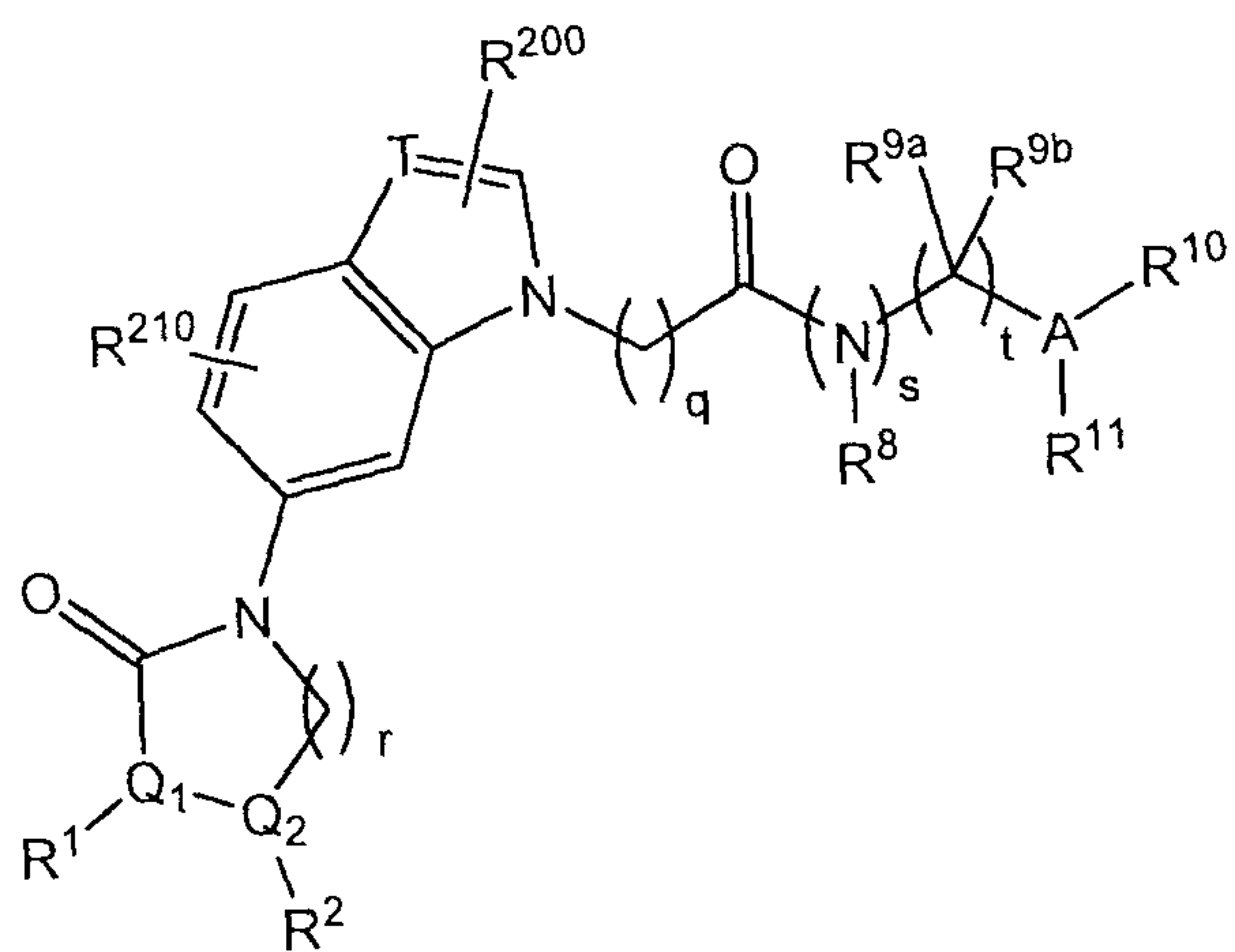
GRA3454-WO
22nd December 2009

R^8 can preferably stand for H, s for 1, t for 1 or 2, M^1 for N and M^2 and M^3 each for CH. In substructure B.32. R^8 can preferably stand for CH_3 , S for 1, t for 3, R^{34} and R^{35} each for CH_3 and R^{190} for H. In substructure B.34. R^8 can preferably stand for CH_3 , s for 1, t for 2 or 3, R^{34} and R^{35} each for CH_3 and R^{190} for H. In substructure B.48. R^8 can preferably stand for H, s for 1, t for 0, R^{34} and R^{35} together with the nitrogen atom linking them for azetidinyI and R^{190} for H. In substructure B.50. R^8 can preferably stand for H, s for 1, t for 3 and R^{38} for ethyl. In substructure B.27. o can preferably stand for 2 and g and h each for 1. In substructure B.47. o can preferably stand for 0, h and g each for 1 and R^{38} for CH_3 . In substructure B.37. M^1 can preferably stand for N, M^2 and M^3 each for CH, r for 2 and R^{34} and R^{35} together with the nitrogen atom linking them for pyrrolidinyI. In substructures B.56. and B.57. R^{190} can preferably stand for H and R^{34} and R^{35} each for CH_3 . In substructure B.19. o can preferably stand for 0 or 1, n and m each for 1 and R^{45} for CH_3 . In substructure B.21. o can preferably stand for 0 and R^{190} for F in the 4-position. In substructure B.49. o can preferably stand for 3 and R^{34} and R^{35} each for CH_3 . In substructure B.20. o can preferably stand for 0, M^1 for N and M^2 and M^3 each for CH. In substructure B.24. o can preferably stand for 1 and R^{190} for F in the 4-position. In substructure B.25. o can preferably stand for 1, M^1 for N and M^2 and M^3 each for CH.

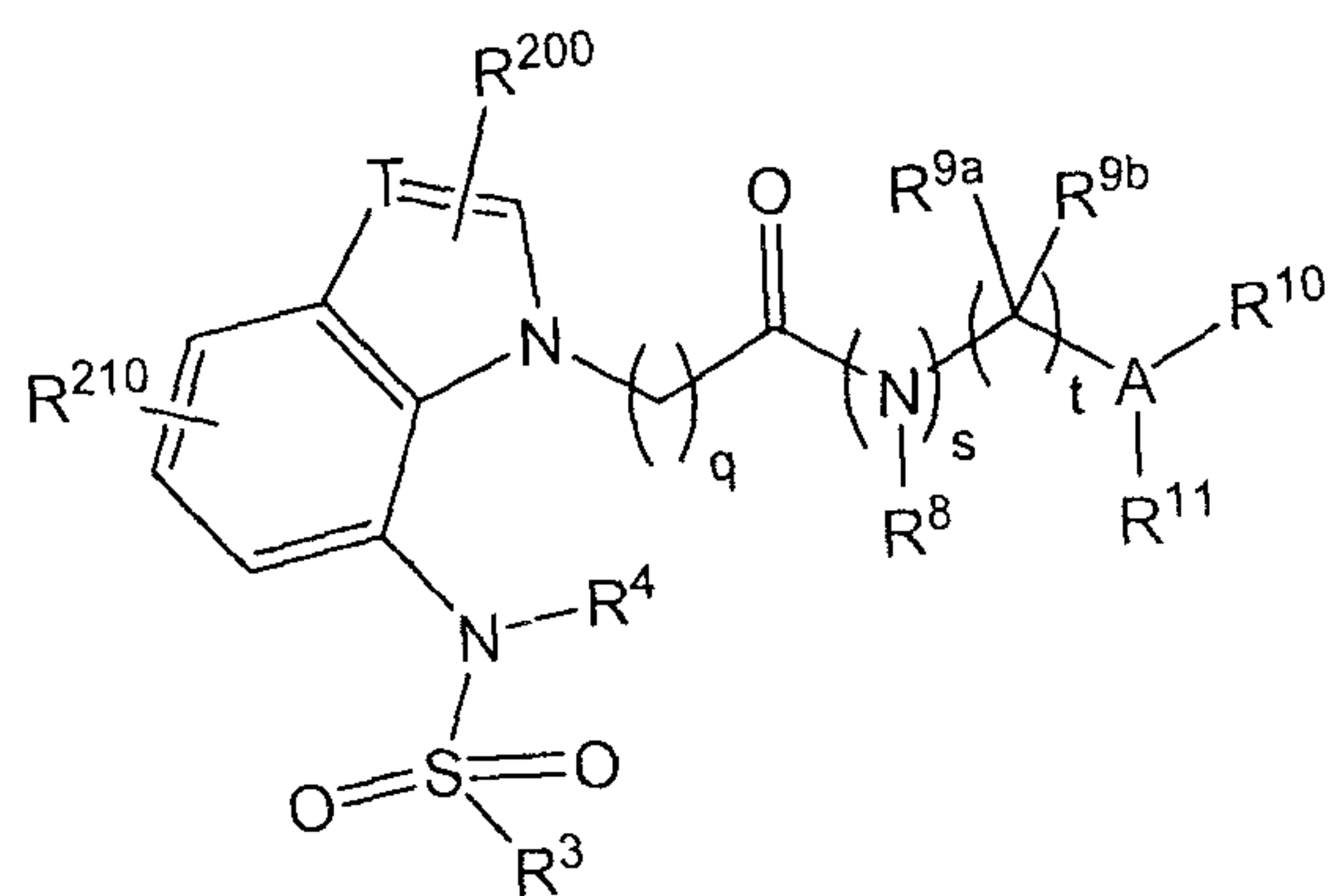
Further embodiments of the compounds according to the invention are those which are represented by the general formulae C1 to C14 shown below:



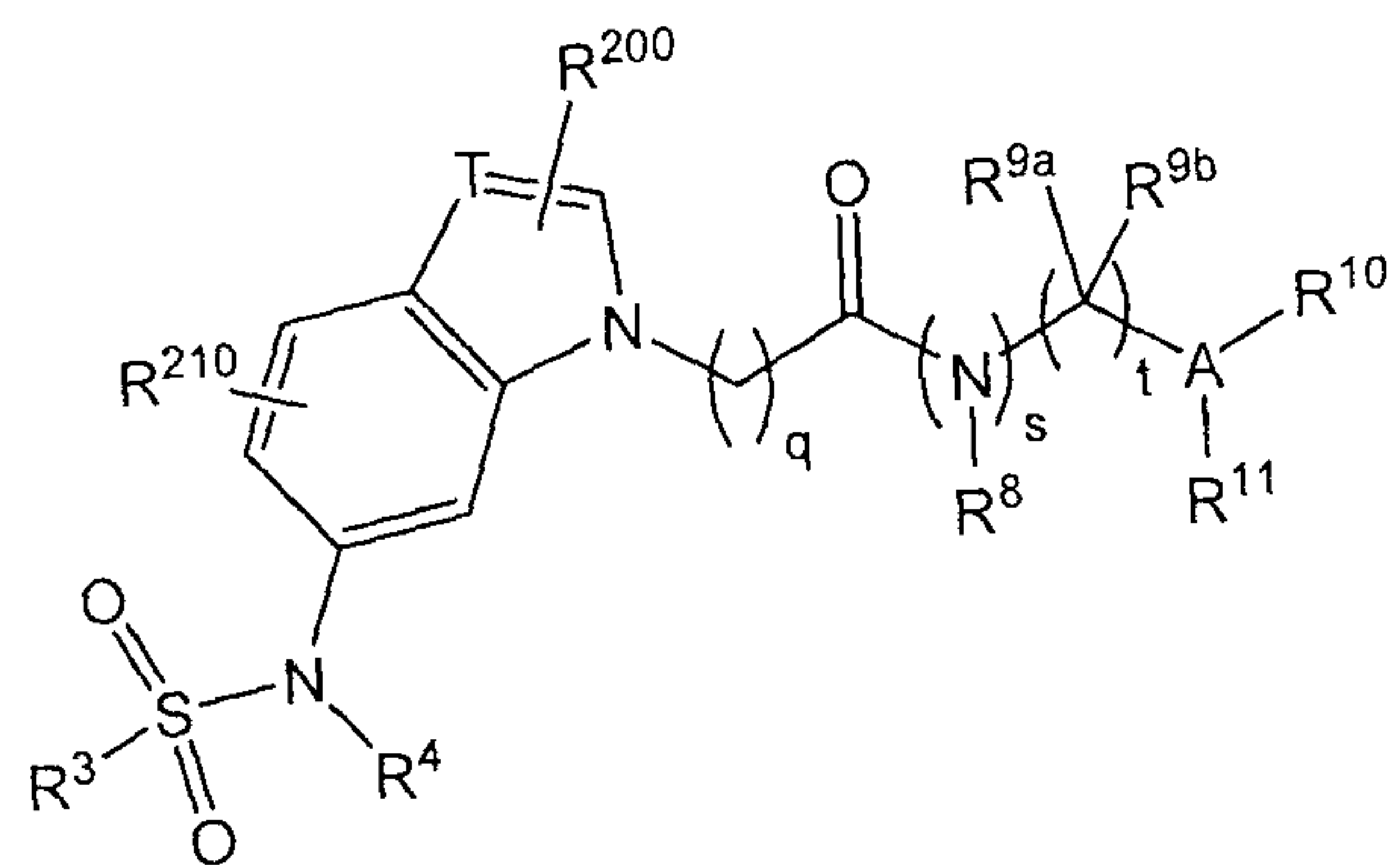
GRA3454-WO
22nd December 2009



C2

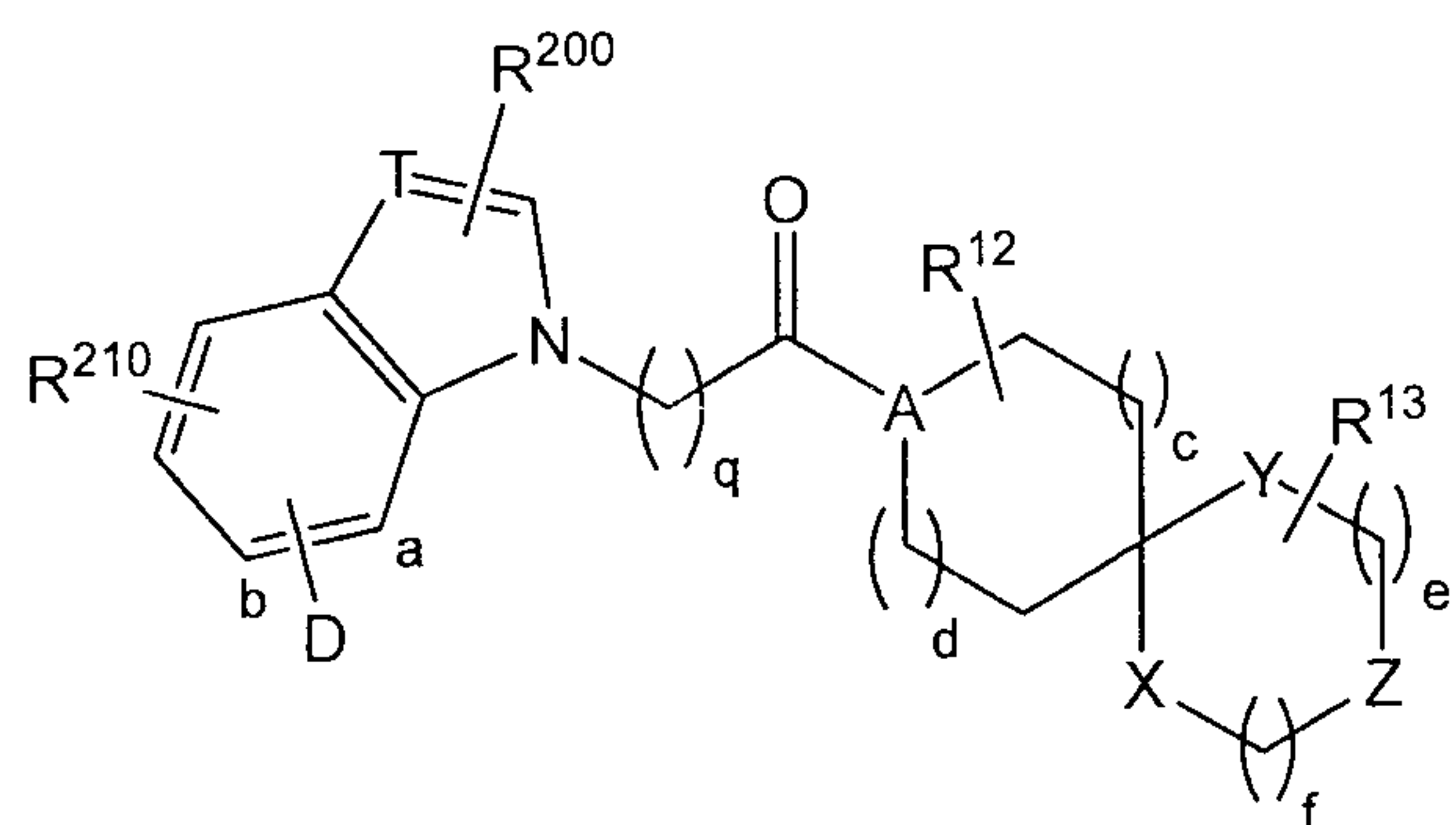


C3

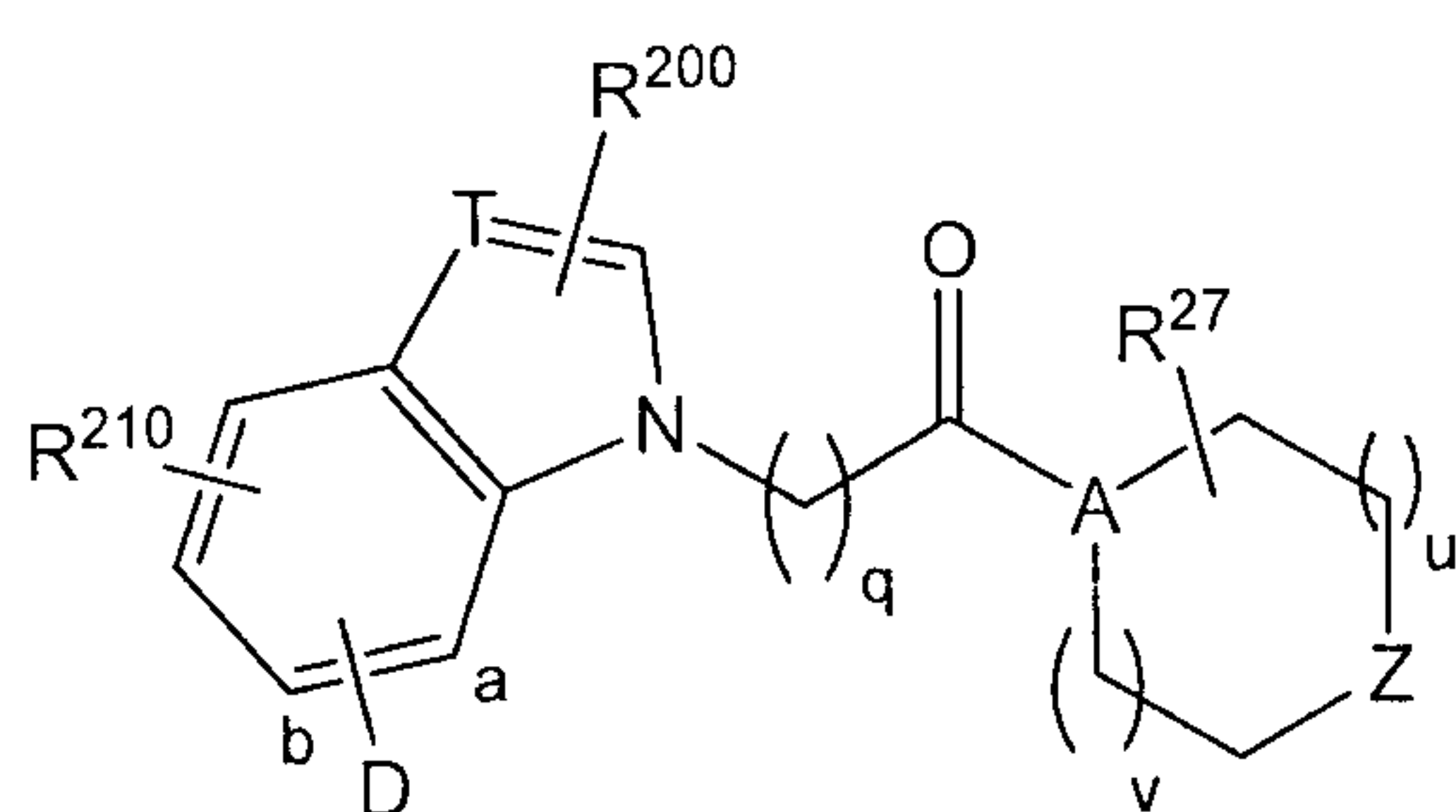


C4

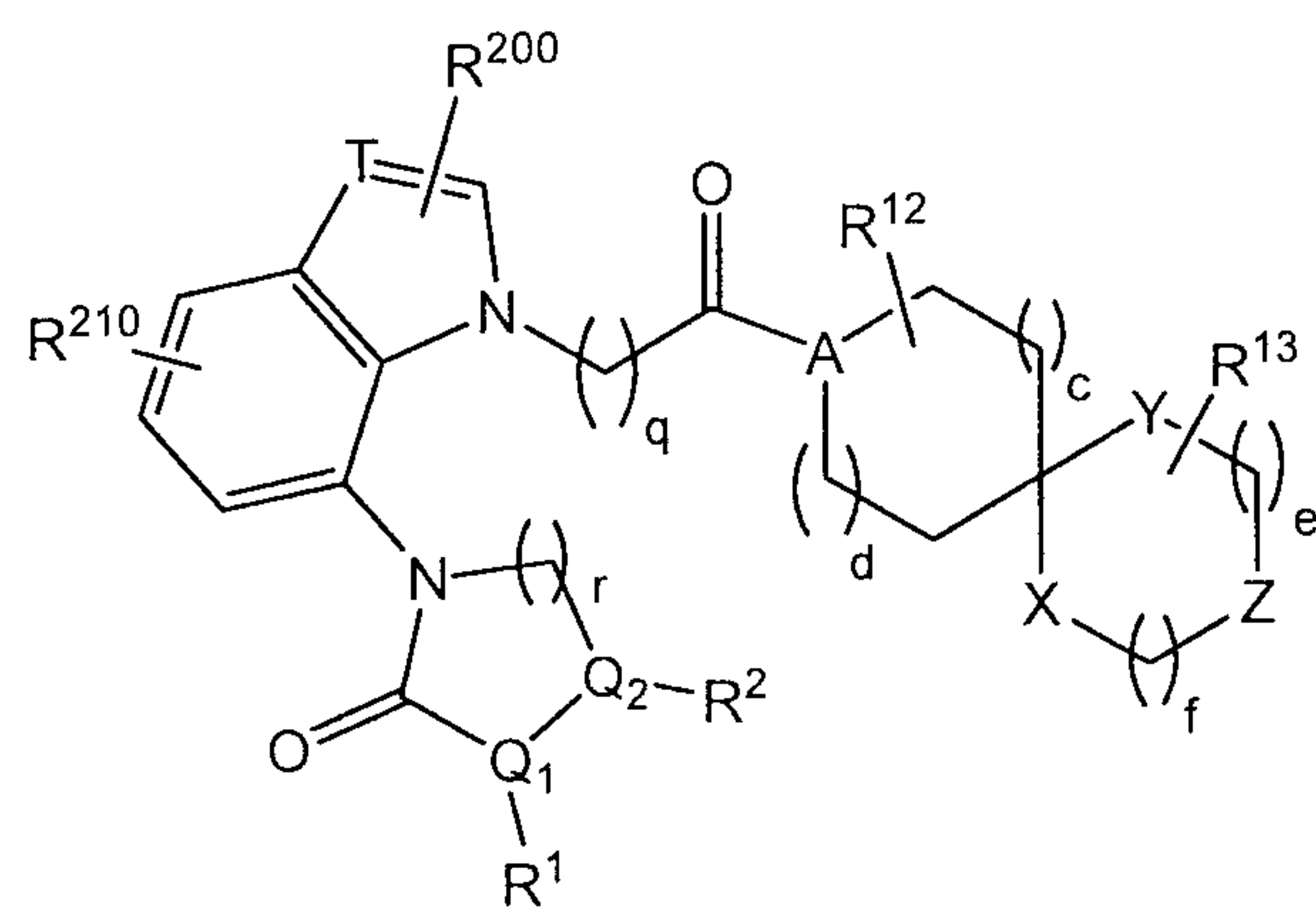
GRA3454-WO
22nd December 2009



C5

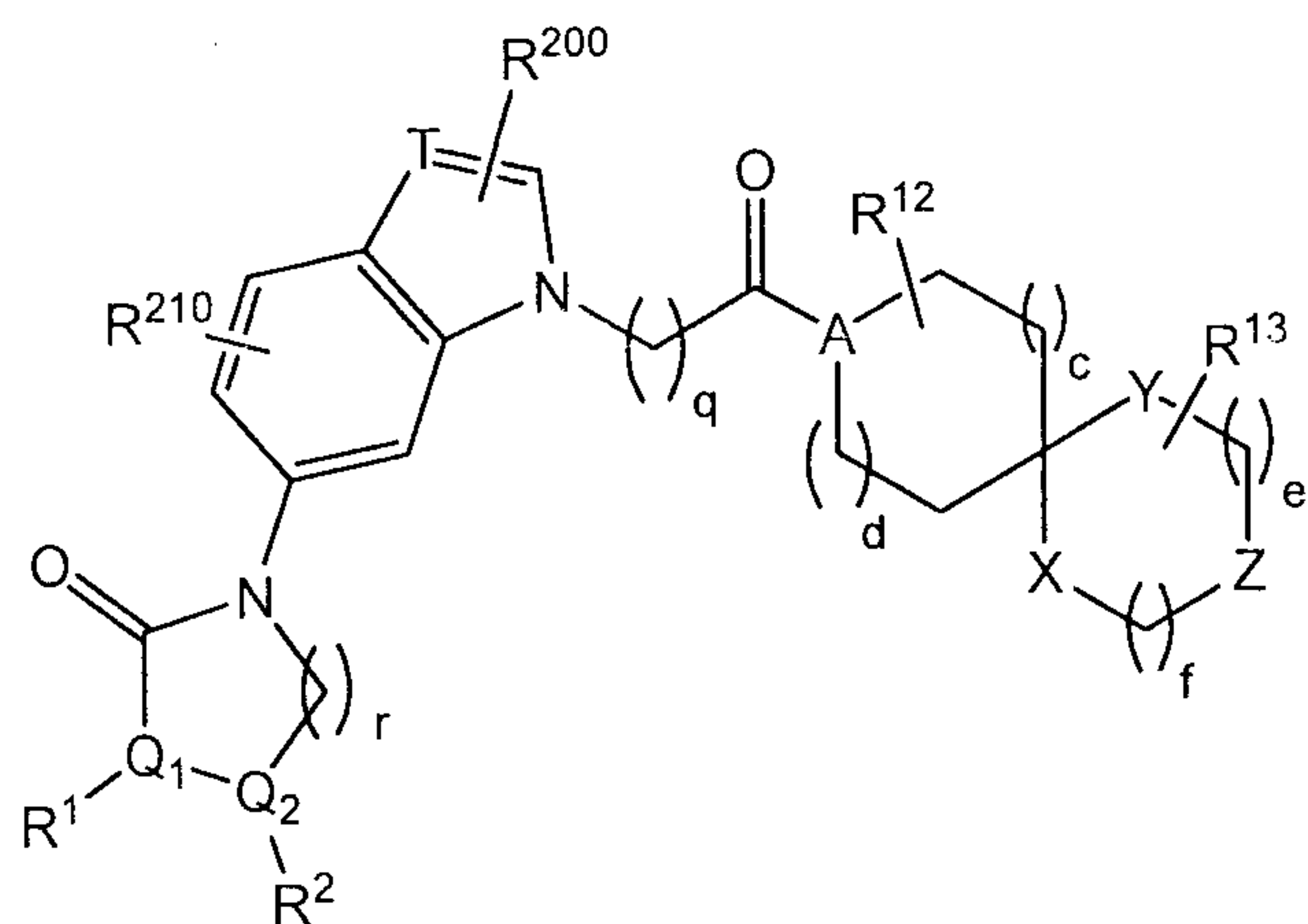


C6

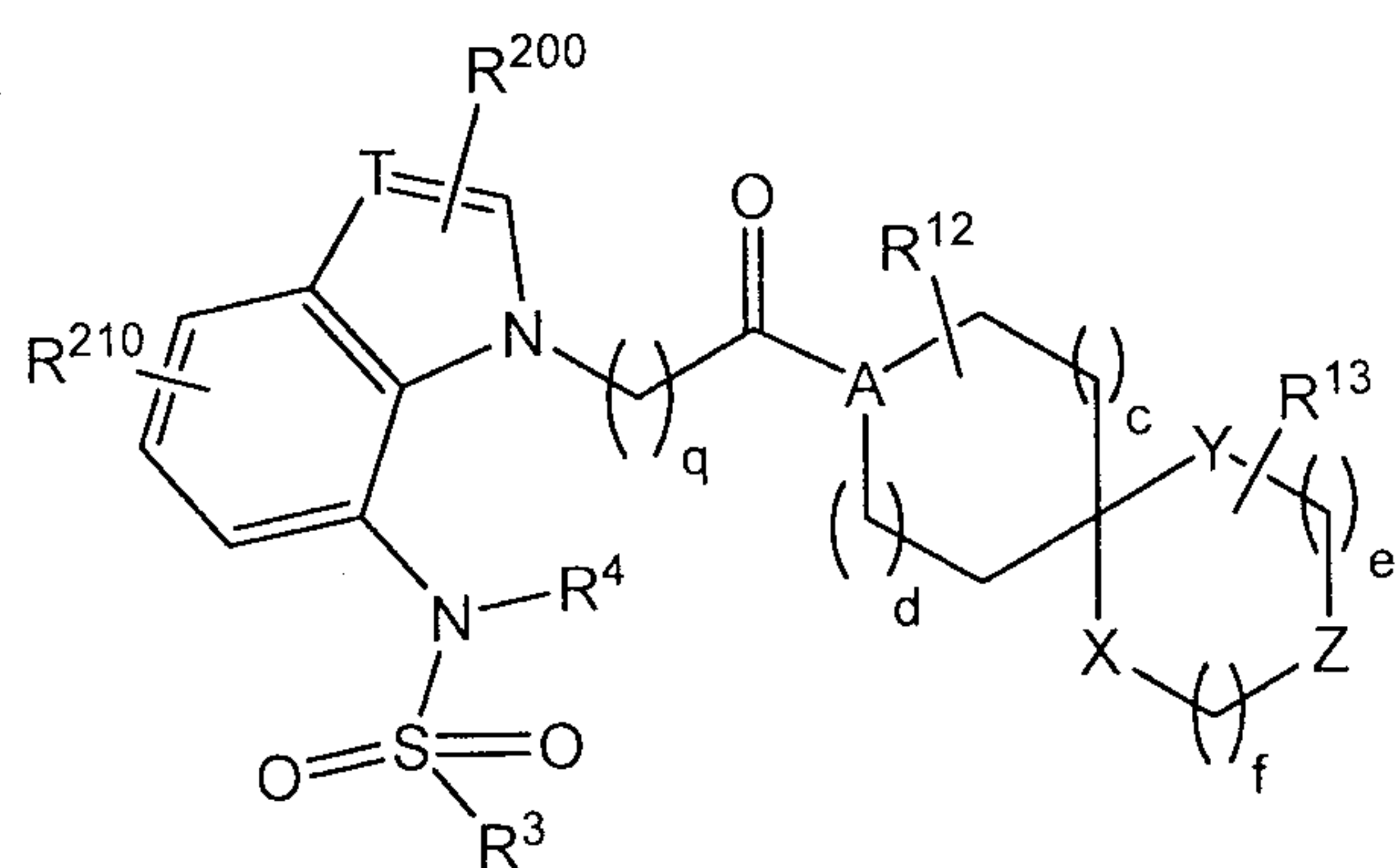


C7

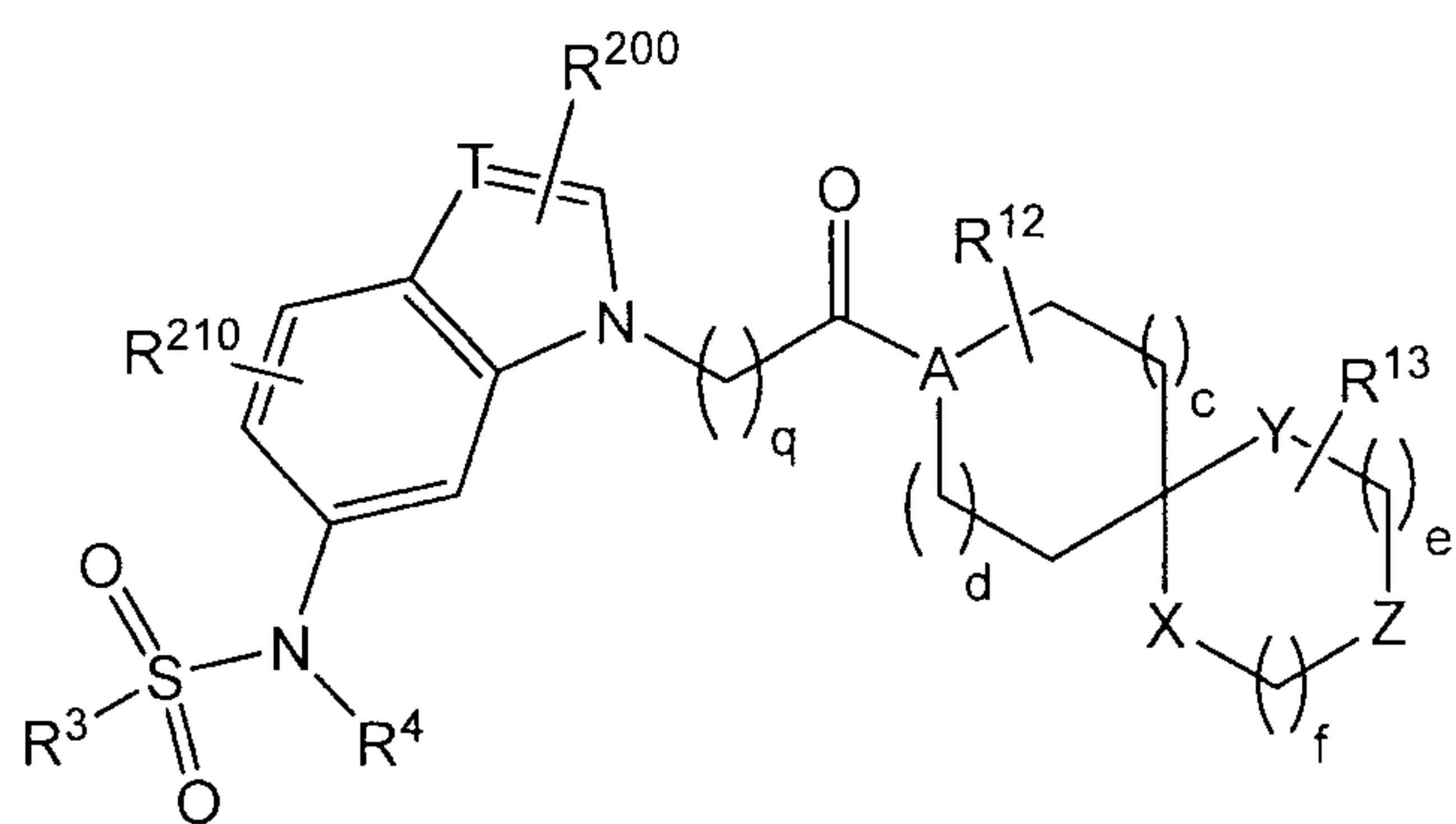
GRA3454-WO
22nd December 2009



C8

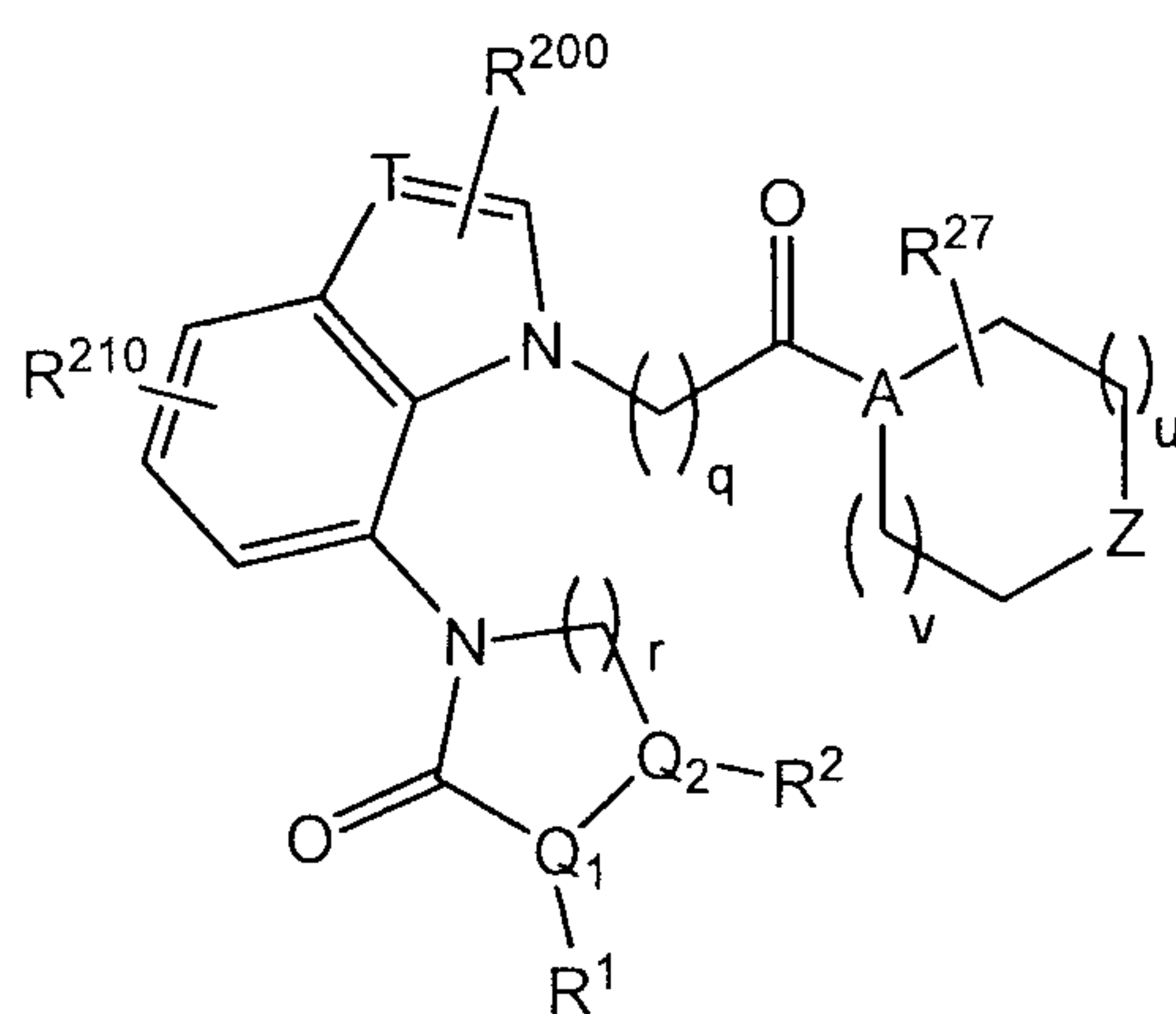


C9

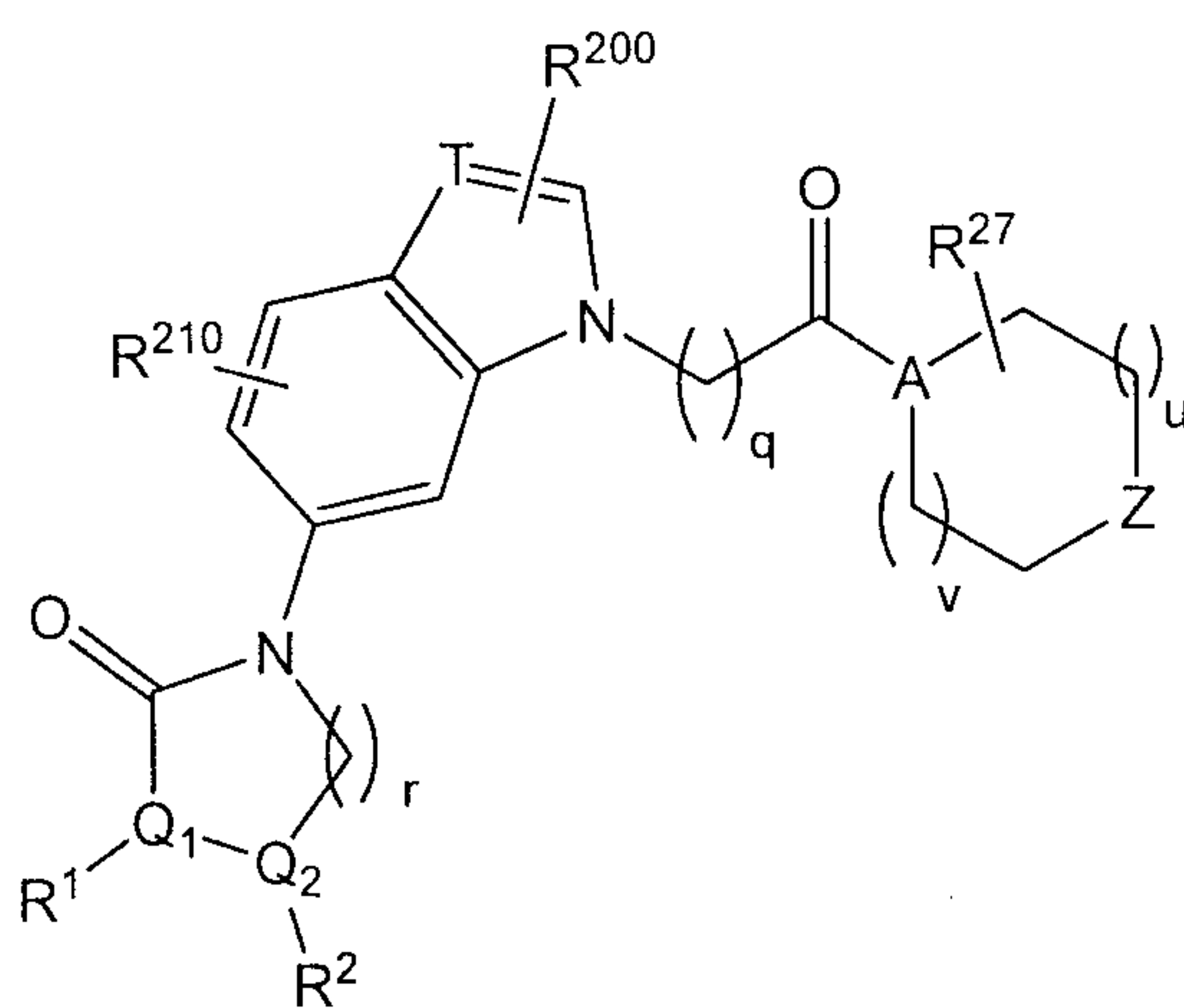


C10

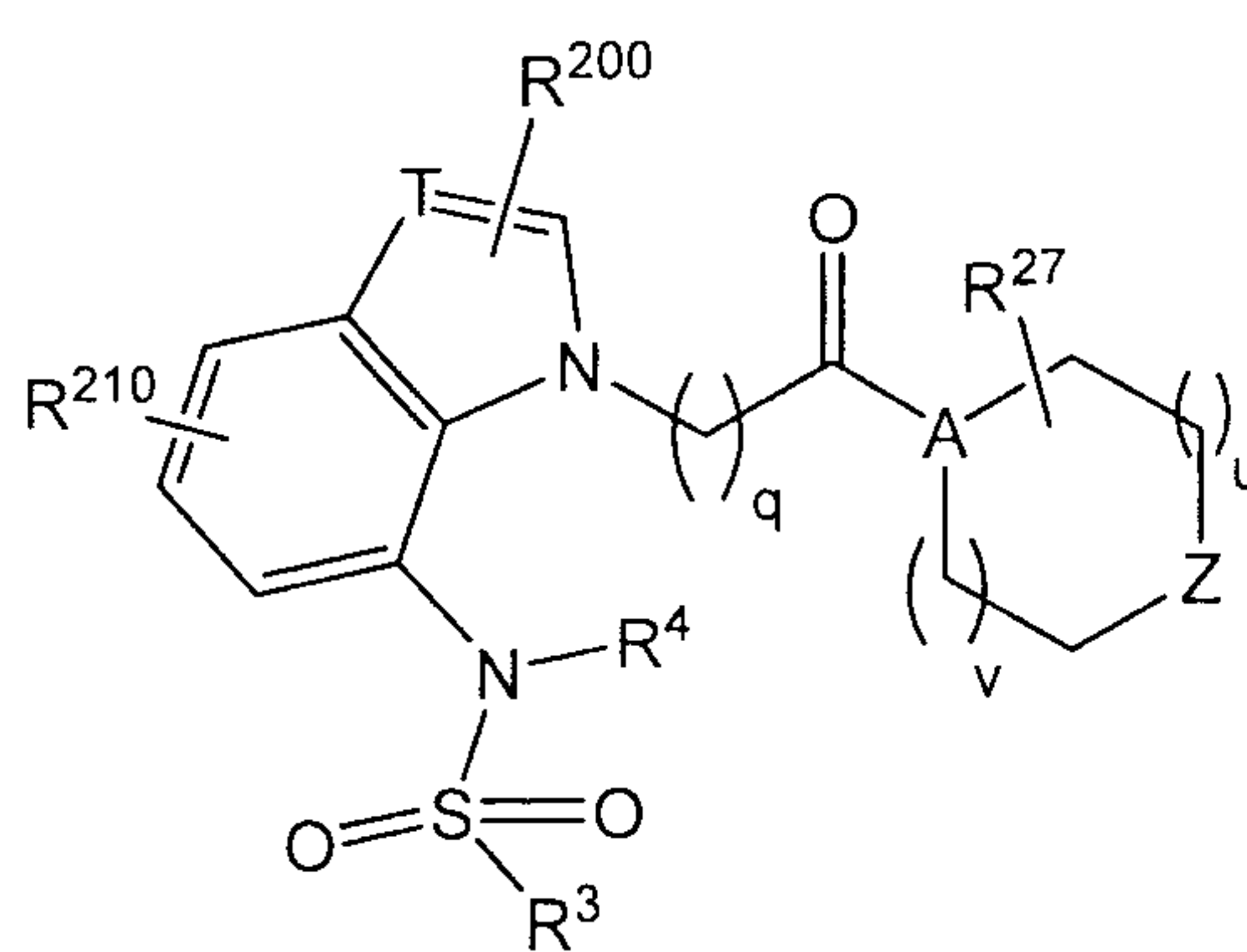
GRA3454-WO
22nd December 2009



C11

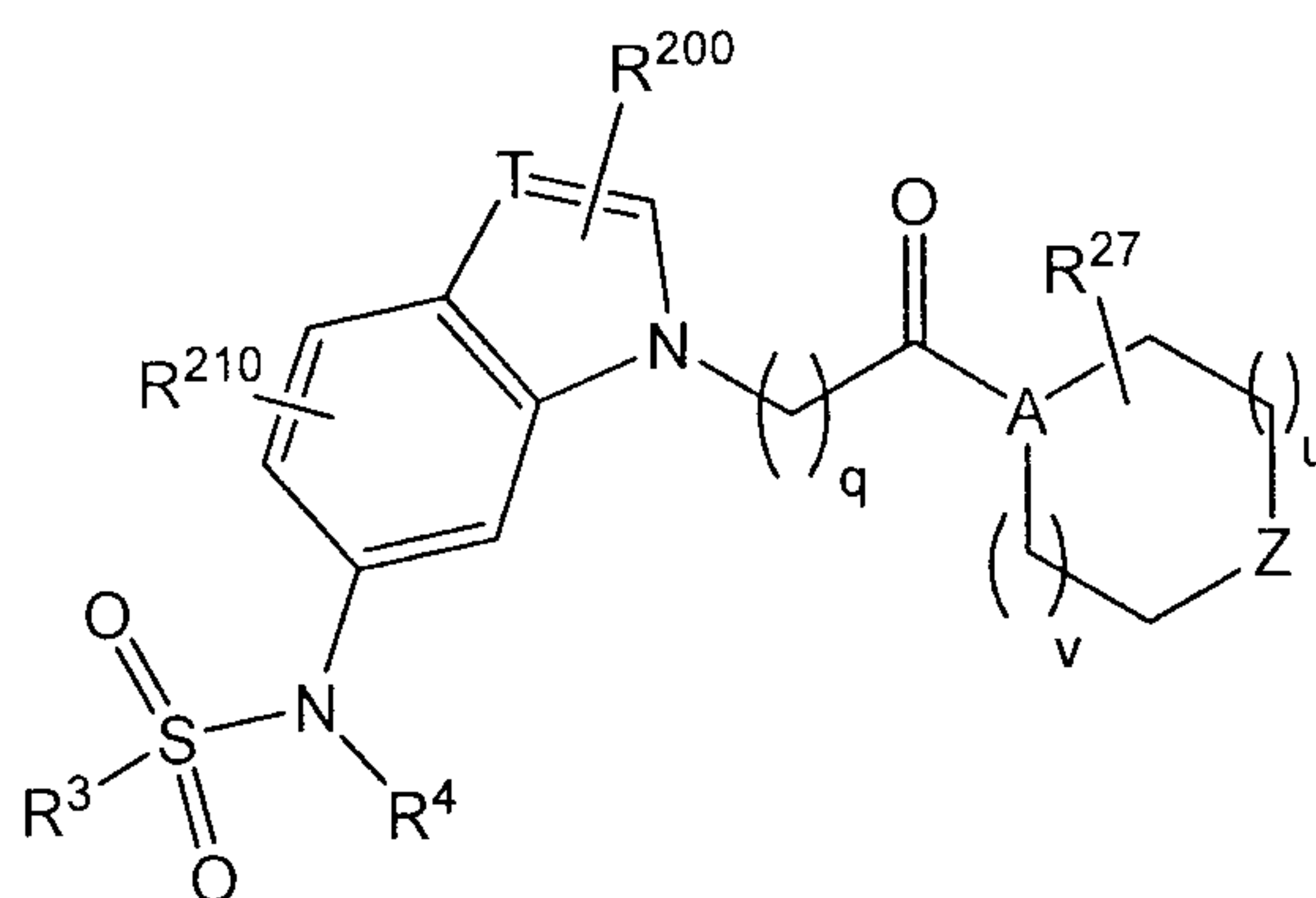


C12



C13

GRA3454-WO
22nd December 2009



C14

wherein the various radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and the preferred embodiments thereof.

In a further preferred embodiment of the present invention the substituted compounds according to the invention can be selected from the group consisting of

No.	Compound
G-01	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G-02	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G-03	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyridin-4-yloxy-piperidin-1-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G-04	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(1-oxo-4-phenyl-2,4,8-triazaspiro[4.5]decan-8-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G-05	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G-06	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-pyridin-3-yl-4-(2-pyrrolidin-1-yl-ethoxy)-piperidin-1-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G-07	7-Chloro-2-[1-[3-oxo-3-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G-08	7-Chloro-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G-10	7-Chloro-2-(1-(3-oxo-3-(9-(pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl)-1H-indol-7-yl)isoindolin-1-one

GRA3454-WO
22nd December 2009

G-11	7-Chloro-2-(1-(2-oxo-2-(9-(pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-1H-indol-7-yl)isoindolin-1-one
G-12	7-Chloro-2-(1-(2-oxo-2-(8-(pyridin-4-yl)-2,8-diazaspiro[4.5]decan-2-yl)ethyl)-1H-indol-6-yl)isoindolin-1-one
G-13	4-Methoxy-2,6-dimethyl-N-(1-(2-oxo-2-(3-(pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-8-yl)ethyl)-1H-indol-7-yl)benzenesulfonic acid amide
G-14	4-Methoxy-2,6-dimethyl-N-(1-(2-oxo-2-(8-(pyridin-4-yl)-2,8-diazaspiro[4.5]decan-2-yl)ethyl)-1H-indol-7-yl)benzenesulfonic acid amide
G-15	7-Chloro-2-(1-(2-oxo-2-(3-(pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-8-yl)ethyl)-1H-indol-6-yl)isoindolin-1-one
G-16	4-Methoxy-2,6-dimethyl-N-(1-(2-oxo-2-(3-(6-(piperidin-1-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl)pyrrolidin-1-yl)ethyl)-1H-indol-7-yl)benzenesulfonic acid amide
G-17	4-Methoxy-2,6-dimethyl-N-(1-(2-oxo-2-(7-(pyridin-4-yl)-2,7-diazaspiro[4.4]nonan-2-yl)ethyl)-1H-indol-7-yl)benzenesulfonic acid amide
G-18	N-(1-(2-(9-(azetidin-1-yl)-3-azaspiro[5.5]undecan-3-yl)-2-oxoethyl)-1H-indol-7-yl)-4-methoxy-2,6-dimethylbenzenesulfonic acid amide
G-19	7-Chloro-2-(1-(2-oxo-2-(9-(pyridin-4-yloxy)-3-azaspiro[5.5]undecan-3-yl)ethyl)-1H-indol-6-yl)isoindolin-1-one
G-20	7-Chloro-2-(1-(2-(9-(3,3-difluoroazetidin-1-yl)-3-azaspiro[5.5]undecan-3-yl)-2-oxoethyl)-1H-indol-6-yl)isoindolin-1-one
G-21	2-(1-(2-(9-(Azetidin-1-yl)-3-azaspiro[5.5]undecan-3-yl)-2-oxoethyl)-1H-indol-6-yl)-7-chloroisoindolin-1-one
G-22	4-Methoxy-2,6-dimethyl-N-(1-(2-oxo-2-(9-(pyridin-4-yloxy)-3-azaspiro[5.5]undecan-3-yl)ethyl)-1H-indol-7-yl)benzenesulfonic acid amide
G-23	8-Chloro-4-methyl-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-3,4-dihydro-2H-pyrrolo[3,4-b]indol-1-one
G-24	4-Methoxy-2,6-dimethyl-N-[[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-7-yl]-methyl]-benzenesulfonic acid amide
G-26	7-Methyl-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G-27	5-Methyl-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-1,2-dihydro-pyrrolo[2,1-e]imidazol-3-one
G-31	10-Chloro-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one
G-33	8-Chloro-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-3,4-dihydro-2H-pyrrolo[1,2-a]pyrazin-1-one
G_CC-1	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-2	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-3	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-4	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide

GRA3454-WO
22nd December 2009

G_CC-5	N-[1-[2-[4-(4-fluorophenyl)-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-6	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-7	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-8	4-Chloro-2,5-dimethyl-N-[1-[2-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-9	2-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[(1-pyridin-4-yl-piperidin-4-yl)-methyl]-acetamide
G_CC-10	N-[1-[2-(3-Benzyl-3,7-diazaspiro[4.4]nonan-7-yl)-2-oxo-ethyl]-1H-indol-6-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-11	N-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-2-[6-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide
G_CC-12	N-[1-[2-[3-(4-Fluorophenyl)-4-oxo-3,8-diazaspiro[4.5]decan-8-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-13	N-[1-[2-(3-Benzyl-3,7-diazaspiro[4.4]nonan-7-yl)-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-14	N-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-2-[7-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide
G_CC-15	2-[6-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[3-(4-dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-N-methyl-acetamide
G_CC-16	N-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-N-methyl-2-[7-[[[naphthalen-1-yl)sulfonyl]amino]-1H-indol-1-yl]-acetamide
G_CC-17	N-[4-(Azetidin-1-yl)-4-phenyl-cyclohexyl]-2-[7-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetamide
G_CC-18	N-[3-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-2-[7-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide
G_CC-19	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-2-[7-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetamide
G_CC-20	N-[1-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-21	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide
G_CC-22	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-3-[6-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionamide
G_CC-23	3-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide
G_CC-24	2-[6-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide
G_CC-25	N-[3-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-N-methyl-2-[7-[[[naphthalen-1-yl)sulfonyl]amino]-1H-indol-1-yl]-acetamide
G_CC-26	2-[7-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[3-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-N-methyl-acetamide
G_CC-27	2-[7-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-acetamide

GRA3454-WO
22nd December 2009

G_CC-28	2-[7-[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide
G_CC-29	N-[3-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-2-[6-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide
G_CC-30	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-2-[6-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetamide
G_CC-31	N-[1-[2-[1-(4-Fluorophenyl)-3-methyl-4-oxo-3,8-diazaspiro[4.5]decan-8-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-32	N-[1-[2-(3-Benzyl-4-oxo-3,8-diazaspiro[4.5]decan-8-yl)-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-33	N-[1-[2-[2-(4-Fluorophenyl)-methyl]-2,5-diazabicyclo[2.2.1]heptan-5-yl]-2-oxo-ethyl]-1H-indol-6-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-34	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[2-(pyridin-4-yl-methyl)-2,5-diazabicyclo[2.2.1]heptan-5-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-35	4-Methoxy-2,6-dimethyl-N-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-36	4-Chloro-2,5-dimethyl-N-[1-[2-oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-37	N-[1-[2-Oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-6-yl]-2-(trifluoromethyl)-benzenesulfonic acid amide
G_CC-38	N-[1-[2-Oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-naphthalene-1-sulfonic acid amide
G_CC-39	4-Chloro-2,5-dimethyl-N-[1-[2-oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-40	4-Methoxy-2,6-dimethyl-N-[1-[3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-41	4-Methoxy-2,6-dimethyl-N-[1-[3-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-42	4-Methoxy-2,6-dimethyl-N-[1-[3-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-43	4-Methoxy-2,6-dimethyl-N-[1-[3-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-44	N-[1-[3-[4-(3-Dimethylamino-propyl)-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-45	N-[1-[3-(4-Hydroxy-4-pyridin-2-yl-piperidin-1-yl)-3-oxo-propyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-46	N-[3-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-3-[7-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide
G_CC-47	3-[7-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide
G_CC-48	N-[1-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-3-oxo-propyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-49	N-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-3-[7-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide

GRA3454-WO
22nd December 2009

G_CC-50	N-[4-(Azetidin-1-yl)-4-phenyl-cyclohexyl]-3-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionamide
G_CC-51	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-3-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionamide
G_CC-52	N-[1-[3-Oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-7-yl]-2-(trifluoromethyl)-benzenesulfonic acid amide
G_CC-53	N-[1-[2-Oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-2-(trifluoromethyl)-benzenesulfonic acid amide
G_CC-54	4-Methoxy-2,6-dimethyl-N-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-56	N-[3-(4-Ethyl-piperazin-1-yl)-propyl]-3-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionamide
G_CC-57	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-pyridin-3-yl-4-(2-pyrrolidin-1-yl-ethoxy)-piperidin-1-yl]-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-59	4-Chloro-2,5-dimethyl-N-[1-[3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-60	4-Chloro-2,5-dimethyl-N-[1-[3-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-61	4-Chloro-2,5-dimethyl-N-[1-[3-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-62	4-Chloro-2,5-dimethyl-N-[1-[3-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-63	7-Chloro-2-[1-[3-oxo-3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G_CC-64	7-Chloro-2-[1-[3-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-3-oxo-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G_CC-65	4-Chloro-2,5-dimethyl-N-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-66	8-[3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-propanoyl]-3-[(4-fluorophenyl)-methyl]-3,8-diazaspiro[4.5]decan-4-one
G_CC-67	7-Chloro-2-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G_CC-68	7-Chloro-2-[1-[3-oxo-3-(4-pyridin-4-yloxy-piperidin-1-yl)-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G_CC-69	7-Chloro-2-[1-[3-(4-hydroxy-4-pyridin-3-yl-piperidin-1-yl)-3-oxo-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G_CC-70	3-[7-[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide
G_CC-71	3-[6-[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide
G_CC-72	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide
G_CC-73	3-[7-[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-propionamide
G_CC-74	3-[6-[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-propionamide

GRA3454-WO
22nd December 2009

G_CC-76	2-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-acetamide (G_CC-76)
G_CC-77	N-[2-(4-Dimethylamino-4-phenyl-cyclohexyl)-ethyl]-2-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-77)
G_CC-81	N-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-3-[6-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide (G_CC-81)
G_CC-84	N-[1-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-84)
G_CC-88	2-[7-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-acetamide (G_CC-88)
G_CC-91	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-91)
G_CC-92	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyridin-4-yloxy-piperidin-1-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-92)
G_CC-95	N-[2-(4-Dimethylamino-4-phenyl-cyclohexyl)-ethyl]-2-[6-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-95)
G_CC-99	N-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-2-[6-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-99)
G_CC-102	N-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-2-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-102)
G_CC-103	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide (G_CC-103)
G_CC-106	7-Chloro-2-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-7-yl]-2,3-dihydro-isoindol-1-one (G_CC-106)
G_CC-108	N-[[1-[2-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetyl]-4-(4-methyl-piperazin-1-yl)-piperidin-4-yl]-methyl]-pyridine-4-carboxylic acid amide (G_CC-108)
G_CC-111	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[(1-pyridin-4-yl-piperidin-4-yl)-methyl]-acetamide (G_CC-111)
G_CC-113	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-[4-(3-fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-N-methyl-acetamide (G_CC-113)

GRA3454-WO
22nd December 2009

G_CC-116	3-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-propionamide (G_CC-116)
G_CC-117	N-[2-(4-Dimethylamino-4-phenyl-cyclohexyl)-ethyl]-3-[6-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide (G_CC-117)
G_CC-119	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-propionamide (G_CC-119)
G_CC-120	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G_CC-120)
G_CC-123	3-[7-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[(1-pyridin-4-yl-piperidin-4-yl)-methyl]-propionamide (G_CC-123)
G_CC-127	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-phenyl-cyclohexyl)-ethyl]-N-methyl-propionamide (G_CC-127)
G_CC-128	7-Chloro-2-[1-[2-[4-(3-fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one (G_CC-128)
G_CC-138	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-acetamide (G_CC-138)
G_CC-139	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(pyridin-3-carbonyl)-piperazin-1-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-139)

optionally in the form of a single enantiomer or a single diastereomer, the racemate, the enantiomers, the diastereomers, mixtures of enantiomers or diastereomers, each in the form of their bases and/or physiologically compatible salts, in particular hydrochloride salts.

The numbering of the individual embodiments of the compounds according to the invention used above is retained in the following explanations of the present invention, particularly in the description of the examples.

According to one aspect of the present invention the compounds according to the invention preferably have an antagonistic action on the human B1R receptor or the B1R receptor of the rat. In a preferred embodiment of the invention the compounds

GRA3454-WO
22nd December 2009

according to the invention have an antagonistic action on both the human B1R receptor (hB1R) and on the B1R receptor of the rat (rB1R).

In a preferred embodiment of the present invention the compounds according to the invention exhibit at least 15%, 25%, 50%, 70%, 80% or 90% inhibition on the human B1R receptor and/or on the B1R receptor of the rat in the FLIPR assay at a concentration of 10 μ M. Most particularly preferred are compounds which exhibit at least 70%, in particular at least 80% and particularly preferably at least 90% inhibition on the human B1R receptor and on the B1R receptor of the rat at a concentration of 10 μ M.

The agonistic or antagonistic action of substances can be quantified on the bradykinin 1 receptor (B1R) of the human and rat species with ectopically expressing cell lines (CHO K1 cells) and with the aid of a Ca^{2+} -sensitive dye (Fluo-4) using a fluorescent imaging plate reader (FLIPR). The indication in % activation is based on the Ca^{2+} signal after addition of Lys-Des-Arg⁹ bradykinin (0.5 nM) or Des-Arg⁹ bradykinin (100 nM). Antagonists lead to a suppression of the Ca^{2+} influx following administration of the agonist. The % inhibition in comparison with the maximum achievable inhibition is indicated.

The substances according to the invention preferably act for example on the B1R of relevance in connection with various diseases, such that they are suitable as a pharmaceutical active ingredient in medicinal products.

The invention therefore also provides medicinal products containing at least one compound according to the invention, optionally along with suitable additives and/or auxiliary substances and/or optionally further active ingredients.

The medicinal products according to the invention optionally contain, in addition to at least one compound according to the invention, suitable additives and/or auxiliary substances, including carrier materials, fillers, solvents, diluents, dyes and/or binders, and can be administered as liquid dosage forms in the form of injection solutions, drops or juices, as semi-solid dosage forms in the form of granules, tablets, pellets, patches, capsules, plasters/spray plasters or aerosols. The choice of auxiliary

GRA3454-WO
22nd December 2009

substances, etc., and the amounts thereof to use depend on whether the medicinal product is to be administered by oral, peroral, parenteral, intravenous, intraperitoneal, intradermal, intramuscular, nasal, buccal, rectal or topical means, for example on the skin, mucous membranes or in the eyes. Preparations in the form of tablets, pastilles, capsules, granules, drops, juices and syrups are suitable for oral administration; solutions, suspensions, easily reconstitutable dry preparations and sprays are suitable for parenteral, topical and inhalative administration. Substituted indole compounds according to the invention in a depot formulation, in dissolved form or in a plaster, optionally with addition of agents promoting skin penetration, are suitable preparations for percutaneous administration. Preparation forms suitable for oral or percutaneous administration can deliver the substituted indole compounds according to the invention on a delayed release basis. The substituted indole compounds according to the invention can also be used in parenteral long-term depot forms, such as implants or implanted pumps, for example. Other additional active ingredients known to the person skilled in the art can be added in principle to the medicinal products according to the invention.

The amount of active ingredient to be administered to the patient varies according to the weight of the patient, the type of administration, the indication and the severity of the illness. 0.00005 to 50 mg/kg, in particular 0.01 to 5 mg/kg, of at least one compound according to the invention are conventionally administered.

One form of the medicinal product contains a substituted indole compound according to the invention optionally as a pure diastereomer and/or enantiomer, as a racemate or as a non-equimolar or equimolar mixture of diastereomers and/or enantiomers.

B1R is involved in particular in the pain mechanism. The substituted indole compounds according to the invention can accordingly be used in particular for the preparation of a medicinal product for the treatment of pain, in particular acute, visceral, neuropathic or chronic pain or inflammatory pain.

The invention therefore also provides the use of at least one substituted indole compound according to the invention to prepare a medicinal product for the treatment of pain, in particular acute, visceral, neuropathic or chronic pain. A particular

GRA3454-WO
22nd December 2009

embodiment of the present invention is the use of at least one of the substituted indole compounds according to the invention to prepare a medicinal product for the treatment of inflammatory pain.

The invention also provides the use of at least one substituted indole compound according to the invention for the treatment of pain, in particular acute, visceral, neuropathic or chronic pain or inflammatory pain.

The invention also provides the use of at least one substituted indole compound according to the invention to prepare a medicinal product for the treatment of diabetes, diseases of the respiratory tract, for example bronchial asthma, allergies, COPD/chronic obstructive pulmonary disease or cystic fibrosis; inflammatory bowel diseases, for example ulcerative colitis or CD/Crohn's disease; neurological diseases, for example multiple sclerosis or neurodegeneration; inflammations of the skin, for example atopic dermatitis, psoriasis or bacterial infections; rheumatic diseases, for example rheumatoid arthritis or osteoarthritis; septic shock; reperfusion syndrome, for example following heart attack or stroke; obesity; and as an angiogenesis inhibitor.

The invention also provides the use of at least one substituted indole compound according to the invention for the treatment of one of the aforementioned indications.

In one of the above uses it can be preferable for a substituted indole compound that is used to be in the form of a pure diastereomer and/or enantiomer, a racemate or a non-equimolar or equimolar mixture of diastereomers and/or enantiomers.

The invention also provides a process for the treatment, in particular in one of the aforementioned indications, of a non-human mammal or human requiring treatment of the corresponding indication, by administration of a therapeutically active dose of a substituted indole compound according to the invention or of a medicinal product according to the invention.

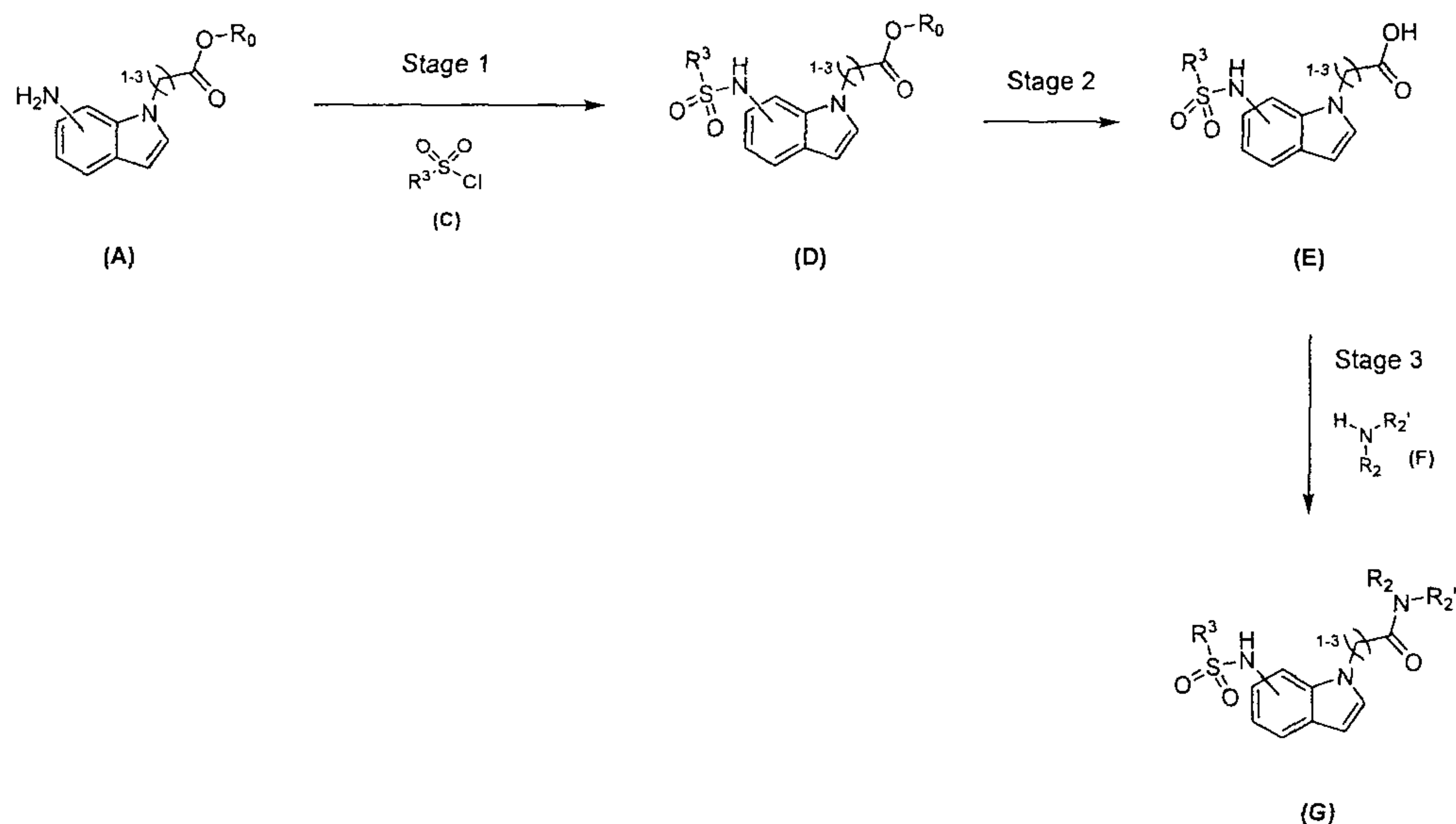
GRA3454-WO
22nd December 2009

The invention also provides a process for the treatment of pain, in particular one of the aforementioned forms of pain, in a non-human mammal or human requiring in particular treatment of pain, in particular of acute, visceral, neuropathic or chronic pain or inflammatory pain, by administration of a therapeutically active dose of a substituted indole compound according to the invention or of a medicinal product according to the invention.

The present invention also provides methods for preparing the substituted indole compounds according to the invention as listed in the description and in the examples.

GRA3454-WO
22nd December 2009

General method for preparing the indolamide derivative G



wherein $N(H)(R^2)(R^{2'})$ stands for $N(H)(R^8)-[CR^{9a}R^{9b}]_t-A(R^{10})(R^{11})$

Scheme 1: Synthesis of the indolamide derivative G

In stage 1 sulfonyl chlorides having the general formula (C), wherein R^3 has the meaning given above, in at least one solvent, preferably selected from the group consisting of dichloromethane, acetonitrile, dimethyl formamide, diethyl ether, dioxane, tetrahydrofuran, methanol, ethanol and isopropanol, are reacted with amino acid esters (A), in the presence of at least one inorganic base, preferably selected from the group consisting of potassium carbonate and caesium carbonate, or an organic base, preferably selected from the group consisting of triethylamine, diisopropylethylamine and pyridine, and optionally with addition of 4-(dimethylamino)pyridine or 1-hydroxybenzotriazole, at temperatures of preferably -15°C to 50°C , to form compounds having the general formula (D).

In stage 2 compounds having the general formula (D) in at least one solvent, preferably selected from the group consisting of water, methanol, ethanol, isopropanol, diethyl ether, tetrahydrofuran, toluene, acetonitrile, dimethyl formamide, dioxane and dimethyl sulfoxide, are reacted with an inorganic base, preferably selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium

GRA3454-WO
22nd December 2009

hydroxide, potassium tert-butanolate, lithium propanethiolate and sodium phenyl selenolate, optionally with addition of HMPA or lithium chloride, or with a Lewis acid, preferably selected from the group consisting of trimethylsilyl chloride, boron tribromide and aluminium trichloride, optionally with addition of thiolene, sodium iodide or lithium chloride, at temperatures of preferably 0°C to 100°C, to form compounds having the general formula (E).

In stage 3 compounds having the general formula (E) in at least one solvent, preferably selected from the group consisting of dichloromethane, acetonitrile, dimethyl formamide, diethyl ether, dioxane and tetrahydrofuran, are reacted with amines (F), with addition of at least one coupling reagent, preferably selected from the group consisting of carbonyl diimidazole (CDI), 2-chloro-1-methylpyridinium iodide (Mukaiyama reagent), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDCI), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU), *N,N'*-dicyclohexylcarbodiimide (DCC) and 1-benzotriazolyloxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), optionally in the presence of at least one inorganic base, preferably selected from the group consisting of potassium carbonate and caesium carbonate, or an organic base, preferably selected from the group consisting of triethylamine, diisopropylethylamine and pyridine, and optionally with addition of 4-(dimethylamino)pyridine or 1-hydroxybenzotriazole, to form compounds having the general formula (G).

GRA3454-WO
22nd December 2009

Pharmacological methods

1. Functional investigation on the bradykinin 1 receptor (B1R)

The agonistic or antagonistic action of substances can be determined on the bradykinin 1 receptor (B1R) of the human and rat species with the following assay. According to this assay, the Ca^{2+} inflow through the channel is quantified with the aid of a Ca^{2+} -sensitive dye (Fluo-4 type, Molecular Probes Europe BV, Leiden, Netherlands) in a fluorescent imaging plate reader (FLIPR, Molecular Devices, Sunnyvale, USA).

2. Method:

Chinese hamster ovary cells (CHO K1 cells) which are stably transfected with the human B1R gene (hB1R cells) or the B1R gene of the rat (rB1R cells) are used. For functional investigations these cells are plated-out onto black 96-well plates with a clear base (BD Biosciences, Heidelberg, Germany or Greiner, Frickenhausen, Germany) in a density of 20,000-35,000 cells/well. Overnight the cells are incubated at 37°C and 5% CO_2 in culture medium (hB1R cells: Ham's Nutrient Mixture F12, Gibco Invitrogen GmbH, Karlsruhe, Germany or DMEM, Sigma-Aldrich, Taufkirchen, Germany; rB1R cells: D-MEM/F12, Gibco Invitrogen, Karlsruhe, Germany) with 10 vol.% FBS (foetal bovine serum, Gibco Invitrogen GmbH, Karlsruhe, Germany or PAN Biotech GmbH, Aidenbach, Germany).

On the following day the cells are loaded with 2.13 μM Fluo-4 (Molecular Probes Europe BV, Leiden, Netherlands) in HBSS buffer (Hank's buffered saline solution, Gibco Invitrogen GmbH, Karlsruhe, Germany) with 2.5 mM probenecid (Sigma-Aldrich, Taufkirchen, Germany) and 10 mM HEPES (Sigma-Aldrich, Taufkirchen, Germany) for 60 min at 37°C. The plates are subsequently washed twice with HBSS buffer, and HBSS buffer which additionally contains 0.1% BSA (bovine serum albumin; Sigma-Aldrich, Taufkirchen, Germany), 5.6 mM glucose and 0.05% gelatine (Merck KGaA, Darmstadt, Germany) is added. After a further incubation of 20 minutes at room temperature, the plates are inserted into the FLIPR for Ca^{2+} measurement.

Alternatively they are washed with buffer A (15 mM HEPES, 80 mM NaCl, 5 mM KCl, 1.2 mM CaCl_2 , 0.7 mM MgSO_4 , 2g/l glucose, 2.5 mM probenecid) and loaded with

GRA3454-WO
22nd December 2009

buffer A with added 2.5 μM Fluo-4 and 0.025% Pluronic F127 (Sigma-Aldrich, Taufkirchen, Germany). The cells are then washed twice with buffer A and incubated for 30 minutes with buffer A, which additionally contains 0.05% BSA and 0.05% gelatine, at room temperature and then used for Ca^{2+} measurement in the FLIPR.

The Ca^{2+} -dependent fluorescence is measured here before and after addition of substances ($\lambda_{\text{ex}}=488\text{ nm}$, $\lambda_{\text{em}}=540\text{ nm}$). The quantification is performed by measuring the highest fluorescence intensity (FC, fluorescence counts) over time.

3. FLIPR assay:

The FLIPR protocol comprises two additions of substance. Test substances (10 μM) are first pipetted onto the cells and the Ca^{2+} inflow is compared with the control (hB1R: Lys-Des-Arg⁹ bradykinin $\geq 50\text{ nM}$; rB1R: Des-Arg⁹ bradykinin 10 μM). The value in % activation based on the Ca^{2+} signal after addition of Lys-Des-Arg⁹ bradykinin ($\geq 50\text{ nM}$) or Des-Arg⁹ bradykinin (10 μM) is obtained therefrom. After incubation for 10-20 minutes, Lys-Des-Arg⁹ bradykinin (hB1R) or Des-Arg⁹ bradykinin (rB1R) is applied in the EC_{80} concentration and the inflow of Ca^{2+} is likewise determined.

Antagonists lead to a suppression of the Ca^{2+} inflow. The % inhibition in comparison with the maximum achievable inhibition is calculated.

The substances are added in varying concentrations in order to determine the IC_{50} value. Double or triple determinations ($n=2$ or $n=3$) are performed and these are repeated in at least one further independent experiment ($N\geq 2$).

The compounds preferably exhibit a B1R antagonistic action on the human receptor and/or on the rat receptor.

The invention is described below by reference to examples, without limiting the general idea of the invention.

GRA3454-WO
22nd December 2009

Examples:

List of abbreviations:

DIPEA	diisopropylethylamine
EDCI	N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride
h	hour(s)
HOBt	1-hydroxy-1H-benzotriazole
conc.	concentrated
min	minute(s)
N	normal
RT	room temperature
THF	tetrahydrofuran
TFA	trifluoroacetic acid
abs.	absolute
eq.	equivalent(s)
equiv.	equivalent(s)
Boc	tert-butyl carbamate
DCM	dichloromethane
M	molar
EtOAc	ethyl acetate
Et ₃ N	triethylamine
Cbz	benzyl carbamate
DMF	dimethyl formamide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

GRA3454-WO
22nd December 2009

1) Synthesis of amino indole esters A:

Structural unit A-01: *tert*-Butyl 2-(7-amino-1H-indol-1-yl) acetate

Stage 1: *tert*-Butyl 2-(7-nitro-1H-indol-1-yl) acetate

7-Nitroindole (77 mmol, 1 equiv.) dissolved in dimethyl formamide (25 ml) was added slowly to a suspension of sodium hydride (85 mmol, 1.1 equiv.) in dimethyl formamide (75 ml) at 0°C, the reaction mixture obtained was stirred for 30 min, then *tert*-butyl bromoacetate (85 mmol, 1.1 equiv.) was added and the mixture was stirred for 12 h at room temperature.

The reaction mixture was processed by adding methanol, diluting with diethyl ether and washing 3 times with water. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The solid that accumulated was filtered off and washed with a little diethyl ether. The desired product was obtained in this way in a yield of 89% (75 mmol).

Stage 2: *tert*-Butyl 2-(7-amino-1H-indol-1-yl) acetate (A-01)

10% palladium on activated carbon (500 mg) was added to a solution of *tert*-butyl 2-(7-nitro-1H-indol-1-yl) acetate (68 mmol, 1 equiv.) in ethyl acetate/methanol (1:1) and the mixture obtained was hydrogenated under 2.5 bar hydrogen pressure for 12 h. The reaction mixture was processed by filtering over celite, rewashing with ethyl acetate, concentrating under reduced pressure and recrystallising from isopropanol. The desired product was obtained in a yield of 80% (54.4 mmol).

Structural unit A-02: *tert*-Butyl 2-(6-amino-1H-indol-1-yl) acetate

Stage 1: *tert*-Butyl 2-(6-nitro-1H-indol-1-yl) acetate

6-Nitroindole (77 mmol, 1 equiv.) dissolved in dimethyl formamide (25 ml) was added slowly to a suspension of sodium hydride (85 mmol, 1.1 equiv.) in dimethyl formamide (70 ml) at 0°C, the reaction mixture obtained was stirred for 30 min, then *tert*-butyl bromoacetate (85 mmol, 1.1 equiv.) was added and the mixture was stirred for 12 h at room temperature.

The reaction mixture was processed by adding methanol, diluting with diethyl ether and washing 3 times with water. The organic phase was dried over magnesium

GRA3454-WO
22nd December 2009

sulfate and concentrated under reduced pressure and recrystallised from diethyl ether. The desired product was obtained in this way in a yield of 69% (53 mmol).

Stage 2: *tert*-Butyl 2-(6-amino-1H-indol-1-yl) acetate (A-02)

10% palladium on activated carbon (500 mg) was added to a solution of *tert*-butyl 2-(6-nitro-1H-indol-1-yl) acetate (54 mmol, 1 equiv.) in ethyl acetate/methanol (3:1) and the mixture obtained was hydrogenated under 2.5 bar hydrogen pressure for 12 h. The reaction mixture was processed by filtering over celite, rewashing with ethyl acetate and concentrating under reduced pressure. The desired product was obtained in a quantitative yield.

Structural unit A-03: Methyl 3-(6-amino-1H-indol-1-yl) propanoate

Stage 1: Methyl 3-(6-nitro-1H-indol-1-yl) propanoate

1,8-Diazabicyclo[5.4.0]undec-7-ene (23 mmol, 0.5 equiv.) was added to a solution of 6-nitroindole (46 mmol, 1 equiv.) and methyl acrylate (69 mmol, 1.5 equiv.) in acetonitrile (25 ml) at 0°C and stirred for 12 h at room temperature. The reaction solution was concentrated under reduced pressure and the residue was purified by column chromatography (silica, ethyl acetate/hexane). The desired product was obtained in a yield of 80% (36.8 mmol).

Stage 2: Methyl 3-(6-amino-1H-indol-1-yl) propanoate (A-03)

10% palladium on activated carbon (500 mg) was added to a solution of methyl 3-(6-nitro-1H-indol-1-yl) propanoate (60 mmol, 1 equiv.) in ethyl acetate/methanol (3:1) and the mixture obtained was hydrogenated under 2.5 bar hydrogen pressure for 12 h. The reaction mixture was processed by filtering over celite, rewashing with ethyl acetate and concentrating under reduced pressure. The desired product was obtained in a quantitative yield.

GRA3454-WO
22nd December 2009

Structural unit A-04: Methyl 3-(7-amino-1H-indol-1-yl) propanoate

Stage 1: Methyl 3-(7-nitro-1H-indol-1-yl) propanoate

1,8-Diazabicyclo[5.4.0]undec-7-ene (31 mmol, 0.5 equiv.) was added to a solution of 7-nitroindole (62 mmol, 1 equiv.) and methyl acrylate (93 mmol, 1.5 equiv.) in acetonitrile (30 ml) at 0°C and stirred for 12 h at room temperature. The reaction solution was concentrated under reduced pressure and the residue was purified by column chromatography (silica, ethyl acetate/hexane). The desired product was obtained in a yield of 38% (23 mmol).

Stage 2: Methyl 3-(7-amino-1H-indol-1-yl) propanoate (A-04)

10% palladium on activated carbon (500 mg) was added to a solution of methyl 3-(7-nitro-1H-indol-1-yl) propanoate (43 mmol, 1 equiv.) in ethyl acetate/methanol (3:1) and the mixture obtained was hydrogenated under 2.5 bar hydrogen pressure for 12 h. The reaction mixture was processed by filtering over celite, washing with ethyl acetate and concentrating under reduced pressure. The desired product was obtained in a quantitative yield.

GRA3454-WO
22nd December 2009

2) Synthesis of sulfonyl chlorides C:

Sulfonyl chloride C-01: 2-(Trifluoromethyl)phenyl-1-sulfonyl chloride (CAS No: 776-04-5) is commercially available from e.g. ABCR. **Sulfonyl chloride C-02: 4-Chloro-2,5-dimethylphenyl-1-sulfonyl chloride** (CAS No: 88-49-3) is commercially available from e.g. ABCR.

Sulfonyl chloride C-03: 4-Methoxy-2,6-dimethylphenyl-1-sulfonyl chloride

Chlorosulfuric acid (1.83 ml, 2.3 equiv.) in dichloromethane (10 ml) was added dropwise to a solution of 3,5-dimethyl anisole (1.632 g, 11.982 mmol) in dichloromethane (15 ml) over 20 min at 0°C. The reaction mixture was then stirred for 10 min at room temperature. The reaction mixture was poured over iced water (3 ml, 5 equiv. relative to chlorosulfuric acid) and the aqueous phase was extracted with dichloromethane (3 x 100 ml). The organic phase was dried (Na₂SO₄) and concentrated to small volume under vacuum.

Yield: 2.6 g (92%)

Sulfonyl chloride C-04: Naphthalene-1-sulfonyl chloride (CAS No: 85-46-1) is commercially available from e.g. ABCR.

GRA3454-WO
22nd December 2009

3) Synthesis of sulfonylated indole esters D

General method for the synthesis of sulfonylated indole esters D

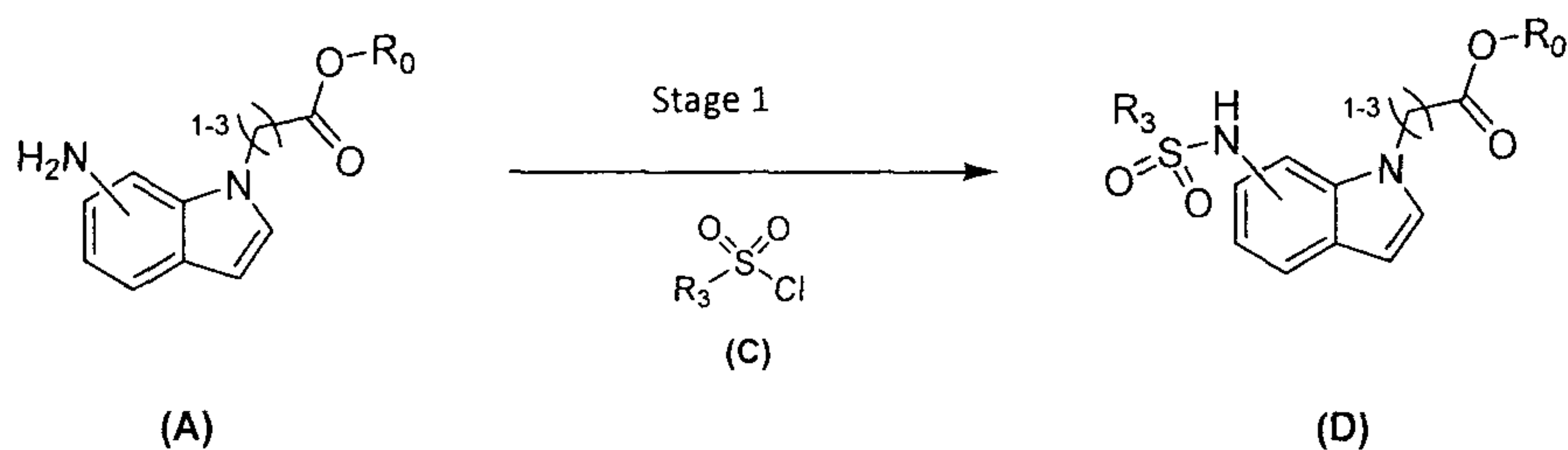
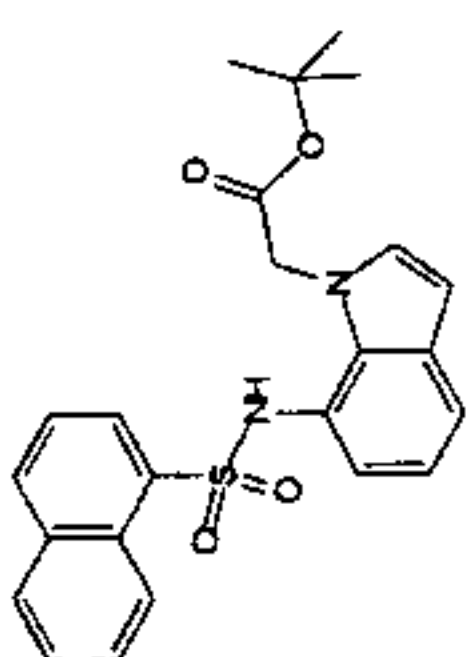
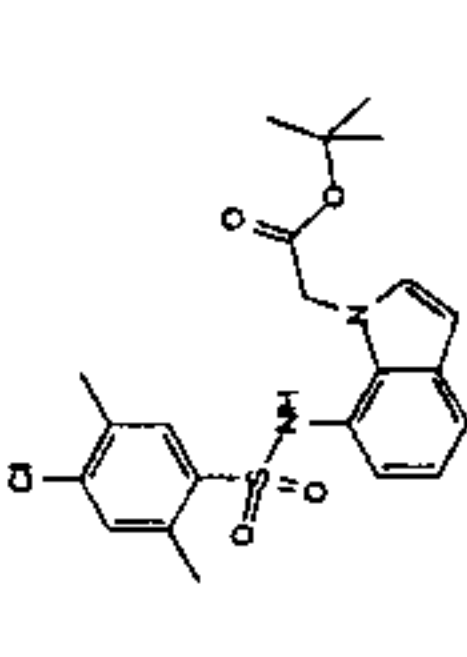
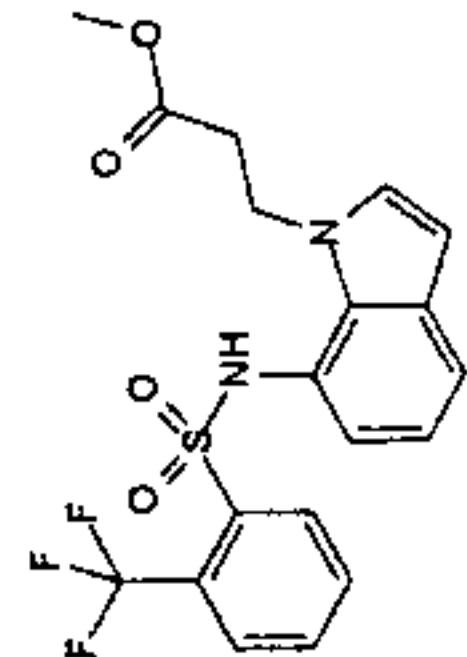
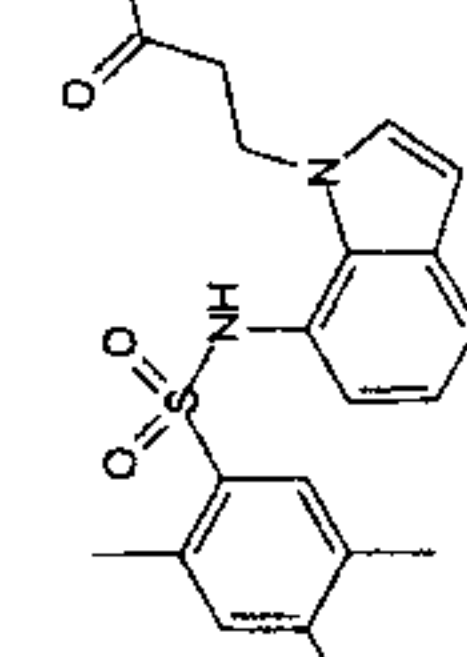
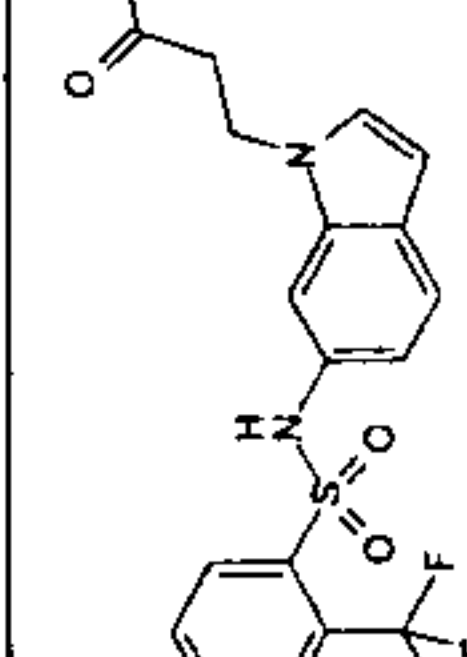
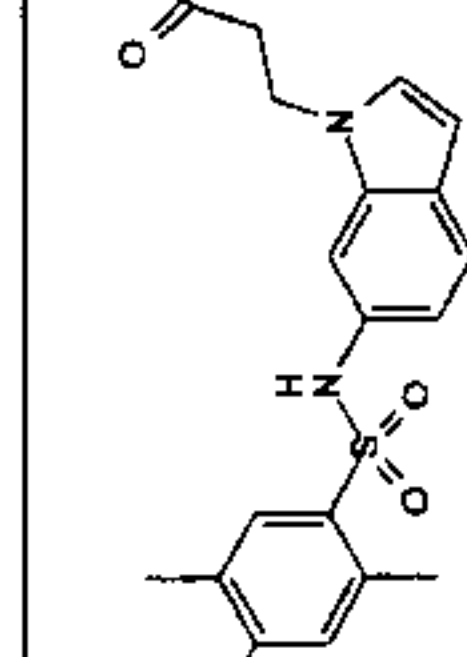


Figure 2: Synthesis of sulfonylated indole esters D

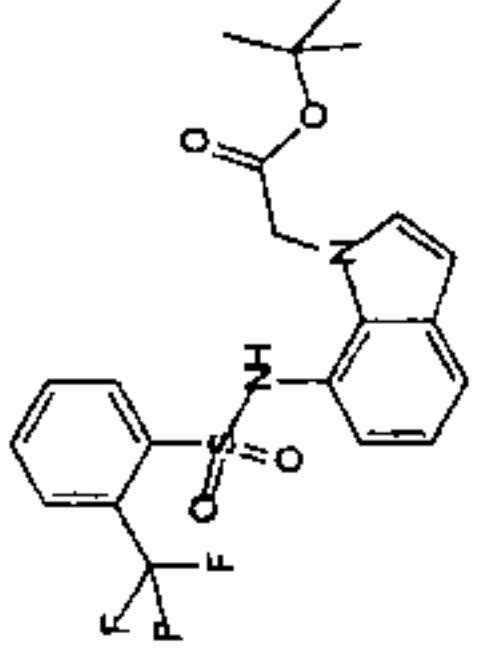
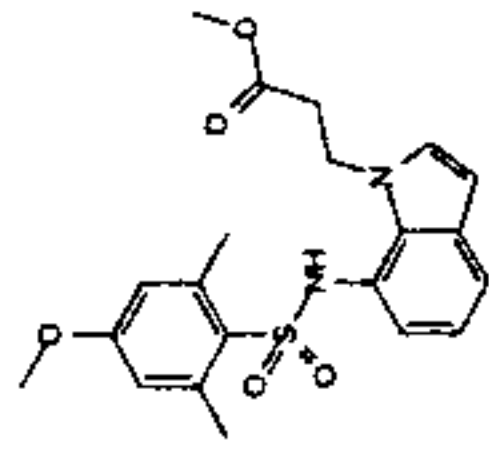
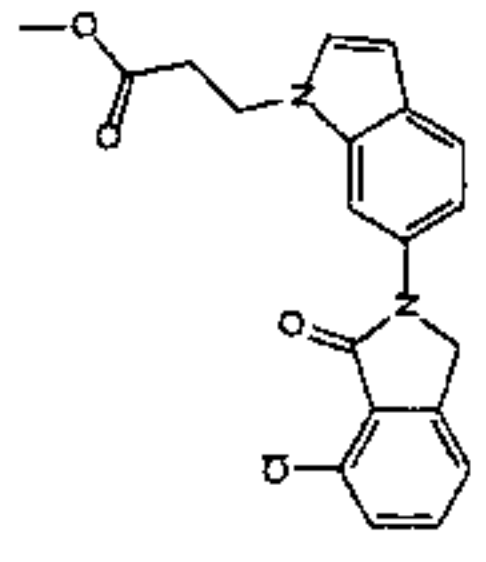
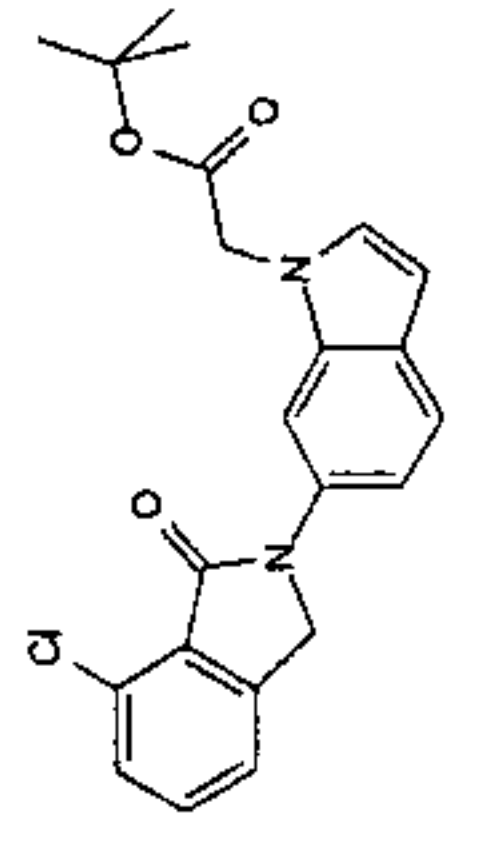
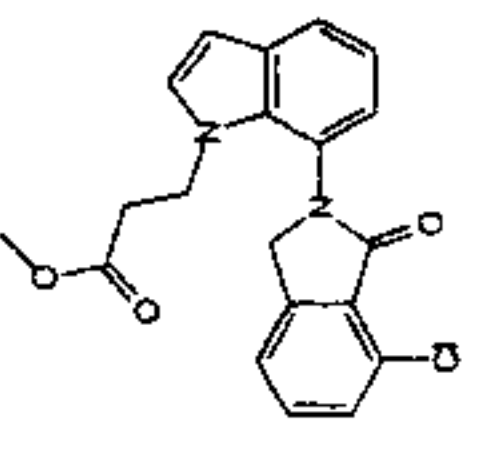
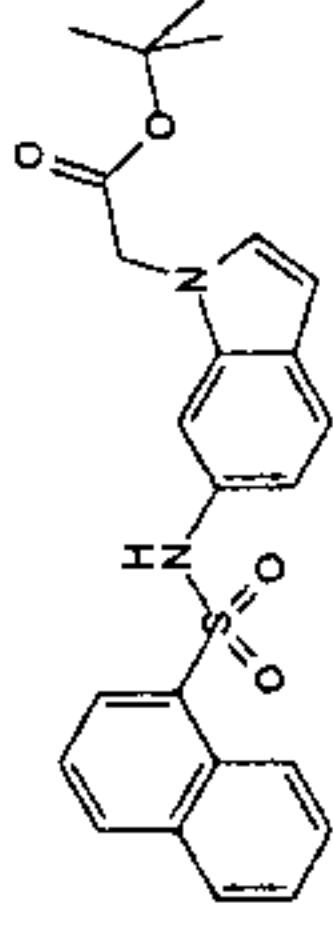
General procedure GP I – sulfonylation: A solution of sulfonyl chloride **C** (1.1 equiv.) in dichloromethane was added to a solution of the corresponding aminoindole ester **A** (1 equiv.) and diisopropyl ethylamine (1.25 equiv.) in dichloromethane at 0°C. The reaction mixture was stirred for 12 h at room temperature, then washed 3 times with a saturated sodium hydrogen carbonate solution, dried over magnesium sulfate and concentrated under reduced pressure. The desired product was obtained after purification by column chromatography (silica; ethyl acetate/hexane).

Ester no.	Structure	Name	Amino acid ester (A)	Carboxylic acid chloride (B) or sulfonyl chloride (C)	Synthesis by	Yield	Note
D-02		<i>tert</i> -Butyl 2-(7-(4-methoxy-2,6-dimethylphenyl)sulfonamido)-1H-indol-1-yl) acetic acid (D-02)	<i>tert</i> -Butyl 2-(7-amino-1H-indol-1-yl) acetic acid (A-01)	4-Methoxy-2,6-dimethylphenyl-1-sulfonyl chloride (C-03)	GP I	62% (12.0 mmol)	
D-03		<i>tert</i> -Butyl 2-(6-(4-methoxy-2,6-dimethylphenyl)sulfonamido)-1H-indol-1-yl) acetic acid (D-03)	<i>tert</i> -Butyl 2-(6-amino-1H-indol-1-yl) acetic acid (A-02)	4-Methoxy-2,6-dimethylphenyl-1-sulfonyl chloride (C-03)	GP I	53% (10.3 mmol)	
D-04		<i>tert</i> -Butyl 2-(6-(4-chloro-2,5-dimethylphenyl)sulfonamido)-1H-indol-1-yl) acetic acid (D-04)	<i>tert</i> -Butyl 2-(6-amino-1H-indol-1-yl) acetic acid (A-02)	4-Chloro-2,5-dimethylphenyl-1-sulfonyl chloride (C-02)	GP I	62% (17.7 mmol)	
D-05		Methyl 3-(6-(4-methoxy-2,6-dimethylphenyl)sulfonamido)-1H-indol-1-yl) propionic acid (D-05)	Methyl 3-(6-amino-1H-indol-1-yl) propionic acid (A-03)	4-Methoxy-2,6-dimethylphenyl-1-sulfonyl chloride (C-03)	GP I	69% (17.4 mmol)	
D-06		<i>tert</i> -Butyl 2-(6-(2-(trifluoromethyl)phenyl)sulfonamido)-1H-indol-1-yl) acetic acid (D-06)	<i>tert</i> -Butyl 2-(6-amino-1H-indol-1-yl) acetic acid (A-02)	2-(Trifluoromethyl)phenyl-1-sulfonyl chloride (C-01)	GP I	92% (16.9 mmol)	

GRA3454-WO
22nd December 2009

D-07		<i>tert</i> -Butyl 2-(7-(naphthalene-1-sulfonamido)-1H-indol-1-yl) acetic acid (D-07)	<i>tert</i> -Butyl 2-(7-amino-1H-indol-1-yl) acetic acid (A-01)	Naphthalene-1-sulfonyl chloride (C-04)	GP I	43% (7.8 mmol)	(a1)
D-08		<i>tert</i> -Butyl 2-(7-(4-chloro-2,5-dimethylphenylsulfonamido)-1H-indol-1-yl) acetic acid (D-08)	<i>tert</i> -Butyl 2-(7-amino-1H-indol-1-yl) acetic acid (A-01)	4-Chloro-2,5-dimethylphenyl-1-sulfonyl chloride (C-02)	GP I	52% (14.7 mmol)	
D-09		Methyl 3-(7-(2-(trifluoromethyl)phenylsulfonamido)-1H-indol-1-yl) propionic acid (D-09)	Methyl 3-(7-amino-1H-indol-1-yl) propionic acid (A-04)	2-(Trifluoromethyl)phenyl-1-sulfonyl chloride (C-01)	GP I	48% (10.1 mmol)	
D-10		Methyl 3-(7-(4-chloro-2,5-dimethylphenylsulfonamido)-1H-indol-1-yl) propionic acid (D-10)	Methyl 3-(7-amino-1H-indol-1-yl) propionic acid (A-04)	4-Chloro-2,5-dimethylphenyl-1-sulfonyl chloride (C-02)	GP I	49% (9.5 mmol)	
D-11		Methyl 3-(6-(2-(trifluoromethyl)phenylsulfonamido)-1H-indol-1-yl) propionic acid (D-11)	Methyl 3-(6-amino-1H-indol-1-yl) propionic acid (A-03)	2-(Trifluoromethyl)phenyl-1-sulfonyl chloride (C-01)	GP I	60% (13.7 mmol)	
D-12		Methyl 3-(6-(4-chloro-2,5-dimethylphenylsulfonamido)-1H-indol-1-yl) propionic acid (D-12)	Methyl 3-(6-amino-1H-indol-1-yl) propionic acid (A-03)	4-Chloro-2,5-dimethylphenyl-1-sulfonyl chloride (C-02)	GP I	84% (21.3 mmol)	

GRA3454-WO
22nd December 2009

D-13		<i>tert</i> -Butyl 2-(7-(2-(trifluoromethyl)phenylsulfonamido)-1H-indol-1-yl) acetic acid (D-13)	<i>tert</i> -Butyl 2-(7-amino-1H-indol-1-yl) acetic acid (A-01)	2-(Trifluoromethyl)phenyl-1-sulfonyl chloride (C-01)	GP I	42% (8.5 mmol)	
D-14		Methyl 3-(7-(4-methoxy-2,6-dimethylphenylsulfonamido)-1H-indol-1-yl) propionic acid (D-14)	Methyl 3-(7-amino-1H-indol-1-yl) propionic acid (A-04)	4-Methoxy-2,6-dimethylphenyl-1-sulfonyl chloride (C-03)	GP I	17% (4.3 mmol)	
D-15		Methyl 3-(6-(7-chloro-1-oxoisindolin-2-yl)-1H-indol-1-yl) propionic acid (D-15)					See E-15
D-16		<i>tert</i> -Butyl 2-(6-(7-chloro-1-oxoisindolin-2-yl)-1H-indol-1-yl) acetic acid (D-16)					See E-16
D-17		Methyl 3-(7-(7-chloro-1-oxoisindolin-2-yl)-1H-indol-1-yl) propionic acid (D-17)					See E-17
D-18		<i>tert</i> -Butyl 2-(6-(naphthalene-1-sulfonamido)-1H-indol-1-yl) acetic acid (D-18)	<i>tert</i> -Butyl 2-(6-amino-1H-indol-1-yl) acetic acid (A-02)	Naphthalene-1-sulfonyl chloride (C-04)	GP I	71% (13.0 mmol)	

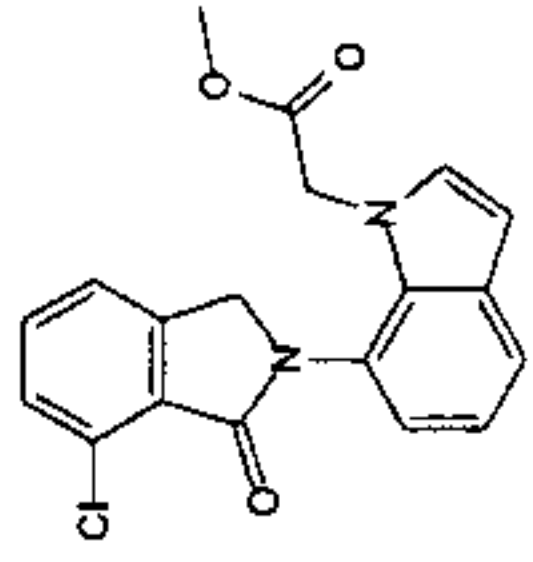
D-19		Methyl 2-(7-(7-chloro-1-oxoisindolin-2-yl)-1H-indol-1-yl) acetic acid (D-19)						See E-19
------	---	--	--	--	--	--	--	----------

Table 1: Synthesis of sulfonylated indole esters D

(a1) The crude product was taken up in 70 ml dichloromethane. A solid was precipitated which was siphoned off and washed with a little dichloromethane. The parent liquor was concentrated and purified by column chromatography.

GRA3454-WO
22nd December 2009

4) Synthesis of sulfonylated indole acids E

General method for the synthesis of sulfonylated indole acids E

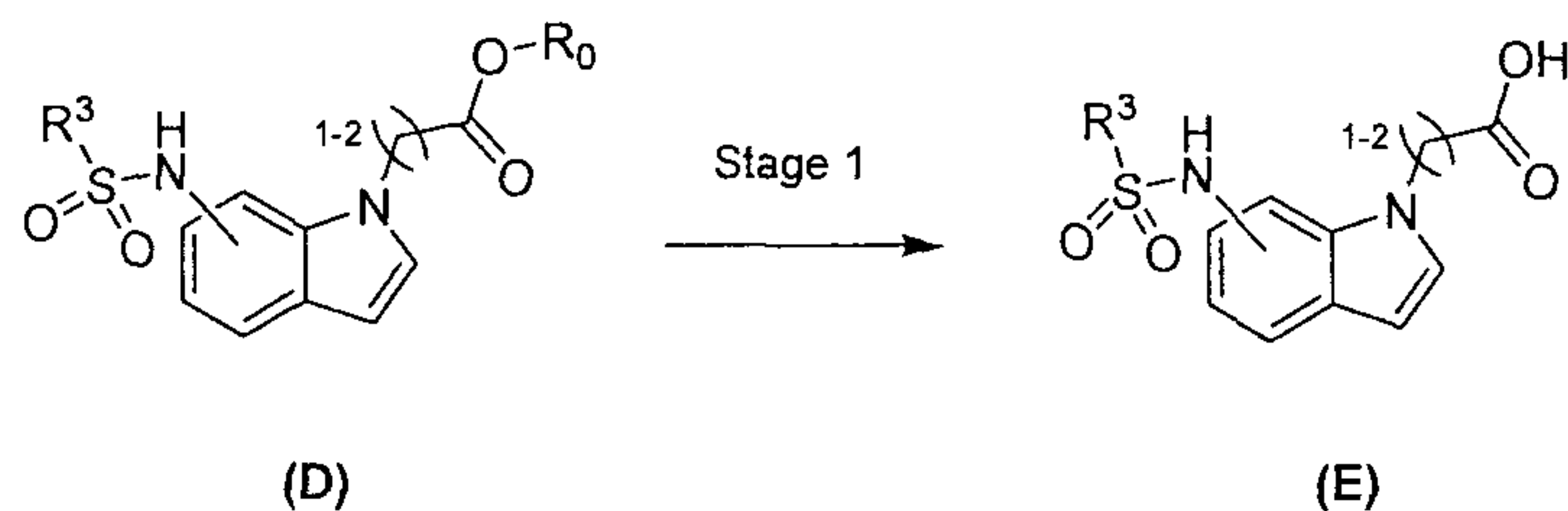
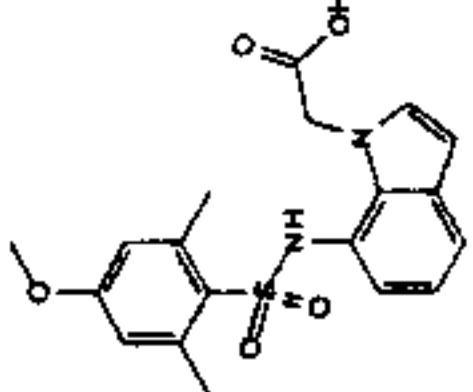
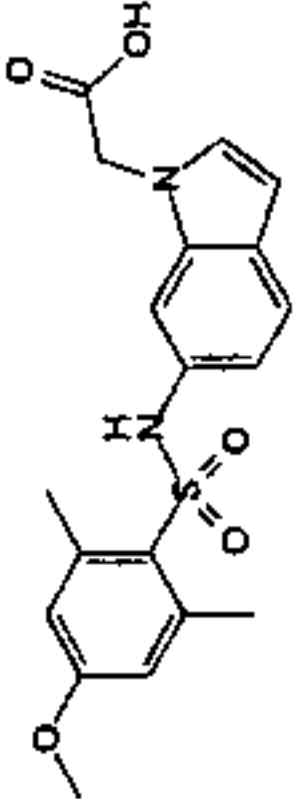
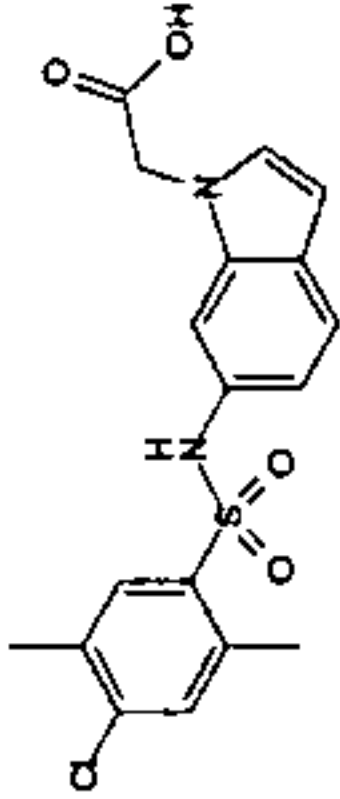
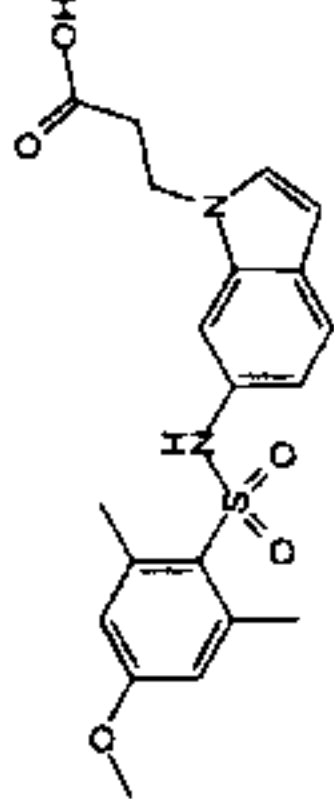
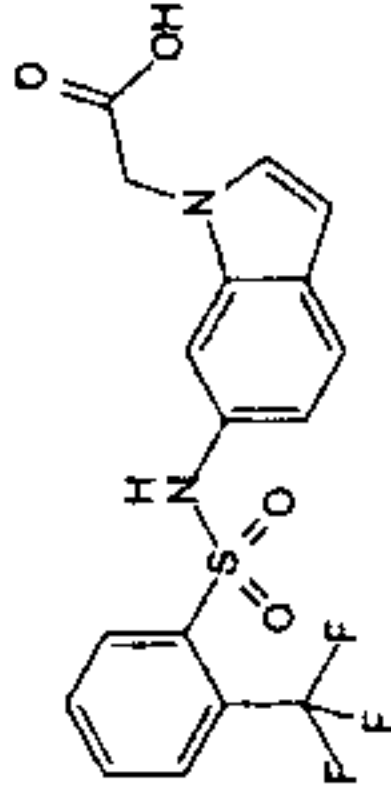


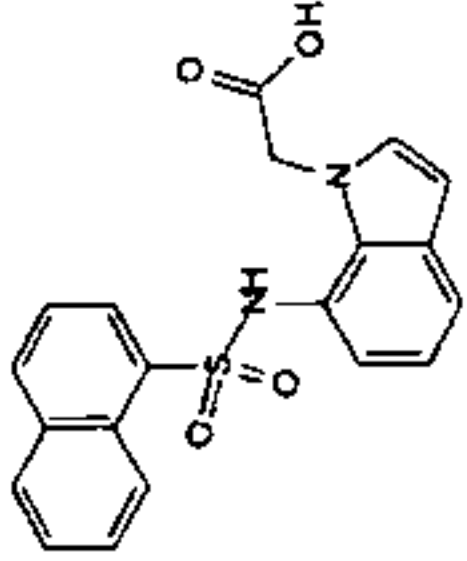
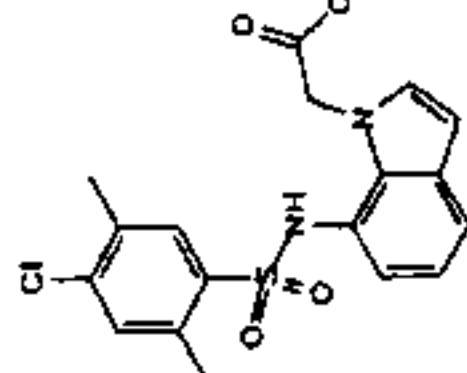
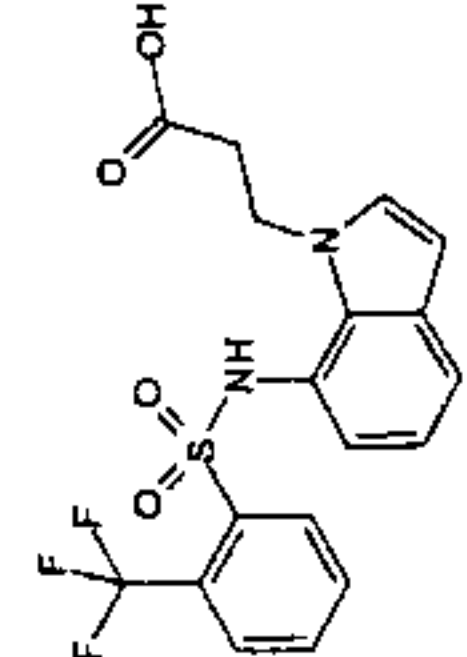
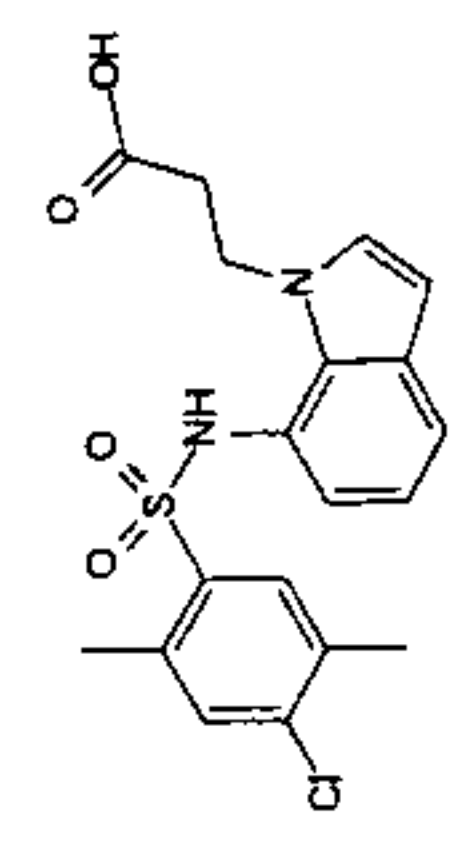
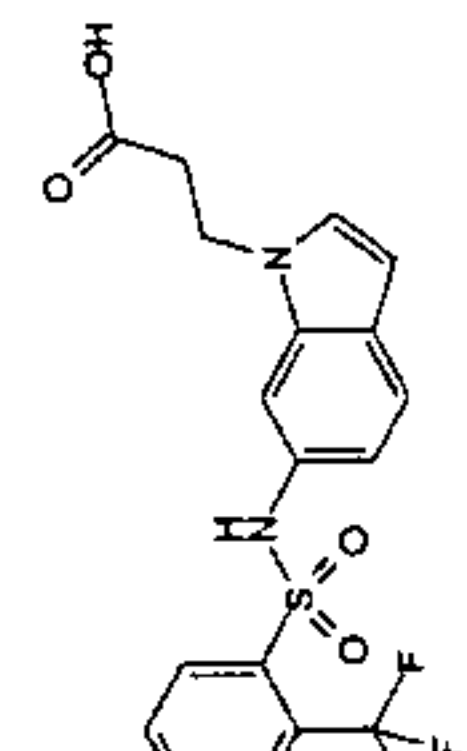
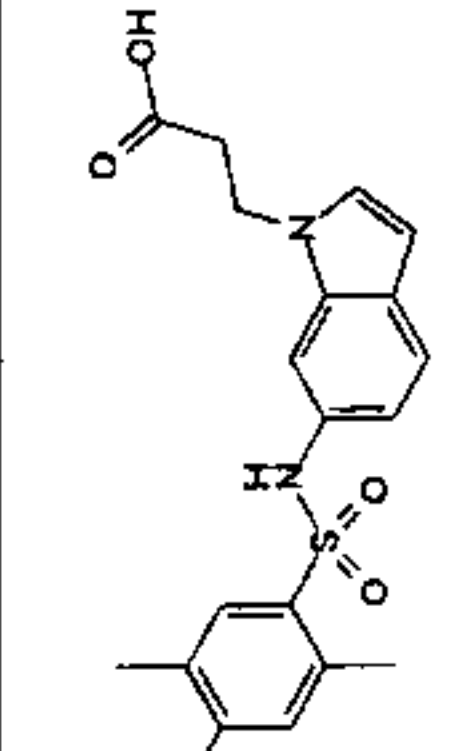
Figure 1: Synthesis of sulfonylated indole acids E

General procedure GP III: Potassium hydroxide (5 to 9 equiv.) and water were added to a solution of ester **D** (1 equiv.) in methanol/tetrahydrofuran with ice cooling. The mixture was stirred at room temperature for 5 hours, diluted with water, washed 3 times with diethyl ether and adjusted to ~ pH 4 with 6N hydrochloric acid. The solid that was precipitated was filtered off, washed with a little water and dried.

GRA3454-WO
22nd December 2009

Amino acid no.	Structure	Name	Amino acid ester (D)	Synthesis by	Yield	Note
E-02		2-[7-[[[(4-Methoxy-2,6-dimethylphenyl)sulfonyl]amino]-1H-indol-1-yl]] acetic acid (E-02)	<i>tert</i> -Butyl 2-(7-(4-methoxy-2,6-dimethylphenylsulfonamido)-1H-indol-1-yl) acetic acid (D-02)	GP III	95% (11.3 mmol)	
E-03		2-[6-[[[(4-Methoxy-2,6-dimethylphenyl)sulfonyl]amino]-1H-indol-1-yl]] acetic acid (E-03)	<i>tert</i> -Butyl 2-(6-(4-methoxy-2,6-dimethylphenylsulfonamido)-1H-indol-1-yl) acetic acid (D-03)	GP III	96% (9.9 mmol)	
E-04		2-[6-[[[(4-Chloro-2,5-dimethylphenyl)sulfonyl]amino]-1H-indol-1-yl]] acetic acid (E-04)	<i>tert</i> -Butyl 2-(6-(4-chloro-2,5-dimethylphenylsulfonamido)-1H-indol-1-yl) acetic acid (D-04)	GP III	98% (17.4 mmol)	
E-05		3-[6-[[[(4-Methoxy-2,6-dimethylphenyl)sulfonyl]amino]-1H-indol-1-yl]] propionic acid (E-05)	Methyl 3-(6-(4-methoxy-2,6-dimethylphenylsulfonamido)-1H-indol-1-yl) propionic acid (D-05)	GP III	96% (16.3 mmol)	
E-06		2-[6-[[[2-(Trifluoromethyl)phenyl]sulfonyl]amino]-1H-indol-1-yl]] acetic acid (E-06)	<i>tert</i> -Butyl 2-(6-(2-(trifluoromethyl)phenylsulfonamido)-1H-indol-1-yl) acetic acid (D-06)	GP III	107% (18.0 mmol)	(a2)

GRA3454-WO
22nd December 2009

E-07		2-[7-[(Naphthalen-1-ylsulfonyl)amino]-1H-indol-1-yl]acetic acid (E-07)	<i>tert</i> -Butyl 2-(7-(naphthalene-1-sulfonamido)-1H-indol-1-yl)acetic acid (D-07)	GP III	110% (8.3 mmol)	(a2)
E-08		2-[7-[(4-Chloro-2,5-dimethylphenyl)sulfonylamino]-1H-indol-1-yl]acetic acid (E-08)	<i>tert</i> -Butyl 2-(7-(4-chloro-2,5-dimethylphenylsulfonamido)-1H-indol-1-yl)acetic acid (D-08)	GP III	104% (15.3 mmol)	
E-09		3-[7-[[[2-(Trifluoromethyl)phenyl]sulfonylamino]-1H-indol-1-yl]propionic acid (E-09)	Methyl 3-(7-(2-(trifluoromethyl)phenylsulfonamido)-1H-indol-1-yl)propionic acid (D-09)	GP III	97% (9.3 mmol)	
E-10		3-[7-[[[4-Chloro-2,5-dimethylphenyl]sulfonylamino]-1H-indol-1-yl]propionic acid (E-10)	Methyl 3-(7-(4-chloro-2,5-dimethylphenylsulfonamido)-1H-indol-1-yl)propionic acid (D-10)	GP III	101% (9.0 mmol)	
E-11		3-[6-[[[2-(Trifluoromethyl)phenyl]sulfonylamino]-1H-indol-1-yl]propionic acid (E-11)	Methyl 3-(6-(2-(trifluoromethyl)phenylsulfonamido)-1H-indol-1-yl)propionic acid (D-11)	GP III	105% (14.3 mmol)	(a2)
E-12		3-[6-[[[4-Chloro-2,5-dimethylphenyl]sulfonylamino]-1H-indol-1-yl]propionic acid (E-12)	Methyl 3-(6-(4-chloro-2,5-dimethylphenylsulfonamido)-1H-indol-1-yl)propionic acid (D-12)	GP III	96% (20.4 mmol)	(a2)

GRA3454-WO
22nd December 2009

E-13		2-[[[2-(Trifluoromethyl)phenyl]sulfonyl]amino]-1H-indol-1-yl]acetic acid (E-13)	<i>tert</i> -Butyl 2-(7-(2-(trifluoromethyl)phenyl)sulfonamido)-1H-indol-1-yl]acetic acid (D-13)	GP III	96% (8.1 mmol)	(a2)
E-14		3-[7-[[4-Methoxy-2,6-dimethylphenyl]sulfonyl]amino]-1H-indol-1-yl]propionic acid (E-14)	Methyl 3-(7-(4-methoxy-2,6-dimethylphenyl)sulfonamido)-1H-indol-1-yl]propionic acid (D-14)	GP III	88% (5.0 mmol)	
E-15		3-[6-(4-Chloro-3-oxo-1,2-dihydroisoindol-2-yl)-1H-indol-1-yl]propionic acid (E-15)				See E-15
E-16		2-[6-(4-Chloro-3-oxo-1,2-dihydroisoindol-2-yl)-1H-indol-1-yl]acetic acid (E-16)				See E-16
E-17		3-[7-(4-Chloro-3-oxo-1,2-dihydroisoindol-2-yl)-1H-indol-1-yl]propionic acid (E-17)				See E-17
E-18		2-[6-[[Naphthalen-1-ylsulfonyl]amino]-1H-indol-1-yl]acetic acid (E-18)	<i>tert</i> -Butyl 2-(6-(naphthalen-1-sulfonamido)-1H-indol-1-yl]acetic acid (D-18)	GP III	92% (11.8 mmol)	

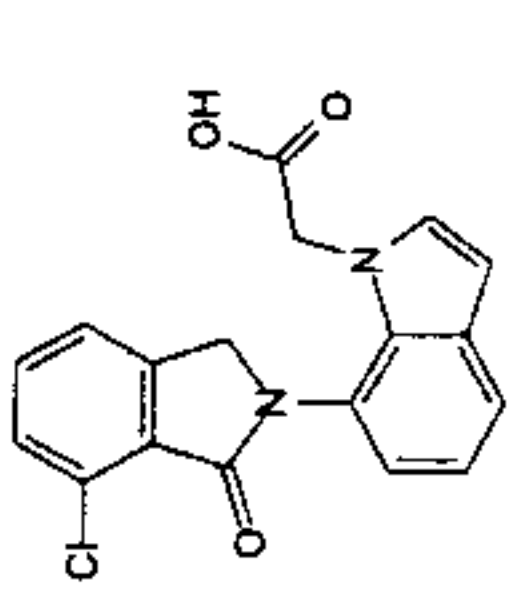
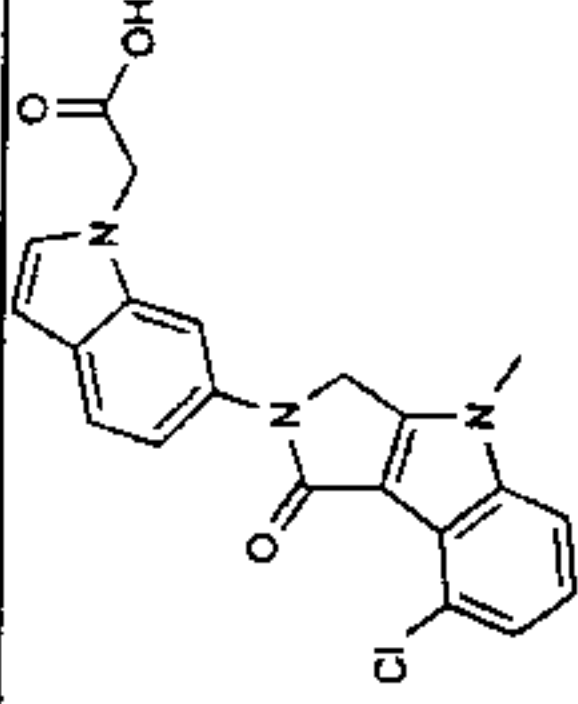
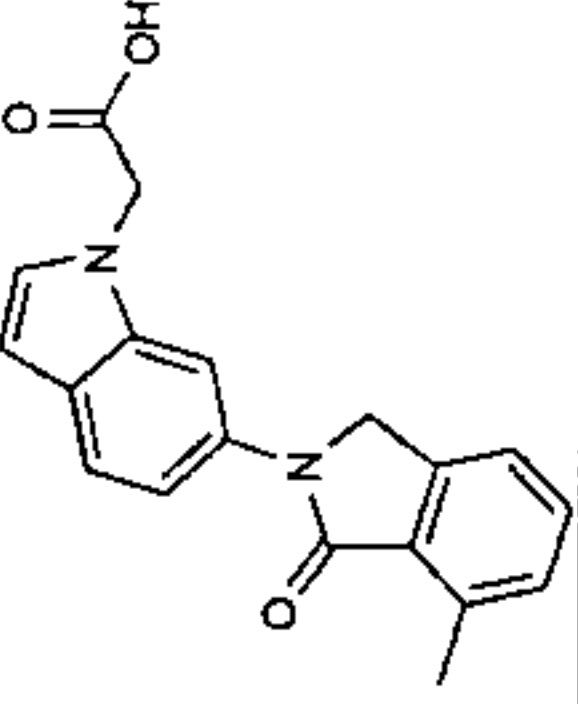
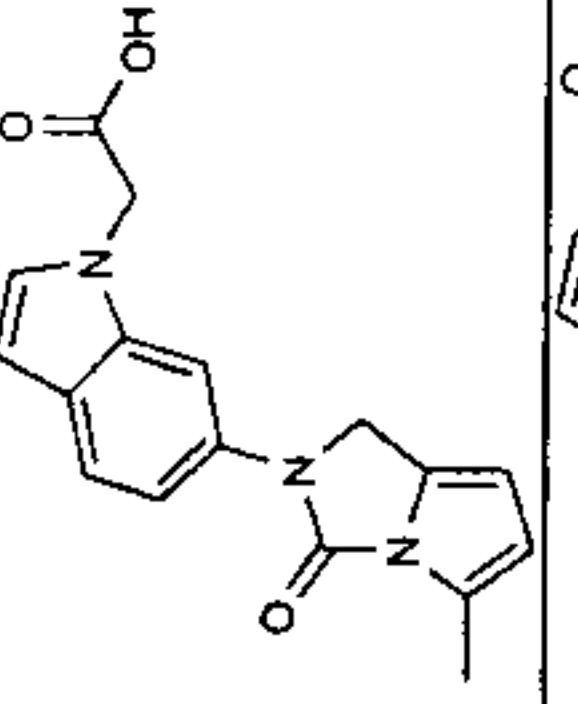
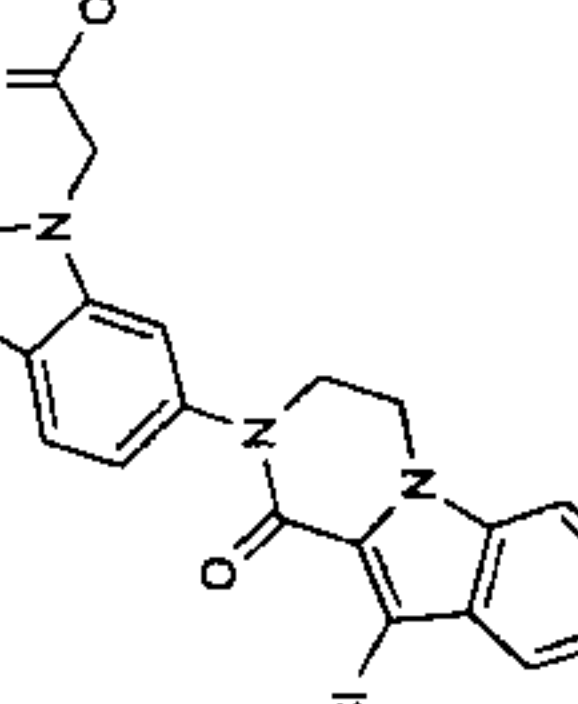
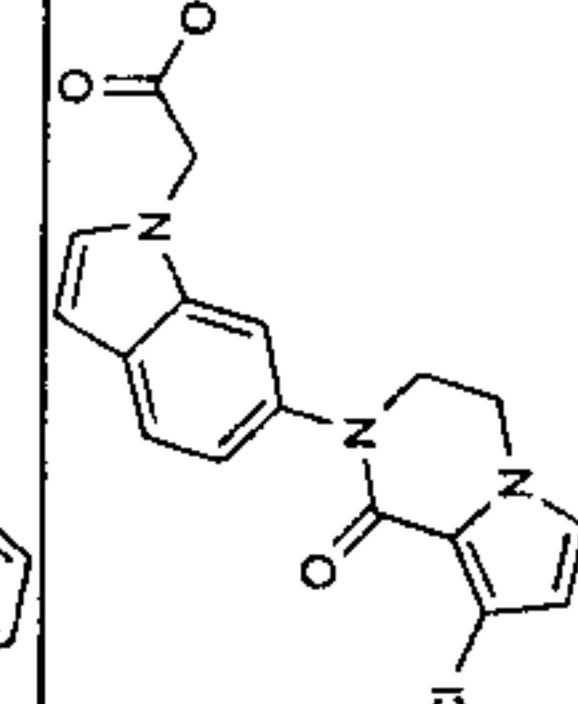
E-19		2-[7-(4-Chloro-3-oxo-1,2-dihydroisoindol-2-yl)-1H-indol-1-yl]acetic acid (E-19)					See E-19
E-20		2-(6-(8-Chloro-4-methyl-1-oxopyrrolo[3,4-b]indol-2(1H,3H,4H)-yl)-1H-indol-1-yl)acetic acid (E-20)					See E-20
E-21		2-(6-(7-Methyl-1-oxoisindolin-2-yl)-1H-indol-1-yl)acetic acid (E-21)					See E-21
E-22		2-(6-(5-Methyl-3-oxo-1H-pyrrolo-[1,2-c]imidazol-2(3H)-yl)-1H-indol-1-yl)acetic acid (E-22)					See E-22
E-23		2-(6-(10-Chloro-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1H-indol-1-yl)acetic acid (E-23)					See E-23
E-24		2-(6-(8-Chloro-1-oxo-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-1H-indol-1-yl)acetic acid (E-24)					See E-24

Table 2: Synthesis of sulfonylated indole acids E

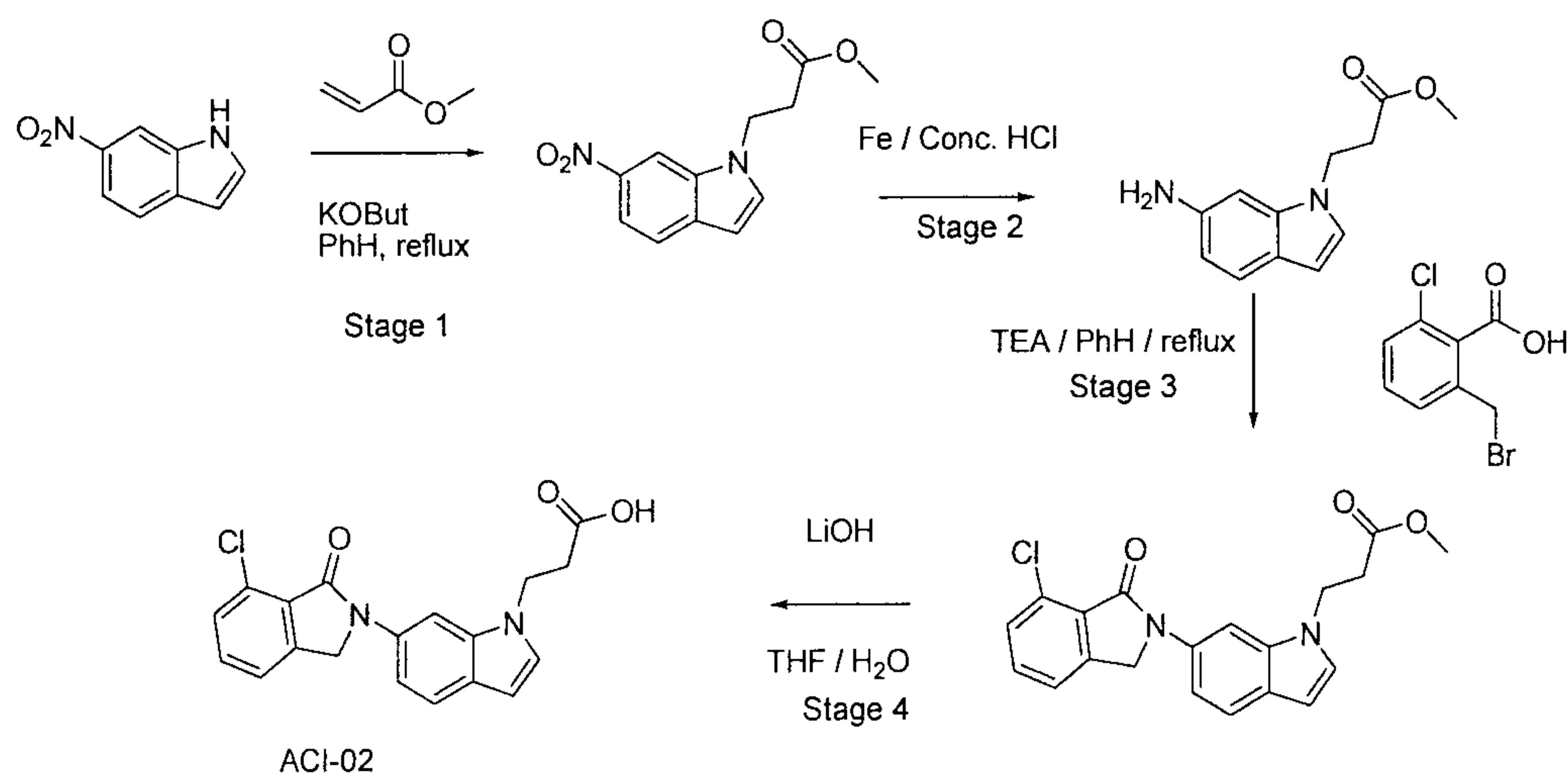
GRA3454-WO
22nd December 2009

(a2) After adjusting to pH 4 a brown oil was precipitated which was extracted 3 times with ethyl acetate. The organic phases were combined, dried over magnesium sulfate and concentrated under reduced pressure.

GRA3454-WO
22nd December 2009

Structural unit E-15: 3-(6-(7-Chloro-1-oxoisindolin-2-yl)-1H-indol-1-yl)

propionic acid



Stage 1: A solution of 6-nitroindole (3 mmol) in dry benzene (15 ml) was added slowly to a solution of potassium tert-butanolate (1 eq.) in dry benzene (5 ml) in an ice bath under a nitrogen atmosphere. Then methyl acrylate (2 eq.) was added and the batch was refluxed for 16 h. After cooling to room temperature the reaction mixture was diluted with water and adjusted to pH 4 with concentrated HCl. The reaction mixture was extracted with dichloromethane. The organic phase was washed successively with water and saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated to small volume under reduced pressure. The crude product was purified by column chromatography with silica gel (DCM/MeOH) and the desired first-stage product was obtained. Yield: 53%

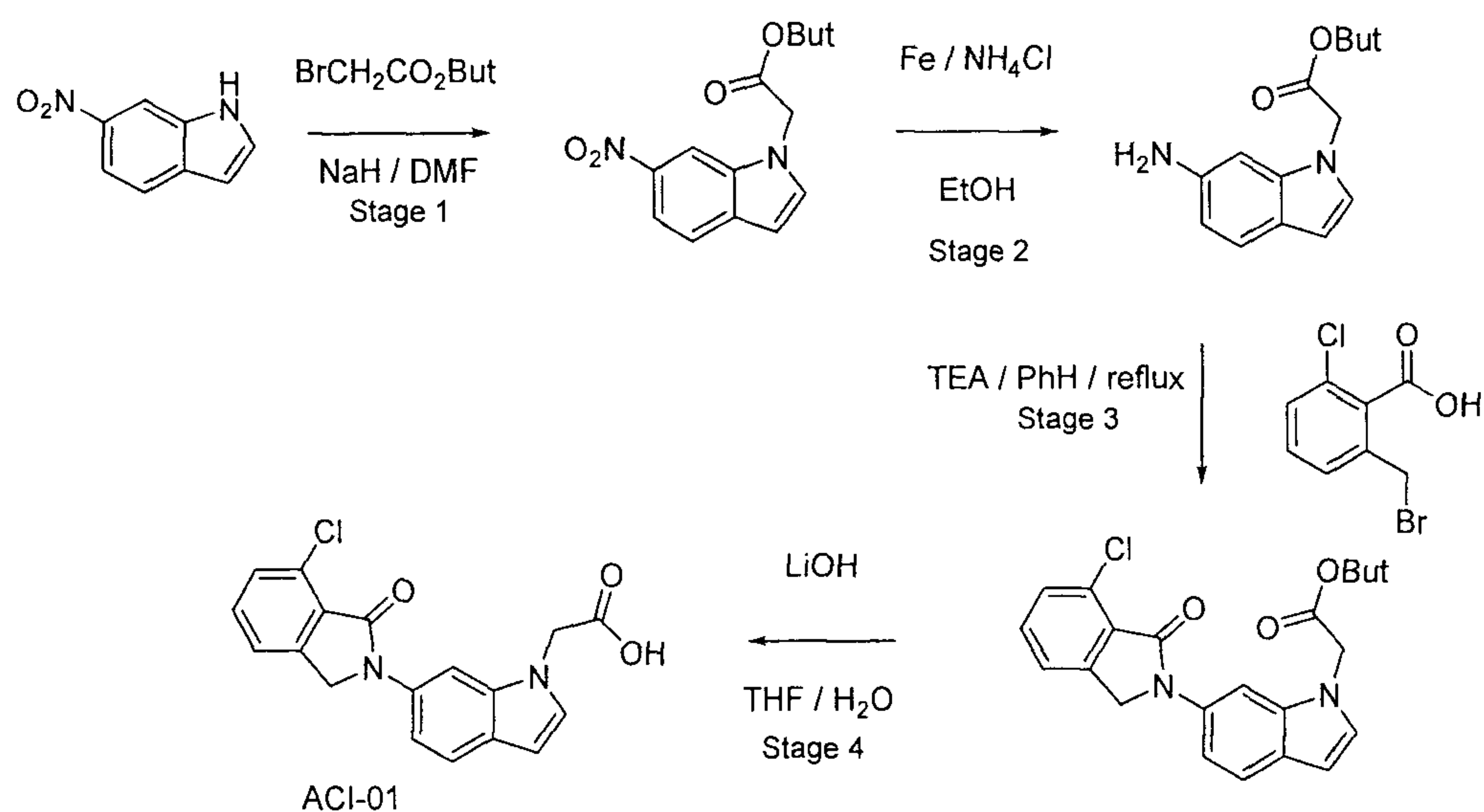
Stage 2: A mixture of the first-stage product (0.9 mmol), iron powder (3.3 eq.) and concentrated HCl (0.1 ml) was refluxed in ethanol (5 ml) for 4 h. After cooling to RT it was filtered through celite. The filtrate was concentrated to small volume, the concentrated mass was taken up with water and adjusted to pH 4 with concentrated HCl. The mixture was extracted with dichloromethane. The organic phase was washed successively with water and saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated to small volume under reduced pressure. The crude product obtained was used directly in the next stage. Yield: 90%

GRA3454-WO
22nd December 2009

Stage 3: A mixture of the second-stage product (0.45 mmol), 2-bromomethyl-6-chlorobenzoate (1 eq.) and TEA (1.2 eq.) was refluxed in benzene (10 ml) under a nitrogen atmosphere for 16 h. The reaction mixture was concentrated to small volume and the concentrated mass was taken up with DCM. The organic phase was washed successively with water and saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated to small volume under reduced pressure. The crude product was purified by column chromatography with silica gel (DCM/MeOH) and the desired third-stage product was obtained. Yield: 48.5%

Stage 4: LiOH.H₂O (5 eq.) was added to a suspension of the third-stage product (0.5 mmol) in methanol (40 ml), tetrahydrofuran (40 ml) and water (30 ml) and the reaction mixture was stirred overnight at 25°C. Methanol and THF were drawn off completely. The aqueous phase was acidified with 1(N) HCl and then filtered. The white solid was stirred for 1 h in a mixture of 350 ml acetone and 50 ml methanol. After filtration the white solid was dried under reduced pressure and the desired pure product **E-15** was obtained. Yield: 61%

Structural unit E-16: 2-(6-(7-Chloro-1-oxoisindolin-2-yl)-1H-indol-1-yl) acetic acid



GRA3454-WO
22nd December 2009

Stage 1: 6-Nitroindole (3 mmol) dissolved in DMF (5 ml) was added to a suspension of sodium hydride (1.5 eq.) in DMF (5 ml) at 0°C and stirred for 30 min. Then *tert*-butyl-bromoacetate (1.2 eq.) was added and the mixture was stirred at RT for 15 h. The batch was quenched with saturated NH₄Cl solution and extracted with ethyl acetate. The organic phase was washed successively with water and saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated to small volume under reduced pressure. The crude product was purified by column chromatography with silica gel (ethyl acetate/hexane) and the desired first-stage product was obtained. Yield: 47%

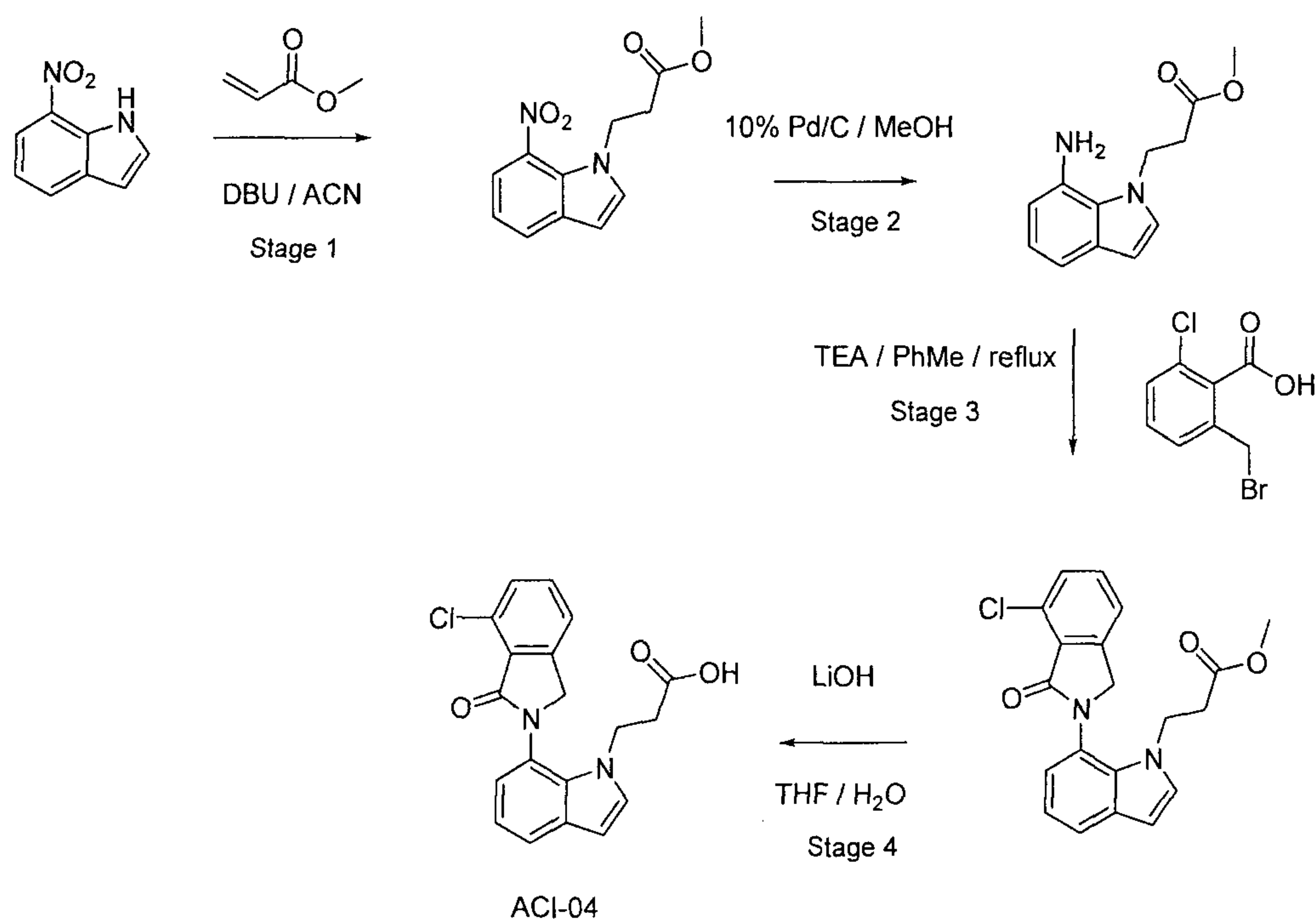
Stage 2: A mixture of the first-stage product (1.44 mmol), iron powder (4 eq.) and ammonium chloride (0.4 eq.) was refluxed in ethanol (10 ml) for 4 h. After cooling to RT it was filtered through celite. The filtrate was concentrated to small volume and the concentrated mass was taken up with water. It was extracted with dichloromethane. The organic phase was washed successively with water and saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated to small volume under reduced pressure. The crude product was purified by recrystallisation with ethyl acetate/hexane. Yield: 61%

Stage 3: A mixture of the second-stage product (25 mmol), 2-bromomethyl-6-chlorobenzoate (1.2 eq.) and TEA (1.2 eq.) was refluxed in benzene (150 ml) under a nitrogen atmosphere for 16 h. The reaction mixture was concentrated to small volume and the concentrated mass was taken up with DCM. The organic phase was washed successively with water and saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated to small volume under reduced pressure. The crude product was purified by column chromatography with silica gel (DCM/MeOH) and the desired third-stage product was obtained. Yield: 42%

Stage 4: LiOH.H₂O (5 eq.) was added to a suspension of the third-stage product (15 mmol) in methanol (25 ml), tetrahydrofuran (25 ml) and water (50 ml) and the reaction mixture was stirred overnight at 25°C. Methanol and THF were drawn off completely. The aqueous phase was acidified with 1(N) HCl and then filtered. The white solid was dried under reduced pressure and the desired product **E-16** was obtained. Yield: 98%

GRA3454-WO
22nd December 2009

**Structural unit E-17: 3-(7-(7-Chloro-1-oxoisindolin-2-yl)-1H-indol-1-yl)
propionic acid**



Stage 1: The DBU was added slowly to a solution of 7-nitroindole (6 mmol) in acetonitrile (10 ml) at 0°C. The solution was stirred for 20 h at RT. Then the reaction mixture was concentrated and the crude mass was diluted with ethyl acetate. The ethyl acetate phase was washed with saturated NH₄Cl solution, water and saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated to small volume under reduced pressure. The crude product was purified by column chromatography with silica gel (ethyl acetate/hexane) and the desired first-stage product was obtained. Yield: 35%

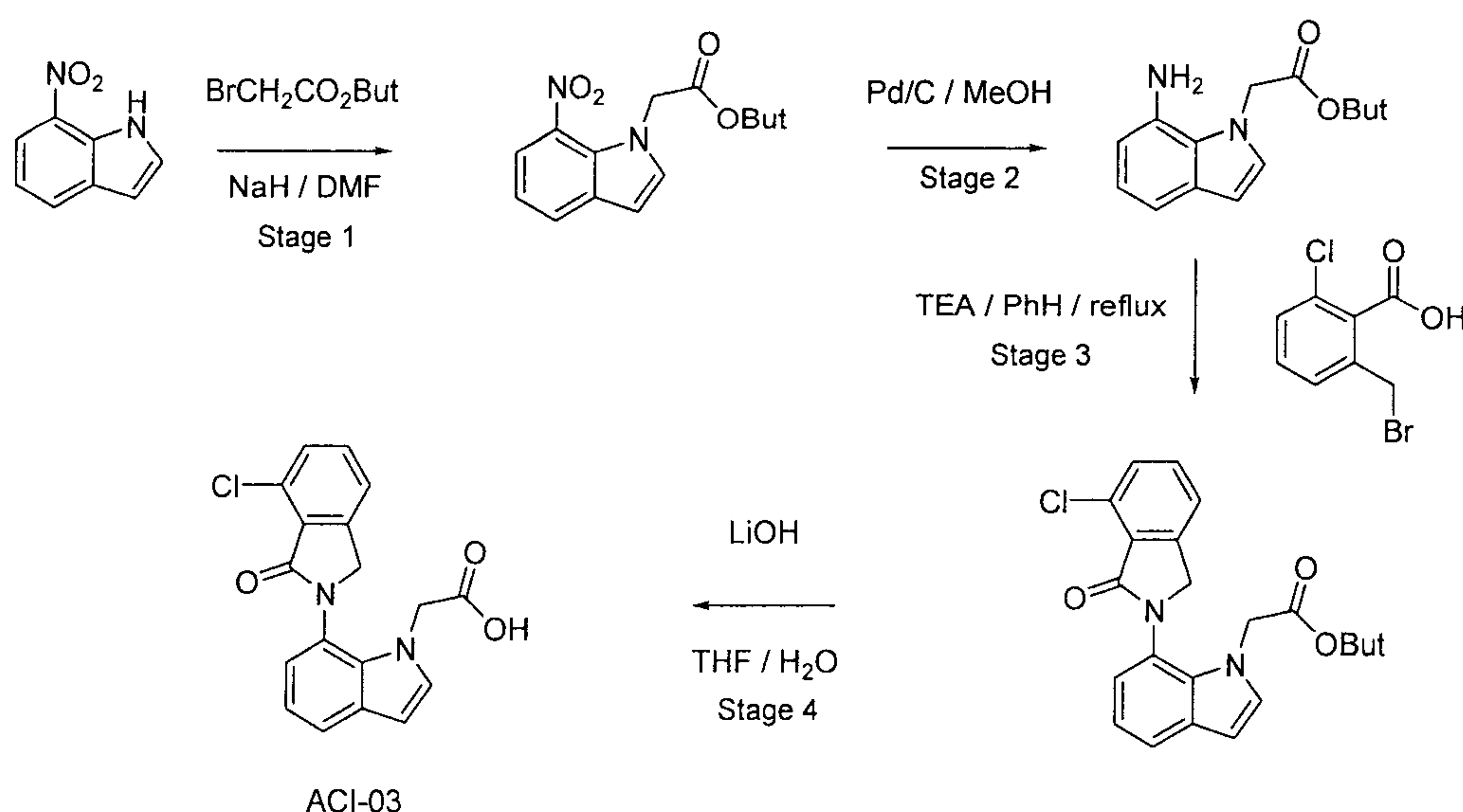
Stage 2: Pd/C 10% was added to a solution of the first-stage product (1.2 mmol) in methanol (10 ml) under a nitrogen atmosphere and the mixture was hydrogenated for 16 h under a pressure of 2 bar. The batch was filtered and the filtrate concentrated to small volume. The second-stage product was obtained and was used directly in the next stage with no further purification. Yield: 63.5%

GRA3454-WO
22nd December 2009

Stage 3: A mixture of the second-stage product (0.45 mmol), 2-bromomethyl-6-chlorobenzoate (1 eq.) and TEA (1.2 eq.) was refluxed in benzene (10 ml) under a nitrogen atmosphere for 16 h. The reaction mixture was concentrated to small volume and the concentrated mass was taken up with DCM. The organic phase was washed successively with water and saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated to small volume under reduced pressure. The crude product was purified by column chromatography with silica gel (DCM/MeOH) and the desired third-stage product was obtained. Yield: 40%

Stage 4: LiOH.H₂O (5 eq.) was added to a suspension of the third-stage product (0.5 mmol) in methanol (40 ml), tetrahydrofuran (40 ml) and water (30 ml) and the reaction mixture was stirred overnight at 25°C. Methanol and THF were drawn off completely. The aqueous phase was acidified with 1(N) HCl and then filtered. The white solid was stirred for 1 h in a mixture of 350 ml acetone and 50 ml methanol. After filtration the white solid was dried under reduced pressure and the desired pure product E-17 was obtained. Yield: 55%

Structural unit E-19: 2-(7-(7-Chloro-1-oxoisindolin-2-yl)-1H-indol-1-yl) acetic acid



GRA3454-WO
22nd December 2009

Stage 1: 6-Nitroindole (30 mmol) dissolved in DMF (100 ml) was added to a suspension of sodium hydride (1.5 eq.) in DMF (5 ml) at 0°C and stirred for 30 min. Then *tert*-butyl-bromoacetate (1.2 eq.) was added and the mixture was stirred at RT for 15 h. The batch was quenched with saturated NH₄Cl solution and extracted with ethyl acetate. The organic phase was washed successively with water and saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated to small volume under reduced pressure. The crude product was purified by column chromatography with silica gel (ethyl acetate/hexane) and the desired first-stage product was obtained. Yield: 82%

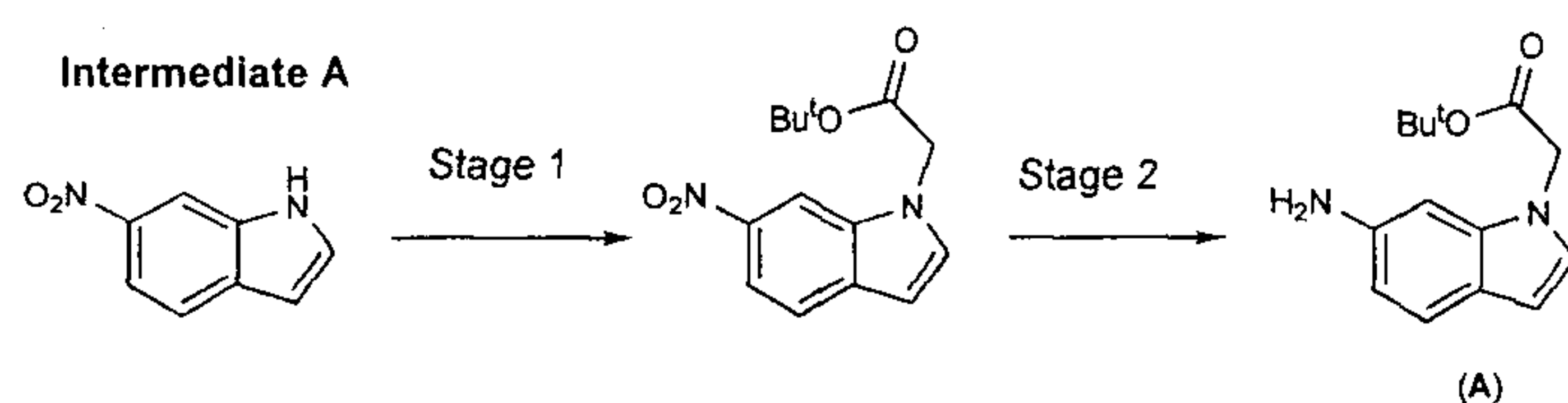
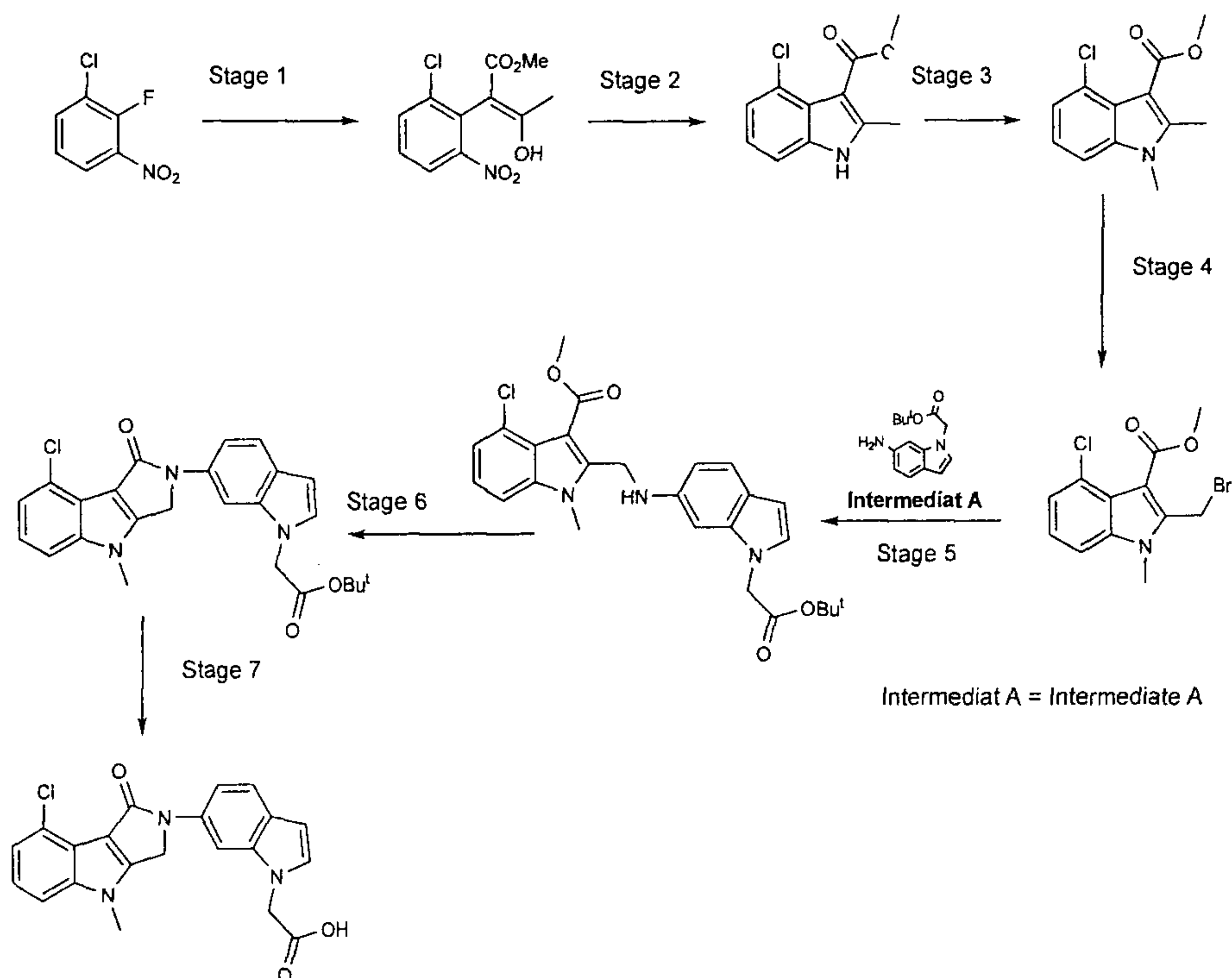
Stage 2: Pd/C 10% was added to a solution of the first-stage product (1.44 mmol) in methanol (10 ml) under a nitrogen atmosphere and the mixture was hydrogenated for 16 h under a pressure of 2 bar. The batch was filtered and the filtrate concentrated to small volume. The second-stage product was obtained and was used directly in the next stage with no further purification. Yield: 89%

Stage 3: A mixture of the second-stage product (25 mmol), 2-bromomethyl-6-chlorobenzoate (1.2 eq.) and TEA (1.2 eq.) was refluxed in benzene (150 ml) under a nitrogen atmosphere for 16 h. The reaction mixture was concentrated to small volume and the concentrated mass was taken up with DCM. The organic phase was washed successively with water and saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated to small volume under reduced pressure. The crude product was purified by column chromatography with silica gel (DCM/MeOH) and the desired third-stage product was obtained. Yield: 48.5%

Stage 4: LiOH.H₂O (5 eq.) was added to a suspension of the third-stage product (15 mmol) in methanol (25 ml), tetrahydrofuran (25 ml) and water (50 ml) and the reaction mixture was stirred overnight at 25°C. Methanol and THF were drawn off completely. The aqueous phase was acidified with 1(N) HCl and then filtered. The white solid was stirred for 1 h in a mixture of 350 ml acetone and 50 ml methanol. After filtration the white solid was dried under reduced pressure and the desired pure product **E-18** was obtained. Yield: 80%

GRA3454-WO
22nd December 2009

Structural unit E-20: 2-(6-(8-Chloro-4-methyl-1-oxopyrrolo[3,4-b]indol-2(1H,3H,4H)-yl)-1H-indol-1-yl)acetic acid



Stage 1: (E)-Methyl 2-(2-chloro-6-nitrophenyl)-3-hydroxybut-2-enoate

Methyl acetoacetate (59.82 mmol, 2.1 equiv.) was added dropwise at 0°C to a suspension of NaH (65.52 mmol, 2.3 equiv.) in DMF (40 ml). Then the mixture was stirred for 10 min and subsequently heated to 25°C. 2-Fluoro-3-chloronitrobenzene (28.49 mmol, 1.0 equiv.) was cooled with an ice bath in a reaction flask, and the NaH suspension was added. Then stirring was carried out for 16 h at 25°C. 2 M HCl (5 ml) and water (10 ml) were then added, and extraction with diethyl ether (3 x 20 ml) was carried out. The combined organic phases were washed with water (10 ml) and sat.

GRA3454-WO
22nd December 2009

NaCl solution (20 ml), dried over Na_2SO_4 and reduced under reduced pressure. The residue was purified by column chromatography (5% ethyl acetate in hexane).

Yield: 51%

Stage 2: Methyl 4-chloro-2-methyl-1H-indole-3-carboxylate

(E)-Methyl 2-(2-chloro-6-nitrophenyl)-3-hydroxybut-2-enoate (14.76 mmol, 1.0 equiv.) was dissolved in acetic acid (96 ml), and a solution of TiCl_3 (20% - w/w in 2 N HCl, 71.6 ml) was added, with stirring. The mixture was then heated for 5-10 min at 90°C. The reaction mixture was cooled with an ice bath and diluted with water and DCM/methanol (9:1, 100 ml). The phases were separated and the organic phase was washed with water and sat. NaCl solution. Drying over Na_2SO_4 was then carried out, followed by concentration under reduced pressure. The product was crystallised from hexane.

Yield: 91%

Stage 3: Methyl 4-chloro-1,2-dimethyl-1H-indole-3-carboxylate

Methyl 4-chloro-2-methyl-1H-indole-3-carboxylate (13.45 mmol, 1.0 equiv.) was dissolved in DMF (7 ml) and added at 0°C to a suspension of NaH (26.90 mmol, 2.0 equiv.) in DMF (13 ml). The mixture was then stirred for 30 min. Methyl iodide (20.17 mmol, 1.5 equiv.) was added dropwise at 0°C and stirring was carried out for 2 h at 25°C. The reaction mixture was diluted with NH_4Cl solution (20 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic phases were washed with water and sat. NaCl solution (in each case 50 ml), dried over Na_2SO_4 and concentrated to dryness under reduced pressure.

Yield: 72%

Stage 4: Methyl 2-(bromo-methyl)-4-chloro-1-methyl-1H-indole-3-carboxylate

Methyl 4-chloro-1,2-dimethyl-1H-indole-3-carboxylate (9.70 mmol, 1.0 equiv.) was dissolved in CCl_4 (97 ml), and NBS (9.70 mmol, 1.0 equiv.) and benzoyl peroxide (0.19 mmol, 0.02 equiv.) were added. The mixture was heated for 1 h at 85°C. The resulting succinimide was filtered off, the filtrate was concentrated, and the residue was purified by column chromatography (20% ethyl acetate in hexane).

Yield: 48%

GRA3454-WO
22nd December 2009

Stage 5: Methyl 2-((1-(2-tert-butoxy-2-oxoethyl)-1H-indol-6-ylamino)methyl)-4-chloro-1-methyl-1H-indole-3-carboxylate

Methyl 2-(bromo-methyl)-4-chloro-1-methyl-1H-indole-3-carboxylate (1.10 mmol, 1.0 equiv.) and tert-butyl 2-(6-amino-1H-indol-1-yl)acetate (intermediate A) (1.10 mmol, 1.0 equiv.) were dissolved in benzene (5 ml) and triethylamine (1.3 mmol, 1.2 equiv.) and refluxed for 16 h. The reaction mixture was cooled to 25°C, diluted with ethyl acetate and washed with water and sat. NaCl solution. Drying over Na₂SO₄ was then carried out, followed by concentration under reduced pressure. The crude product was purified by column chromatography (40% ethyl acetate in hexane).

Yield: 55%

Stage 6: tert-Butyl 2-(6-(8-chloro-4-methyl-1-oxopyrrolo[3,4-b]indol-2(1H,3H,4H)-yl)-1H-indol-1-yl)acetate

Methyl 2-((1-(2-tert-butoxy-2-oxoethyl)-1H-indol-6-ylamino)methyl)-4-chloro-1-methyl-1H-indole-3-carboxylate (2.416 mmol, 1 equiv.) was dissolved in dichloromethane (36 ml), and (CH₃)₃Al (2 M solution in toluene, 4.83 mmol) was added at 0°C, under nitrogen. After 10 min, the reaction mixture was heated to 25°C and then stirred for 2 h. The reaction mixture was diluted with dichloromethane and hydrolysed with 2 M HCl. The phases were separated, and the organic phase was washed with water and sat. NaCl solution (in each case 10 ml). Drying over Na₂SO₄ was then carried out, followed by concentration under reduced pressure. The product was crystallised from ethyl acetate.

Yield: 89%

Stage 7: 2-(6-(8-Chloro-4-methyl-1-oxopyrrolo[3,4-b]indol-2(1H,3H,4H)-yl)-1H-indol-1-yl)acetic acid

tert-Butyl 2-(6-(8-chloro-4-methyl-1-oxopyrrolo[3,4-b]indol-2(1H,3H,4H)-yl)-1H-indol-1-yl)acetate (1.6 mmol, 1 equiv.) was dissolved in DCM (40 ml); TFA (16 ml) was added and the mixture was stirred for 2 h at 25°C. The solvent was reduced under reduced pressure, dichloromethane was added 2x to the residue, and in each case concentration to dryness again was carried out. The residue was used in the next step without being purified further.

GRA3454-WO
22nd December 2009

Intermediate A:

Stage 1: tert-Butyl 2-(6-nitro-1H-indol-1-yl)acetate

NaH (4.5 mmol, 1.5 equiv.) was suspended in DMF (5 ml), and 6-nitro-indole (3 mmol, 1 equiv.), dissolved in DMF (5 ml), was added at 0°C. The mixture was stirred for 30 min. Then tert-butyl bromoacetate (3.6 mmol, 1.2 equiv.) was added and the mixture was stirred for 15 h at 25°C. The reaction mixture was hydrolysed with ammonium chloride and extracted with ethyl acetate (3 x 20 ml). The combined organic phases were washed with water and sat. NaCl solution (in each case 20 ml), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography.

Yield: 47%

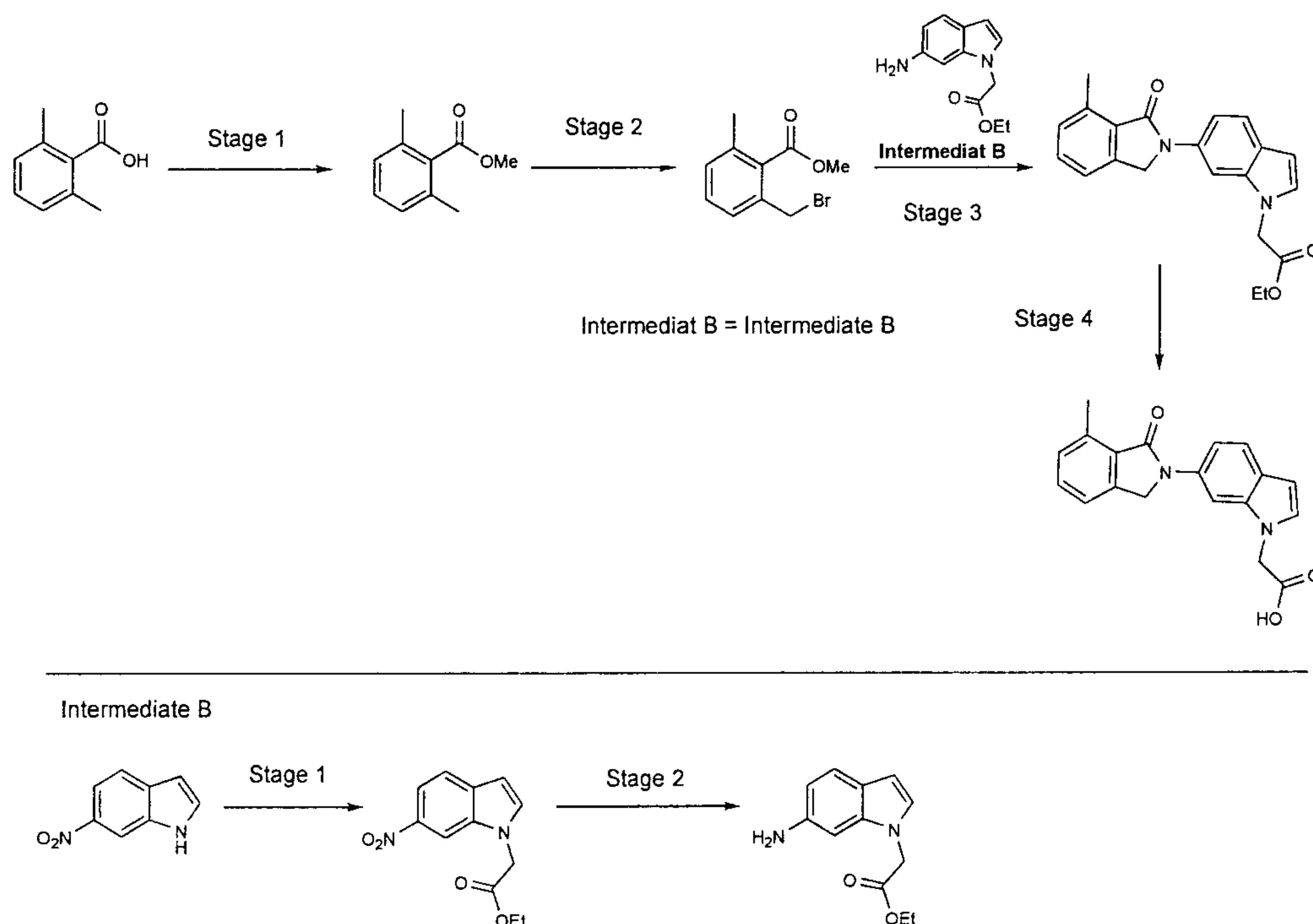
Stage 2: tert-Butyl 2-(6-amino-1H-indol-1-yl)acetate

A mixture of tert-butyl 2-(6-nitro-1H-indol-1-yl)acetate (1.44 mmol, 1 equiv.), iron powder (5.76 mmol, 4 equiv.), ammonium chloride (4 equiv.) and ethanol (10 ml) was stirred for 4 h at boiling temperature. The reaction mixture was cooled to 25°C and filtered over celite. The filtrate was concentrated, diluted with water (50 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic phases were washed with water and sat. NaCl solution (in each case 10 ml), dried over Na₂SO₄ and concentrated under reduced pressure. For purification, the product was recrystallised from ethyl acetate/hexane.

Yield: 61%

GRA3454-WO
22nd December 2009

Structural unit E-21: 2-(6-(7-Methyl-1-oxoisindolin-2-yl)-1H-indol-1-yl)acetic acid



Stage 1: Methyl 2,6-dimethylbenzoate

K_2CO_3 (10.1 mmol, 1.5 equiv.) and dimethyl sulfate (7.4 mmol, 1.1 equiv.) were added at 25°C to a solution of 2,6-dimethylbenzoic acid (6.7 mmol, 1 equiv.), and the mixture was stirred for 1 h. The solvent was reduced under reduced pressure, the residue was taken up in ethyl acetate (100 ml), and water (20 ml) was added. The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 50 ml). The combined organic phases were washed with sat. NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was used in the next stage without being purified further.

Yield: quantitative

Stage 2: Methyl 2-(bromo-methyl)-6-methylbenzoate

NBS (40.85 mmol, 1 equiv.) and benzoyl peroxide (10.21 mmol, 0.25 equiv.) were added to a solution of methyl 2,6-dimethylbenzoate (40 mmol, 1 equiv.) in CCl_4 (75 ml), and the mixture was heated for 20 min at boiling temperature. The reaction mixture was filtered off over celite and the filtrate was concentrated under reduced

GRA3454-WO
22nd December 2009

pressure. The residue was purified by column chromatography (1.5% ethyl acetate/hexane).

Yield: 32%

Stage 3: Ethyl 2-(6-(7-methyl-1-oxoisoindolin-2-yl)-1H-indol-1-yl)acetate

Ethyl 2-(6-amino-1H-indol-1-yl)acetate (intermediate B) (7.66 mmol, 1 equiv.) was dissolved in benzene (30 ml), and methyl 2-(bromo-methyl)-6-methylbenzoate (8.42 mol, 1.1 equiv.) and TEA (9.19 mmol, 1.2 equiv.) were added at 25°C and the mixture was refluxed for 12 h. The reaction mixture was reduced under reduced pressure and the residue was taken up in dichloromethane (30 ml), washed with water and sat. NaCl solution (5 ml), dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (10% ethyl acetate in hexane).

Yield: 64%

Stage 4: 2-(6-(7-Methyl-1-oxoisoindolin-2-yl)-1H-indol-1-yl)acetic acid

NaOH (1.86 mmol, 1.3 equiv.), dissolved in water (6 ml), was added to a solution of ethyl 2-(6-(7-methyl-1-oxoisoindolin-2-yl)-1H-indol-1-yl)acetate (1.44 mmol, 1 equiv.) in THF/MeOH (1:1, 5 ml), and the mixture was stirred for 2 h at 25°C. The reaction solution was concentrated under reduced pressure, and the aqueous residue was adjusted to pH 3 with 1 M HCl and extracted with ethyl acetate (3 x 50 ml). The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure.

Yield: quantitative

Intermediate B:

Stage 1: Ethyl 2-(6-nitro-1H-indol-1-yl)acetate

NaH (37 mmol, 2 equiv.) was taken up in DMF (25 ml) and cooled to 0°C. 6-Nitro-1H-indole (18.5 mmol, 1 equiv.) was added in portions, and the mixture was stirred for 1 h at 25°C. The reaction mixture was cooled to 0°C again, ethyl bromoacetate (22.22 mmol, 1.2 equiv.) was added dropwise, and the mixture was stirred for 2 h at 25°C. The reaction mixture was then poured into ice-water and extracted with ethyl acetate (2 x 100 ml). The combined organic phases were washed with sat. NaCl

GRA3454-WO
22nd December 2009

solution (30 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The product was crystallised from hexane and was used in the next step without being purified further.

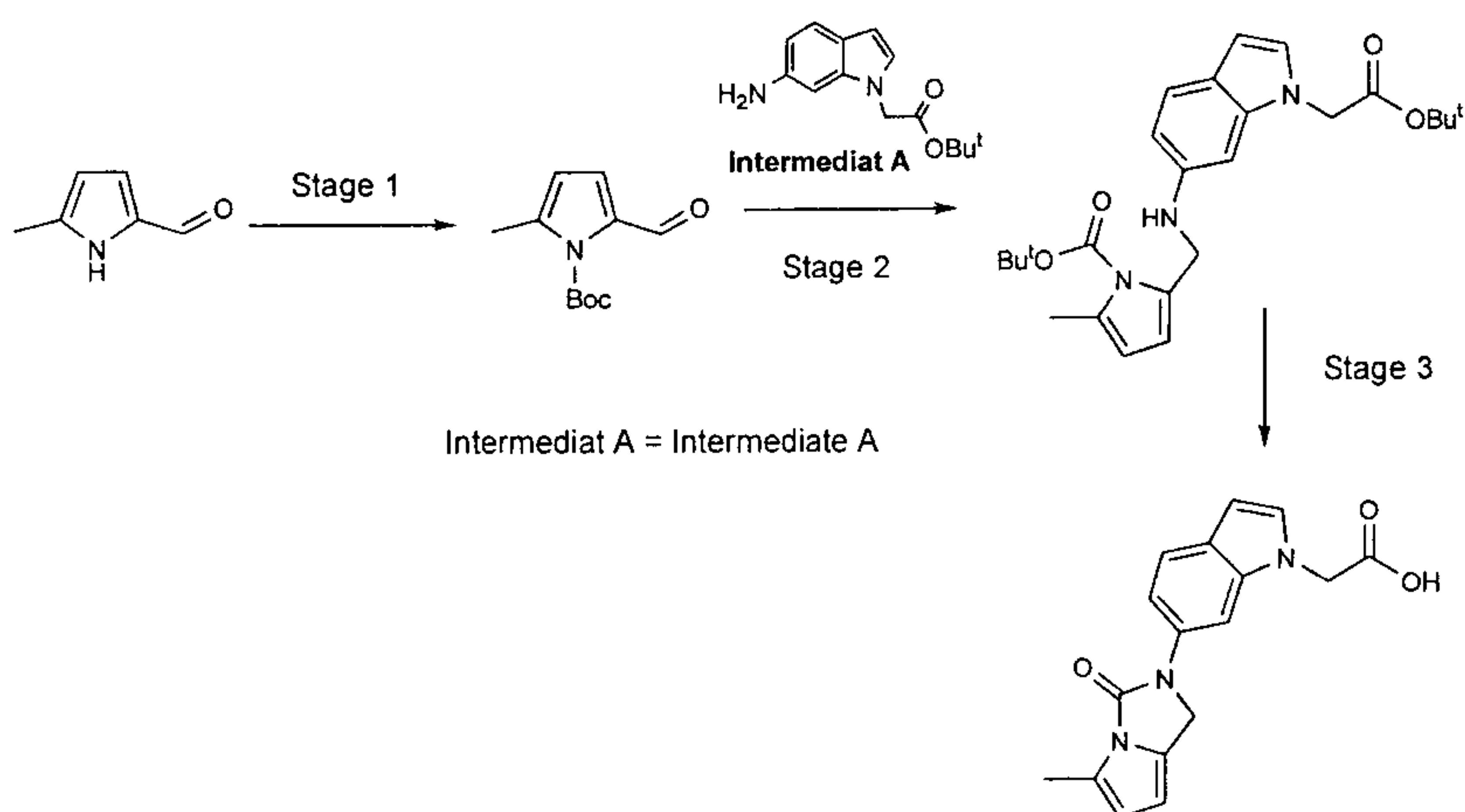
Yield: 57%

Stage 2: Ethyl 2-(6-amino-1H-indol-1-yl)acetate

A mixture of ethyl 2-(6-nitro-1H-indol-1-yl)acetate (20.96 mmol, 1 equiv.), iron powder (83.8 mmol, 4 equiv.), ammonium chloride (83.87 mmol, 1 equiv.) and ethanol/water (2.5:1, 56 ml) was stirred for 2 h at boiling temperature. The reaction mixture was cooled to 25°C and filtered over celite. The filtrate was diluted with ethyl acetate and water, the phases were separated, and the organic phase was washed with sodium hydrogen carbonate solution and sat. NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (15% ethyl acetate in hexane).

Yield: 55%

Structural unit E-22: 2-(6-(5-Methyl-3-oxo-1H-pyrrolo[1,2-c]imidazol-2(3H)-yl)-1H-indol-1-yl)acetic acid



GRA3454-WO
22nd December 2009

Stage 1: tert-Butyl 2-formyl-5-methyl-1H-pyrrole-1-carboxylate

(Boc)₂O (5.498 mmol, 1.2 equiv.) was added at 0°C to a solution of 5-methyl-1H-pyrrole-2-carbaldehyde (4.58 mmol, 1.0 equiv.) and DMAP (0.3665 mmol, 0.08 equiv.) in acetonitrile (10 ml), and the mixture was stirred for 2 h at 25°C. The solvent was reduced under reduced pressure and the residue was purified by column chromatography (4% ethyl acetate in hexane).

Yield: 94%

Stage 2: tert-Butyl 2-((1-(2-tert-butoxy-2-oxoethyl)-1H-indol-6-ylamino)methyl)-5-methyl-1H-pyrrole-1-carboxylate

A solution of tert-butyl 2-(6-amino-1H-indol-1-yl)acetate (intermediate A – for synthesis see above) (1.7368 mmol, 1.1 equiv.) in DCM (3 ml) was added at 0°C to tert-butyl 2-formyl-5-methyl-1H-pyrrole-1-carboxylate (1.5789 mmol, 1.0 equiv.), dissolved in DCM (12 ml), and the mixture was stirred for 30 min at 25°C. At 0°C, Na(OAc)₃BH (4.7368 mmol, 3.0 equiv.) was added in portions, and then the mixture was stirred for 12 h at 25°C. The reaction mixture was diluted with DCM (100 ml), washed with water and sat. NaCl solution (in each case 2 x 50 ml), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (5% ethyl acetate in hexane).

Yield: 58%

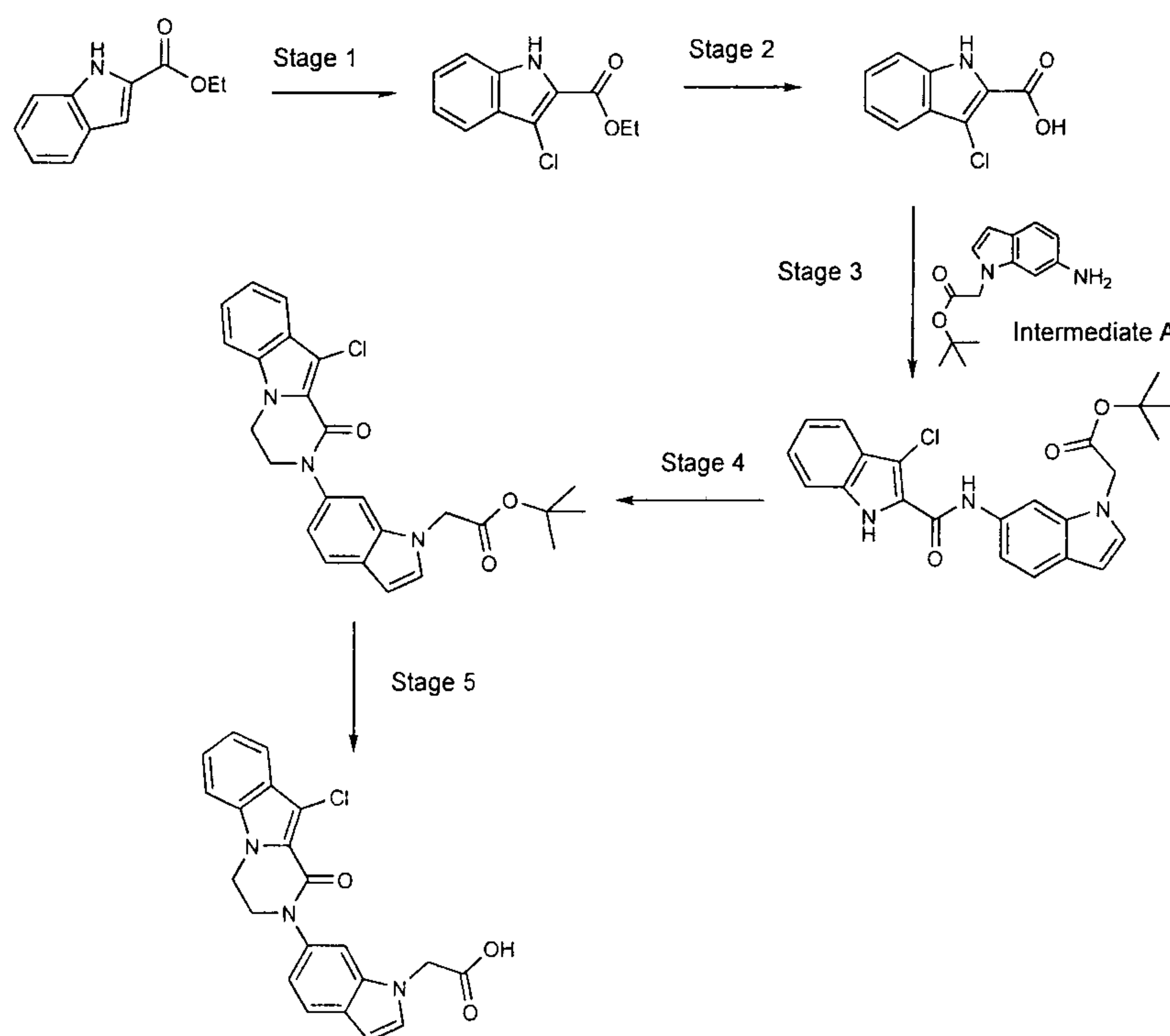
Stage 3: 2-(6-(5-Methyl-3-oxo-1H-pyrrolo[1,2-c]imidazol-2(3H)-yl)-1H-indol-1-yl)acetic acid

NaH (2.0 equiv., 60% in mineral oil) was suspended at 0°C in THF (6 ml). A solution of tert-butyl 2-((1-(2-tert-butoxy-2-oxoethyl)-1H-indol-6-ylamino)methyl)-5-methyl-1H-pyrrole-1-carboxylate (0.797 mmol, 1.0 equiv.) in THF (2 ml) was added, and the mixture was stirred for 14 h at 25°C. The reaction mixture was hydrolysed with water (50 ml) and diluted with ethyl acetate (100 ml). The aqueous phase was adjusted to an acidic pH value with acetic acid and extracted with ethyl acetate (2 x 50 ml). The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. The product was crystallised from the residue with hexane.

Yield: 81%

GRA3454-WO
22nd December 2009

Structural unit E-23: 2-(6-(10-Chloro-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1H-indol-1-yl)acetic acid



Stage 1: Ethyl 3-chloro-1H-indole-2-carboxylate

Ethyl 1H-indole-2-carboxylate (26.45 mmol, 1.0 equiv.) was dissolved in CCl_4 (26 ml); NCS (29.10 mmol, 1.1 equiv.) was added and the mixture was heated for 16 h at boiling temperature. The resulting solid was filtered off, and the filtrate was washed with water (2 x 50 ml) and sat. NaCl solution (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (10% ethyl acetate in hexane).

Yield: 73%

Stage 2: 3-Chloro-1H-indole-2-carboxylic acid

Ethyl 3-chloro-1H-indole-2-carboxylate (19.28 mmol, 1.0 equiv.) was dissolved in THF-MeOH- H_2O (2:1:1; 85 ml); $\text{LiOH}\cdot\text{H}_2\text{O}$ (57.84 mmol, 3.0 equiv.) was added at 0°C and the mixture was stirred for 12 h at 25°C . The solvent was reduced under reduced pressure, and the residue was taken up in water (50 ml), adjusted to pH 3 with 1 M

GRA3454-WO
22nd December 2009

HCl and extracted with ethyl acetate (2 x 100 ml). The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure, and then the product was crystallised with hexane.

Yield: 82%

Stage 3: tert-Butyl 2-(6-(3-chloro-1H-indole-2-carboxamido)-1H-indol-1-yl)acetate

DIPEA (2.5 equiv.), EDCI (2.73 mmol, 1.2 equiv.) and HOBt (2.73 mmol, 1.2 equiv.) were added at 0°C to a solution of 3-chloro-1H-indole-2-carboxylic acid (2.27 mmol, 1.0 equiv.) in DMF (6 ml), and the mixture was stirred for 15 min. tert-Butyl 2-(6-amino-1H-indol-1-yl)acetate (intermediate A – for synthesis see above) (2.27 mmol, 1.0 equiv.) was dissolved in DMF (1 ml) and added, with stirring, and the reaction mixture was then stirred for 12 h at 25°C. The mixture was diluted with dichloromethane (50 ml), washed with sat. ammonium chloride solution (20 ml), water (20 ml) and sat. NaCl solution (20 ml), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (10-15% ethyl acetate in hexane).

Yield: 55%

Stage 4: tert-Butyl 2-(6-(10-chloro-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1H-indol-1-yl)acetate

tert-Butyl 2-(6-(3-chloro-1H-indole-2-carboxamido)-1H-indol-1-yl)acetate (1.41 mmol, 1.0 equiv.) and TBAB (1.41 mmol, 1.0 equiv.) were dissolved in 1 N NaOH (12 ml); 1,2-dibromoethane (14.18 mmol, 10.0 equiv.) was added, and the mixture was stirred for 12 h at 25°C. The reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (100 ml). The organic phase was washed with sat. NaCl solution (50 ml), dried over Na₂SO₄ and concentrated under reduced pressure, and the desired product was obtained by purification by column chromatography.

Yield: 78%

Stage 5: 2-(6-(10-Chloro-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1H-indol-1-yl)acetic acid

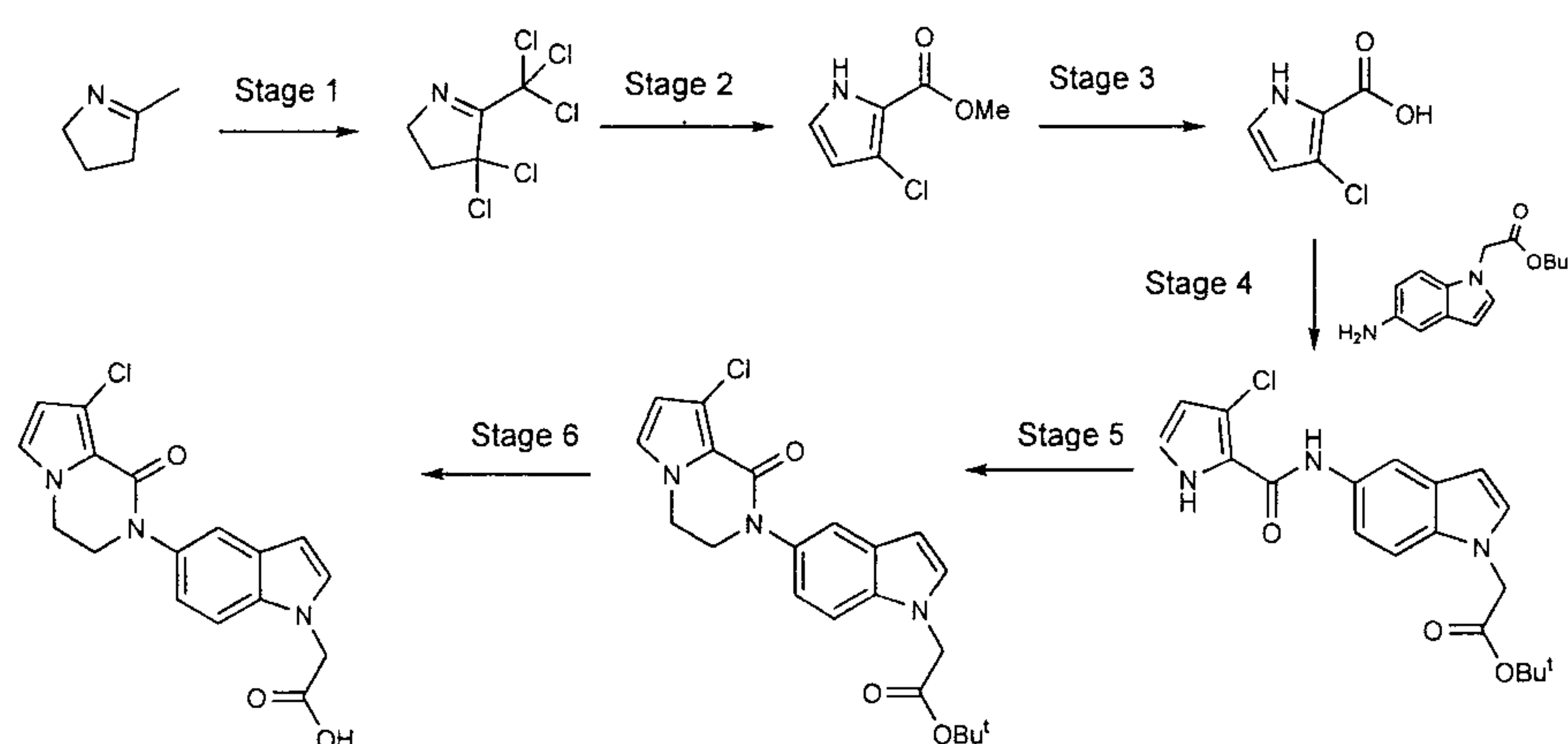
tert-Butyl 2-(6-(10-chloro-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1H-indol-1-yl)acetate (2.22 mmol, 1.0 equiv.) was dissolved in DCM (15 ml); TFA (3 ml) was

GRA3454-WO
22nd December 2009

added, and the mixture was stirred for 2 h at 25°C. The solvent was concentrated under reduced pressure, and the residue was taken up in DCM (60 ml), washed with water (25 ml) and sat. NaCl solution (25 ml), dried over Na₂SO₄ and concentrated to dryness under reduced pressure.

Yield: 91%

Structural unit E-24: 2-(6-(8-Chloro-1-oxo-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-1H-indol-1-yl)acetic acid



Stage 1: 4,4-Dichloro-5-(trichloromethyl)-3,4-dihydro-2H-pyrrole

5-Methyl-3,4-dihydro-2H-pyrrole (60.2 mmol, 1.0 equiv.) was dissolved in CCl₄ (100 ml); at 0°C, N-chlorosuccinimide (8.0 equiv.) was added in portions, and the mixture was heated for 72 h at boiling temperature. The reaction mixture was cooled to 0°C, and the resulting solid was filtered off and washed with cooled (0°C) CCl₄ (2 x 50 ml). The filtrate was concentrated to dryness under reduced pressure.

Yield: 90%

Stage 2: Methyl 3-chloro-1H-pyrrole-2-carboxylate

4,4-Dichloro-5-(trichloromethyl)-3,4-dihydro-2H-pyrrole (47.4 mmol, 1.0 equiv.) was added to a solution of sodium methanolate (284.5 mmol, 6.0 equiv.) in methanol (126 ml), and the mixture was heated for 1.5 h at boiling temperature. The reaction mixture was cooled to 25°C, the solvent was concentrated under reduced pressure, the residue was taken up in diethyl ether (470 ml), and the mixture was stirred for 30 min. The resulting solid (sodium chloride) was filtered off, and the filtrate was dried

GRA3454-WO
22nd December 2009

over K_2CO_3 and concentrated under reduced pressure. The residue was taken up in DCM (600 ml), extracted with 2 N HCl (2 x 150 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was used in the next step without being purified further.

Yield: 83%

Stage 3: 3-Chloro-1H-pyrrole-2-carboxylic acid

Methyl 3-chloro-1H-pyrrole-2-carboxylate (18.86 mmol, 1.0 equiv.) was dissolved in MeOH- H_2O (2:1, 120 ml); at 0°C, LiOH. H_2O (75.4 mmol, 4 equiv.) was added and the mixture was stirred for 16 h at 25°C. The methanol was concentrated under reduced pressure, and the aqueous residue was diluted with water (60 ml) and extracted with ethyl acetate (2 x 50 ml). The aqueous phase was adjusted to pH 3-4 with 1 M HCl, and the resulting solid was filtered off.

Yield: 90%

Stage 4: tert-Butyl 2-(5-(3-chloro-1H-pyrrole-2-carboxamido)-1H-indol-1-yl)acetate

DIPEA (4.0 equiv.), EDCI (1.5 equiv.) and HOBt (1.0 equiv.) were added at 0°C to a solution of 3-chloro-1H-pyrrole-2-carboxylic acid (5.24 mmol, 1.0 equiv.) in DCM (25 ml). The mixture was stirred for 15 min at 25°C and then cooled to 0°C again. A solution of tert-butyl 2-(6-amino-1H-indol-1-yl)acetate (intermediate A – for synthesis see above) (5.24 mmol, 1.0 equiv.) in DCM (10 ml) was added, and the reaction mixture was stirred for 16 h at 25°C. It was then diluted with DCM (200 ml), washed with sat. ammonium chloride solution (2 x 50 ml), sat. sodium hydrogen carbonate solution (2 x 50 ml) and sat. NaCl solution (2 x 50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (6% methanol in DCM).

Yield: 56%

Stage 5: tert-Butyl 2-(5-(8-chloro-1-oxo-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-1H-indol-1-yl)acetate

1,2-Dibromoethane (22.7 mmol, 10.0 equiv.) was added to a solution of tert-butyl 2-(5-(8-chloro-1-oxo-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-1H-indol-1-yl)acetate (2.27 mmol, 1.0 equiv.) and tetrabutylammonium bromide (2.27 mmol, 1.0 equiv.) in

GRA3454-WO
22nd December 2009

1 N NaOH (14 ml), and the mixture was stirred for 12 h at 25°C. The reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (150 ml). The organic phase was washed with water (2 x 50 ml) and sat. NaCl solution (2 x 50 ml), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (10-12% ethyl acetate in hexane).

Yield: 93%

Stage 6: 2-(5-(8-Chloro-1-oxo-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-1H-indol-1-yl)acetic acid

A solution of LiOH.H₂O (4.0 equiv.) in water (5 ml) was added at 0°C to a solution of tert-butyl 2-(5-(8-chloro-1-oxo-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-1H-indol-1-yl)acetate (1.5 mmol, 1.0 equiv.) in MeOH (20 ml), and the mixture was heated for 16 h at 50°C. The methanol was concentrated under reduced pressure, and the aqueous residue was diluted with water (20 ml) and extracted with ethyl acetate (2 x 15 ml). The aqueous phase was adjusted to pH 4 with 1 M HCl, the desired product precipitating in the form of a white solid. The solid was filtered off and dried.

Yield: 78%

GRA3454-WO
22nd December 2009

5) Synthesis of amine structural units F

Amine F-01: Dimethyl-(3-piperazin-1-yl propyl)amine [877-96-3] commercially available from e.g. Acros. **Amine F-02:** 1-(1-Methylpiperidin-4-yl) piperazine [12345-34-56] commercially available from e.g. Aldrich. **Amine F-03:** 3-(4-Ethylpiperazin-1-yl) propylamine [4524-96-3] commercially available from e.g. Fluorochem. **Amine F-05:** 4-(2-Pyrrolidin-1-yl ethyl) piperidine [14759-08-1] commercially available from e.g. ABCR.

Amine F-07: Dimethyl-(4-phenyl piperidin-4-yl)amine dihydrochloride

Stage 1: 1-Benzyl-4-(dimethylamino)piperidine-4-carbonitrile

208 g (3 eq.) *N,N*-dimethylamine hydrochloride, 154 g (3 eq.) potassium cyanide in 154 ml water and 1050 ml (7 eq.) of a 40% dimethylamine solution were added to a solution of 150 g (1 eq.) 1-benzylpiperidin-4-one in 300 ml methanol and the mixture was cooled to 0°C. 75 ml (0.5 eq.) concentrated hydrochloric acid were then added at 0°C and the reaction mixture was stirred for 24 h at room temperature. The reaction course was monitored by thin-layer chromatography (20% EtOAc/hexane). Once the conversion was complete, the solid that had formed was filtered off and washed with iced water (4 l). The solid obtained was then dissolved in ethyl acetate and dried with Na₂SO₄. Following removal of the solvent under reduced pressure, 165 g (85%) of crude product were obtained in the form of a solid.

Stage 2: 1-Benzyl-*N,N*-dimethyl-4-phenylpiperidin-4-amine

A little iodine was added to a mixture of 34.5 g (3.5 eq.) magnesium and 100 ml dry diethyl ether, followed over a period of 10 min by 10 g (0.15 eq.) bromobenzene, and the mixture was stirred for a further 10 min. Once the reaction had started, 183 g (2.85 eq.) bromobenzene dissolved in 500 ml diethyl ether were added dropwise over a period of 2 h and the mixture was stirred for a further 15 min. 100 g (1 eq.) 1-benzyl-4-(dimethylamino)piperidine-4-carbonitrile dissolved in 900 ml diethyl ether were added over a period of 2 h to the Grignard reagent prepared in the preceding step and the mixture was then heated for 12 h at 80°C. The reaction course was monitored by thin-layer chromatography (10% MeOH/CHCl₃).

GRA3454-WO
22nd December 2009

Once the conversion was complete, the reaction solution was cooled to 0°C, mixed with saturated NH₄Cl solution, extracted with ethyl acetate (3 x 300 ml) and the combined organic phases were dried with Na₂SO₄. Following removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel; 1% MeOH/CHCl₃). 30 g (35%) of product were obtained in the form of a yellow solid.

Stage 3: Benzyloxycarbonyl-4-(dimethylamino)-4-phenylpiperidine

500 ml (10 eq.) Cbz chloride were added dropwise to 50 g (1 eq.) 1-benzyl-*N,N*-dimethyl-4-phenylpiperidin-4-amine over a period of 1 h and the reaction mixture obtained was stirred for 2 h at room temperature. The reaction course was monitored by thin-layer chromatography (10% MeOH/CHCl₃). Once the conversion was complete, the reaction mixture was cooled to 0°C, made alkaline with saturated sodium hydrogen carbonate solution and extracted 3 times with 300 ml EtOAc. The combined organic phases were dried with Na₂SO₄. Following removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel; 50% EtOAc/heptane). 12 g (21%) of product were obtained in the form of an oil.

Stage 4: *tert*-Butyloxycarbonyl-4-(dimethylamino)-4-phenylpiperidine

12.2 g KOH were added to a solution of 12 g (1 eq.) benzyloxycarbonyl-4-(dimethylamino)-4-phenylpiperidine in 120 ml ethanol and the reaction mixture was refluxed for 48 h. The reaction course was monitored by thin-layer chromatography (20% MeOH/CHCl₃).

Once the conversion was complete, the solvent was distilled off completely, the residue suspended in ethyl acetate, filtered, and the organic phase dried over sodium sulfate. Following removal of the solvent under reduced pressure, the crude product was dissolved in dioxane, mixed with saturated sodium hydrogen carbonate solution and 11.9 g (1.5 eq.) of Boc anhydride and stirred for 30 min at room temperature. Once the conversion was complete, the reaction mixture was extracted with 3 x 200 ml ethyl acetate and the combined organic phases were dried over Na₂SO₄. Following removal of the solvent under reduced pressure, 8.5 g (77%) of crude product were obtained in the form of a colourless solid.

GRA3454-WO
22nd December 2009

Stage 5: N,N-Dimethyl-4-phenylpiperidin-4-amine dihydrochloride

10 equivalents of acetyl chloride were added to a solution of *tert*-butyloxycarbonyl-4-(dimethylamino)-4-phenylpiperidine in methanol at 0°C.

The reaction course was monitored by thin-layer chromatography (10% MeOH/CHCl₃). Once the conversion was complete, the solvent was removed under reduced pressure and the product obtained in the form of a solid.

Amine F-08: [1-(2-Aminoethyl)-4-thiophen-2-yl-piperidin-4-yl] dimethylamine trihydrochloride

Stage 1: *tert*-Butyloxycarbonyl-4-cyano-4-(dimethylamino)piperidine

500 ml (10 eq.) dimethylamine solution and 109.9 g (5 eq.) dimethylamine hydrochloride were added to a solution of 50 g (1 eq.) *tert*-butyloxycarbonyl-4-oxopiperidine in 100 ml methanol and the mixture was cooled to 5°C. 5 ml (0.1 eq.) hydrochloric acid were then added dropwise to the reaction mixture over a period of 10 min and the mixture was stirred for 60 min at room temperature. 48.9 g (3 eq.) potassium cyanide were added in portions to this reaction mixture and the mixture was stirred for 24 h at room temperature. The reaction course was monitored by thin-layer chromatography (50% EtOAc/hexane).

Once the conversion was complete, 150 ml water were added to the reaction mixture and it was extracted 3 times with 100 ml ethyl acetate. The combined organic phases were dried with Na₂SO₄. Following removal of the solvent under reduced pressure, crude product was obtained which was recrystallised out of hexane. 57 g (90%) of product were obtained in the form of a colourless solid.

Stage 2: *tert*-Butyloxycarbonyl-4-(dimethylamino)-4-(thiophen-2-yl)piperidine

A little iodine was added to a mixture of 5.6 g (3 eq.) magnesium and 20 ml dry diethyl ether, followed over a period of 10 min by 5 g 2-bromothiophene, and the mixture was stirred for a further 10 min. Once the reaction had started, 33.5 g (2.6 eq.) 2-bromothiophene dissolved in 80 ml diethyl ether were added dropwise and the mixture was stirred for a period of 2 h at room temperature. The Grignard reagent prepared in the preceding step was added dropwise to a solution of 20 g (1 eq.) *tert*-butyloxycarbonyl-4-cyano-4-(dimethylamino)piperidine dissolved in 200 ml

GRA3454-WO
22nd December 2009

THF and stirred overnight at room temperature. The reaction course was monitored by thin-layer chromatography (50% EtOAc/hexane).

Once the conversion was complete, the reaction solution was cooled to 0°C, mixed with saturated NH₄Cl solution, extracted with ethyl acetate (3 x 100 ml) and the combined organic phases were dried with Na₂SO₄. Following removal of the solvent under reduced pressure, the residue was purified by column chromatography (alox neutral; 30% EtOAc/hexane). 6.1 g (25%) of product were obtained in the form of a white solid.

Stage 3: *N,N*-Dimethyl-4-(thiophen-2-yl)piperidin-4-amine

HCl gas was passed through a solution of 10 g (1 eq.) *tert*-butyloxycarbonyl-4-(dimethylamino)-4-(thiophen-2-yl)piperidine in chloroform at 0°C for ~ 1 h. Once the conversion was complete, 200 ml water were added to the reaction mixture, it was adjusted to a pH of ~ 8 with Na₂CO₃ and then extracted with 15% IPA/CHCl₃. The combined organic phases were dried over Na₂SO₄. Following removal of the solvent under reduced pressure, 6 g (89%) of product were obtained in the form of a white solid.

Stage 4: *tert*-Butyl 2-(4-(dimethylamino)-4-(thiophen-2-yl)piperidin-1-yl)ethylcarbamate

11.1 g (1.5 eq.) *tert*-butyl-2-bromoethylcarbamate dissolved in 65 ml THF and 9.19 g (2 eq.) potassium carbonate were added to a solution of 7 g (1 eq.) *N,N*-dimethyl-4-(thiophen-2-yl)piperidin-4-amine in 40 ml THF. The reaction mixture was heated for 6 h at 70°C. The reaction course was monitored by thin-layer chromatography (20% MeOH/CHCl₃).

Once the conversion was complete, the solvent was distilled off completely, the residue mixed with 200 ml water and the aqueous phase extracted with 20% IPA/CHCl₃. The combined organic phases were dried over Na₂SO₄. Following removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel; 10% MeOH/CHCl₃). 9 g (76%) of product were obtained in the form of an oil.

GRA3454-WO
22nd December 2009

Stage 5: 1-(2-Aminoethyl)-*N,N*-dimethyl-4-(thiophen-2-yl)piperidin-4-amine tris hydrochloride

HCl gas was passed through a solution of 9 g (1 eq.) *tert*-butyl 2-(4-(dimethylamino)-4-(thiophen-2-yl)piperidin-1-yl)ethylcarbamate in chloroform at 0°C for ~ 30 min. The reaction mixture was then stirred at room temperature for one hour.

The reaction course was monitored by thin-layer chromatography (10% MeOH/CHCl₃). Once the conversion was complete, the solvent was removed under reduced pressure and 9 g (97%) of product were obtained in the form of a white solid.

Amine F-09: Dimethyl-[1-(3-methylaminopropyl)-4-thiophen-2-yl-piperidin-4-yl]amine

Stage 1: *tert*-Butyl-3-hydroxypropyl(methyl)carbamate

84.2 g (1.2 eq.) sodium carbonate followed by 100 ml water were added in portions to a solution of 50 g (1 eq.) 3-aminopropan-1-ol in 500 ml THF at 0°C. 156.5 ml (1.02 eq.) di-*tert*-butyl dicarbonate were added dropwise over a period of 30 min to the solution at 0°C. On completion of the addition, the mixture was stirred for 30 min at room temperature. The reaction course was monitored by thin-layer chromatography (10% MeOH/CHCl₃).

Once the conversion was complete, the reaction mixture was filtered over celite and the filtrate concentrated under reduced pressure. The residue was mixed with 300 ml water and extracted with 2 x 250 ml ethyl acetate. The combined organic phases were dried over Na₂SO₄. Following removal of the solvent under reduced pressure, 116 g (100%) of product were obtained in the form of an oil.

GRA3454-WO
22nd December 2009

Stage 2: *tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)propylcarbamate

11.6 g (1.3 eq.) imidazole were added to a solution of 23 g (1 eq.) *tert*-butyl 3-hydroxypropylcarbamate in 230 ml dichloromethane. The reaction solution was stirred for 10 min at room temperature and then cooled to 0°C. 21.79 g (1.1 eq.) TBDMSCl were added to this solution at 0°C and on completion of the addition the mixture was stirred for 1 h at room temperature. The reaction course was monitored by thin-layer chromatography (30% EtOAc/hexane).

Once the conversion was complete, the reaction mixture was filtered over celite and the filtrate mixed with 200 ml water and extracted with dichloromethane. The combined organic phases were dried over Na₂SO₄. Following removal of the solvent under reduced pressure, 32 g (84%) of product were obtained in the form of an oil.

Stage 3: *tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)propyl(methyl)carbamate

50 g (1 eq.) *tert*-butyl 3-(*tert*-butyldimethylsilyloxy)propylcarbamate dissolved in 200 ml THF were added dropwise to a mixture of 20.7 g (5 eq.) sodium hydride and 300 ml THF at 0°C. After heating the reaction mixture to 10°C, 32.3 ml (3 eq.) methyl iodide were added dropwise. On completion of the addition, the mixture was stirred for 3 h at room temperature. The reaction course was monitored by thin-layer chromatography (30% EtOAc/hexane).

Once the conversion was complete, the reaction mixture was quenched with saturated NH₄Cl solution and then extracted with ethyl acetate. The combined organic phases were dried over Na₂SO₄. Following removal of the solvent under reduced pressure, 48 g (92%) of product were obtained in the form of an oil.

Stage 4: *tert*-Butyl-3-hydroxypropyl(methyl)carbamate

482.5 ml (5 eq.) acetic acid dissolved in 386 ml water were added dropwise over a period of 45 min to a solution of 95.6 g (1 eq.) *tert*-butyl 3-(*tert*-butyldimethylsilyloxy)propyl(methyl)carbamate dissolved in 386 ml THF at 0°C and the reaction mixture was then stirred for 20 h at room temperature. As the starting product had not yet been completely converted, the mixture was cooled to 0°C, 50 ml dilute acetic acid were added over a period of 20 min and the mixture was stirred for a further 1 h at 0°C. The reaction course was monitored by thin-layer chromatography (10% EtOAc/hexane).

GRA3454-WO
22nd December 2009

Once the conversion was almost complete, the reaction mixture was concentrated under reduced pressure, adjusted to a pH of ~ 9 with saturated Na₂CO₃ solution and extracted with 10% IPA/CH₃Cl. The combined organic phases were dried over Na₂SO₄. Following removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel; 10% EtOAc/hexane). 40 g (66%) of product were obtained in the form of a colourless oil.

Stage 5: *tert*-Butyl methyl(3-oxopropyl)carbamate

A catalytic amount of TEMPO was added to a mixture of 20 g (1 eq.) *tert*-butyl 3-hydroxypropyl(methyl)carbamate in 200 ml dichloromethane and 17.7 g (2 eq.) sodium hydrogen carbonate in 100 ml water at 0°C. 140 ml (7 eq.) NaOCl were then added dropwise over a period of 30 min to the solution at a temperature of 0°C and the reaction mixture obtained was stirred for a further 15 min at 0°C. The reaction course was monitored by thin-layer chromatography (40% EtOAc/hexane). Once the conversion was complete, the reaction mixture was mixed with 150 ml water and the phases were separated. The organic phase was dried over Na₂SO₄. Following removal of the solvent under reduced pressure, 16 g (85%) of product were obtained in the form of a yellowish oil.

Stage 6: *N,N*-Dimethyl-4-(thiophen-2-yl)piperidin-4-amine bis hydrochloride

HCl gas was passed through a solution of 6 g (1 eq.) *tert*-butyloxycarbonyl-4-(dimethylamino)-4-(thiophen-2-yl)piperidine in 120 ml chloroform at 0°C for 1 h. The reaction course was monitored by thin-layer chromatography (75% EtOAc/hexane). Once the conversion was complete, the solvent was removed under reduced pressure and 5.3 g (98%) of product were obtained in the form of a white solid.

GRA3454-WO
22nd December 2009

Stage 7: *tert*-Butyl 3-(4-(dimethylamino)-4-(thiophen-2-yl)piperidin-1-yl)propyl(methyl)carbamate

6.4 g (1.3 eq.) *tert*-butyl methyl(3-oxopropyl)carbamate were added to a solution of 7.5 g (1 eq.) *N,N*-dimethyl-4-(thiophen-2-yl)piperidin-4-amine bis hydrochloride in 75 ml methanol at 0°C and the reaction mixture was stirred for 15 min at 0°C. 4.9 g (3 eq.) sodium cyanoboron hydride were then added in portions and the mixture was stirred for 90 min at room temperature. The reaction course was monitored by thin-layer chromatography (20% MeOH/CHCl₃). As the conversion was not yet complete, the pH of the reaction mixture was adjusted to 5-6 with acetic acid and the mixture was stirred for 12 h at room temperature.

Once the conversion was complete, the methanol was distilled off, water was added, the mixture obtained was extracted with IPA/chloroform (2 x 100 ml) and the combined organic phases were dried over Na₂SO₄. Following removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel; 5% MeOH/CHCl₃). 8.5 g (84%) of product were obtained.

Stage 8: *N,N*-Dimethyl-1-(3-(methylamino)propyl)-4-(thiophen-2-yl)piperidin-4-amine tris hydrochloride

HCl gas was passed through a solution of 1.5 g (1 eq.) *tert*-butyl 3-(4-(dimethylamino)-4-(thiophen-2-yl)piperidin-1-yl)propyl(methyl)carbamate in 30 ml chloroform at 0°C for ~ 30 min. The reaction course was monitored by thin-layer chromatography (20% MeOH/CHCl₃).

Once the conversion was complete, the solvent was removed under reduced pressure. After trituration with diethyl ether, 1.5 g (98%) of product were obtained in the form of a white solid. The corresponding free base was released using potassium hydroxide.

Amine F-10: Dimethyl-(4-thiophen-2-yl piperidin-4-yl)amine dihydrochloride

Stage 1: *tert*-Butyloxycarbonyl-4-cyano-4-(dimethylamino)piperidine

500 ml (10 eq.) dimethylamine solution and 109.9 g (5 eq.) dimethylamine hydrochloride were added to a solution of 50 g (1 eq.) *tert*-butyloxycarbonyl-4-oxopiperidine in 100 ml methanol and the mixture was cooled to 5°C. 5 ml (0.1 eq.) hydrochloric acid were then added dropwise to the reaction mixture over a period of

GRA3454-WO
22nd December 2009

10 min and the mixture was stirred for 60 min at room temperature. 48.9 g (3 eq.) potassium cyanide were added in portions to this reaction mixture and the mixture was stirred for 24 h at room temperature. Once the conversion was complete, 150 ml water were added to the reaction mixture and it was extracted 3 times with 100 ml ethyl acetate. The combined organic phases were dried with Na₂SO₄. Following removal of the solvent under reduced pressure, crude product was obtained which was recrystallised out of hexane. 57 g (90%) of product were obtained in the form of a colourless solid.

Stage 2: *tert*-Butyloxycarbonyl-4-(dimethylamino)-4-(thiophen-2-yl)piperidine

A little iodine was added to a mixture of 5.6 g (3 eq.) magnesium and 20 ml dry diethyl ether, followed over a period of 10 min by 5 g 2-bromothiophene, and the mixture was stirred for a further 10 min. Once the reaction had started, 33.5 g (2.6 eq.) 2-bromothiophene dissolved in 80 ml diethyl ether were added dropwise and the mixture was stirred for a period of 2 h at room temperature. The Grignard reagent prepared in the preceding step was added dropwise to a solution of 20 g (1 eq.) *tert*-butyloxycarbonyl-4-cyano-4-(dimethylamino)piperidine dissolved in 200 ml THF and stirred overnight at room temperature. Once the conversion was complete, the reaction solution was cooled to 0°C, mixed with saturated NH₄Cl solution, extracted with ethyl acetate (3 x 100 ml) and the combined organic phases were dried with Na₂SO₄. Following removal of the solvent under reduced pressure, the residue was purified by column chromatography (alox neutral; 30% EtOAc/hexane). 6.1 g (25%) of product were obtained in the form of a white solid.

Stage 3: *N,N*-Dimethyl-4-(thiophen-2-yl)piperidin-4-amine bishydrochloride

HCl gas was passed through a solution of 10 g (1 eq.) *tert*-butyloxycarbonyl-4-(dimethylamino)-4-(thiophen-2-yl)piperidine in chloroform at 0°C for ~ 1 h. Once the conversion was complete, 200 ml water were added to the reaction mixture, it was adjusted to a pH of ~ 8 with Na₂CO₃ and then extracted with 15% IPA/CHCl₃. The combined organic phases were dried over Na₂SO₄. Following removal of the solvent under reduced pressure, 6 g (89%) of product were obtained in the form of a white solid.

GRA3454-WO
22nd December 2009

Amine F-11: Dimethyl-[1-(3-methylaminopropyl)-4-phenyl piperidin-4-yl]amine trihydrochloride

Stage 1: *tert*-Butyl 3-(4-(dimethylamino)-4-phenylpiperidin-1-yl)propyl(methyl)carbamate

11.1 g (1.3 eq.) *tert*-butyl methyl(3-oxopropyl)carbamate were added to a solution of 11 g (1 eq.) *N,N*-dimethyl-4-phenylpiperidin-4-amine dihydrochloride in 110 ml methanol at 0°C and the reaction mixture was stirred for 15 min at 0°C. 6.2 g (3 eq.) sodium cyanoboron hydride were then added in portions and the mixture was stirred for 30 min at room temperature. The reaction mixture obtained was adjusted to a pH of 5-6 with acetic acid and stirred for 12 h at room temperature. The reaction course was monitored by thin-layer chromatography (20% MeOH/CHCl₃). As the conversion was still not complete, 2.4 g sodium cyanoboron hydride were added and the reaction mixture obtained was adjusted to pH 5-6 with acetic acid and stirred for 60 min at room temperature.

Once the conversion was complete, the methanol was distilled off, the mixture was made alkaline with saturated NaHCO₃ solution, the mixture obtained was extracted with chloroform (3 x 100 ml) and the combined organic phases were dried over Na₂SO₄. Following removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel; 5% MeOH/CHCl₃). 9 g (60%) of product were obtained.

Stage 2: *N,N*-Dimethyl-1-(3-(methylamino)propyl)-4-phenylpiperidin-4-amine hydrochloride

HCl gas was passed through a solution of 9 g (1 eq.) *tert*-butyl 3-(4-(dimethylamino)-4-phenylpiperidin-1-yl)propyl(methyl)carbamate in 100 ml chloroform at 0°C for 1 h. The reaction course was monitored by thin-layer chromatography (20% MeOH/CHCl₃).

Once the conversion was complete, the solvent was removed under reduced pressure and after trituration with diethyl ether 10 g (100%) of product were obtained in the form of a white solid.

GRA3454-WO
22nd December 2009

Amine F-12: [4-(Azetidin-1-yl)-4-phenyl-cyclohexyl]amine hydrochloride

Stage 1: 4-(Azetidin-1-yl)-4-phenylcyclohexanone oxime

A solution of 4-(azetidin-1-yl)-4-phenylcyclohexanone (8.4 g) in methanol (84 ml), water (84 ml) and sodium hydrogen carbonate (10.08 g) was stirred for 5 min at room temperature, then hydroxylamine hydrochloride (6.95 g) was added in portions and the mixture was stirred for 8 hours at RT. A further 0.4 equiv. of sodium hydrogen carbonate and hydroxylamine hydrochloride were then added, and stirring was carried out for 16 h at room temperature. Then the reaction mixture was concentrated under reduced pressure, the organic phase was separated off and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure to yield the desired crude product. Yield: 6 g (67% crude)

Stage 2: [4-(Azetidin-1-yl)-4-phenyl-cyclohexyl]-amine

To a solution of the oxime (6 g) obtained above in methanol (60 ml) there was added Raney nickel (2 g) followed by ammonia (30 ml), and the reaction mixture was stirred for 24 hours at room temperature under a hydrogen atmosphere. The reaction mixture was filtered over celite and then washed with methanol. Methanol was distilled off, and the solid residue was washed with ethyl acetate/hexane, dried and purified to yield the desired product. Yield: 5 g (88%)

Amine F-13: 2-(1-Pyridin-4-yl-piperidin-4-yl)ethylamine dihydrochloride

(i): *tert*-Butyl 2-(piperidin-4-yl)ethylcarbamate (0.2 g, 0.876 mmol), 4-chloropyridinium chloride (0.197 g, 1.314 mmol) and N-ethyl diisopropylamine (0.37 ml, 2.19 mmol) were refluxed in 2-propanol (10 ml) for 15 h. Saturated sodium hydrogen carbonate solution (20 ml) and ethyl acetate (50 ml) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 50 ml). The combined organic phases were dried over magnesium sulfate and concentrated to small volume under vacuum. The crude product was purified by column chromatography (silica gel) with ethyl acetate/dichloromethane/methanol/ammonia (25% eq.) 400/100/50/1. Yield: 80 mg, 30%

GRA3454-WO
22nd December 2009

(ii): Hydrogen chloride (1.25 M solution in methanol, 1.25 ml) was added to a solution of *tert*-butyl 2-(1-(pyridin-4-yl)piperidin-4-yl)ethylcarbamate (0.12 g, 0.393 mmol) in methanol (3 ml) at room temperature and the reaction mixture was refluxed for 1 h. The solvent was removed under vacuum and the residue was dried.

Yield: quantitative

Amine F-14: 3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride

(i): *tert*-Butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (1 g, 3.931 mmol), 4-chloropyridinium chloride (1.765 g, 11.794 mmol) and triethylamine (2.2 ml, 15.725 mmol) were refluxed for 15 h in 1-butanol (50 ml). Saturated sodium hydrogen carbonate solution (30 ml) and ethyl acetate (80 ml) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 80 ml). The combined organic phases were dried over magnesium sulfate and concentrated to small volume under vacuum. The crude product was purified by column chromatography (silica gel) with ethyl acetate/hexane/methanol/ammonia (25% eq.) 400/40/40/1.

Yield: 0.52 g, 39%

(ii): Hydrogen chloride in methanol (1.25 mol/l, 6.3 ml) was added to *tert*-butyl 9-(pyridin-4-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (0.52 g, 1.569 mmol) and refluxed for 1 h. The solvent was removed under vacuum, the residue taken up in ethanol (3 ml) and cooled. Acetone (80 ml) was added and the mixture was stirred for 30 min in an ice bath. The precipitate was siphoned off, washed with diethyl ether and dried under vacuum.

Yield: 0.4 g, 83%

Alternatively, the Boc cleavage can also be carried out in the presence of TFA in DCM.

Amine F-15: (1-Pyridin-4-yl-piperidin-4-yl)methylamine dihydrochloride

(i) Potassium carbonate (3 eq.), L-proline (0.4 eq.), CuI (0.2 eq.) and 4-bromopyridine (1 eq.) were added to a solution of *tert*-butyl piperidin-4-ylmethylcarbamate (3g, 15 mmol) in DMSO under a protective gas atmosphere. The reaction mixture was

GRA3454-WO
22nd December 2009

heated to 100°C for 20 hours, diluted with ethyl acetate and saturated sodium chloride solution after cooling to room temperature, filtered over celite and the residue was rewashed with ethyl acetate. The phases were separated, dried and concentrated under reduced pressure. The crude product was processed by column chromatography. Yield 30%

(ii) *tert*-Butyl (1-(pyridin-4-yl)piperidin-4-yl)methylcarbamate (7 g, 24.4 mmol) was dissolved in methanol, cooled in an ice bath, mixed with acetyl chloride (8.6 ml, 121.8 mmol) and stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was taken up in water/dichloromethane. The phases were separated, the aqueous phase was washed with dichloromethane (twice) and freeze dried.

Yield: quantitative

Amine F-16: 1-(4-Fluorophenyl)-piperazine [16141-90-5] commercially available from e.g. Aldrich. **Amine F-17:** 2-Piperazin-1-yl-pyrimidine [20980-22-7] commercially available from e.g. Aldrich. **Amine F-18:** 1-Pyridin-4-yl piperazine [1008-91-9] commercially available from e.g. ABCR.

GRA3454-WO
22nd December 2009

Amine F-19: 4-Pyridin-3-yl piperidin-4-ol

(i) (Apparatus: 1-l three-necked flask with nitrogen balloon flask) Magnesium (5.7 g) was introduced into anhydrous ether (125 ml), 1,1-dibromoethane (0.5 g) and isopropylchloride (17.3 ml) were added dropwise and the mixture was stirred for 15 min to initiate the magnesium. A solution of 3-bromopyridine (25 g) in anhydrous tetrahydrofuran (400 ml) was added dropwise over 20 min at 40°C, then the mixture was refluxed for 2 h. Then a solution of 1-benzylpiperidin-4-one (30 g) in anhydrous tetrahydrofuran (100 ml) was added dropwise over 20 min at 40°C and the mixture was stirred overnight at room temperature. Analysis by thin-layer chromatography: 10% methanol in chloroform. The reaction mixture was hydrolysed at 0°C with water (50 ml) and filtered over celite. It was extracted with dichloromethane (2 x 100 ml), the combined organic phases were washed with water (50 ml), dried over sodium sulfate and concentrated to small volume under vacuum. The crude product was purified by column chromatography (alox neutral) with 5% methanol in chloroform. Yield: 8.2 g (19.3%)

(ii) (Apparatus: 1-l three-necked flask with cooler) Palladium on carbon (10%, catalytic amount) followed by ammonium formate solution (22.7 g in 50 ml water) was added to a solution of 1-benzyl-4-(pyridin-3-yl)piperidin-4-ol (32 g) in methanol (220 ml). The reaction mixture was refluxed overnight at 68°C. Analysis by thin-layer chromatography: 20% methanol in chloroform. The mixture was filtered over celite and the filtrate concentrated to small volume under vacuum. The residue was washed with acetone (100 ml) in order to obtain the desired compound in a clean state.

Yield: 17.3 g (81.3%)

Amine F-20: 4-Pyridin-2-yl piperidin-4-ol [50461-56-8] commercially available from e.g. Tyger Scientific. **Amine F-21: 1-Methyl-4-piperidin-4-yl piperazine** [436099-90-0] commercially available from e.g. ABCR. **Amine F-22: 1-[(1-Methyl-piperidin-4-yl)-methyl] piperazine** [735262-46-1] commercially available from e.g. Otava. **Amine F-23: 3-(4-Fluorophenyl)-3,8-diazaspiro[4.5]decan-4-one hydrochloride** (MDL No.: MFCD05861564) commercially available from e.g. ASW MedChem.

GRA3454-WO
22nd December 2009

Amine F-24: 4-Piperidin-4-yloxy pyridine hydrochloride

(i) *tert*-Butyl-4-hydroxypiperidine-1-carboxylate (6.348 g, 31.546 mmol) and triphenylphosphine (10.256 g, 39.432 mmol) were added to a solution of 4-hydroxypyridine (3 g, 31.546 mmol) in tetrahydrofuran (50 ml) at room temperature. Then diisopropyl azodicarboxylate (7.66 ml, 39.432 mmol) was added dropwise and the mixture was then stirred for 15 h at 55°C. Saturated sodium hydrogen carbonate solution (50 ml) was added to the reaction mixture and it was extracted with ethyl acetate (4 x 80 ml). The combined organic phases were washed with saturated sodium chloride solution (20 ml), dried (Na₂SO₄) and concentrated to small volume under vacuum. Then the crude product was purified by column chromatography (silica gel) with ethyl acetate/hexane (4:1).

Yield: 4.11 g (46%)

(ii) Hydrogen chloride (47 ml, 59 mmol, 1.25 M solution in methanol) was added to a solution of *tert*-butyl 4-(pyridin-3-yloxy)piperidine-1-carboxylate (4.1 g, 14.727 mmol) in methanol (10 ml) at room temperature and the reaction mixture was refluxed for 30 min. The solvent was removed under vacuum and the residue taken up in a little ethanol and mixed with diethyl ether. Then the mixture was cooled for 30 min in an ice bath and the solid that was formed was filtered off and dried.

Yield: 3.46 g (93%)

Amine F-25: 1-(4-Fluorophenyl)-3-methyl-3,8-diazaspiro[4.5]decan-4-one hydrochloride (MDL No: MFCD08460813) commercially available from e.g. ASW MedChem. **Amine F-26: 3-[(4-Fluorophenyl)-methyl]-3,8-diazaspiro[4.5]decan-4-one hydrochloride** (MDL No: MFCD08461093) commercially available from e.g. ASW MedChem. **Amine F-27: 3-Benzyl-3,8-diazaspiro[4.5]decan-4-one hydrochloride** (MDL No: MFCD02179153) commercially available from e.g. ASW MedChem. **Amine F-28: 3-Benzyl-3,7-diazaspiro[4.4]nonane** (MDL No: MFCD04115133) commercially available from e.g. Tyger.

GRA3454-WO
22nd December 2009

Amine F-29: 3-[4-(2-Pyrrolidin-1-yl-ethoxy)piperidin-4-yl] pyridine
dihydrochloride

(i) n-Butyl lithium (2 eq.) was added to a solution of 3-bromopyridine (7.94 g, 1 eq.) in dry THF (1600 ml) at -70°C and the mixture was stirred at this temperature for 1 h. Then a solution of N-Boc piperidone (10 g, 1 eq.) in THF (400 ml) was added at -70°C and the mixture was stirred at this temperature for 2 h (DC control). On completion of the reaction the mixture was hydrolysed with saturated ammonium chloride solution and then slowly heated to RT. It was diluted with ethyl acetate. The organic phase was washed with sodium chloride solution and dried over sodium sulfate. The solvent was removed in a rotary evaporator and the crude product obtained was purified by column chromatography (silica gel, DCM/methanol, 9:1).

(ii) The alcohol (2 g) was dissolved in benzene (20 ml), mixed with sodium amide (10 eq.) at 25°C and stirred at this temperature for 15 min. Then 1-(2-chloroethyl)pyrrolidine (1.2 eq.) was added and the mixture was refluxed for 16 h. On completion of the reaction (DC control) the mixture was cooled to 0°C and hydrolysed with ice. The aqueous phase was extracted with ethyl acetate. The organic phase was washed with water and saturated NaCl solution and dried over Na₂SO₄. The solvent was removed in a rotary evaporator and the crude product obtained was purified by column chromatography (silica gel, DCM/methanol, 95:5).

(iii) *tert*-Butyl 4-(pyridin-3-yl)-4-(2-(pyrrolidin-1-yl)ethoxy)piperidine-1-carboxylate (12.7 g, 33.82 mmol) was dissolved in methanol (80 ml), cooled in an ice bath and mixed with acetyl chloride (12 ml, 169.1 mmol). After 3 h DC control (dichloromethane/methanol 9/1) indicated that the reaction was complete; the solvent was removed under vacuum and the residue taken up in water/dichloromethane. The phases were separated, the aqueous phase was washed with dichloromethane (twice) and freeze dried.

Yield: quantitative

GRA3454-WO
22nd December 2009

Amine F-30: 2-(Pyridin-4-yl-methyl)-2,5-diazabicyclo[2.2.1]heptane dihydrochloride

(i): *tert*-Butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5 g, 25.214 mmol) and pyridine-4-carbaldehyde (2.97 g, 27.74 mmol) were introduced into dichloromethane (650 ml), mixed with sodium triacetoxyboron hydride (10.6 g, 50.43 mmol) and glacial acetic acid (0.14 ml, 2.521 mmol) and the reaction mixture was stirred at room temperature for 15 h. The mixture was then hydrolysed with saturated sodium hydrogen carbonate solution, the phases were separated and the aqueous phase was extracted twice with diethyl ether. The combined organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (silica gel; dichloromethane/methanol).

Yield: 5.8 g, 79%

(ii): *tert*-Butyl 5-(pyridin-4-ylmethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5.8 g, 20.0 mmol) was dissolved in methanol (50 ml), cooled in an ice bath and mixed with acetyl chloride (7.1 ml). The reaction mixture was stirred for 15 h at room temperature and then concentrated under reduced pressure. The residue was taken up in water, the aqueous phase was washed twice with dichloromethane, frozen and the water removed by freeze drying.

Yield: 5.2 g, 99%

Amine **F-31** was prepared from *tert*-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate by reacting it with the corresponding aldehyde and then eliminating the protective group in a manner analogous to amine **F-31**.

Amine	Aldehyde	Yield (after 2 stages)
2-[(4-Fluorophenyl)methyl]-2,5-diazabicyclo[2.2.1]heptane dihydrochloride (F-31)	4-Fluoro-benzaldehyde	77%

GRA3454-WO
22nd December 2009

Amine F-32: (1-Pyridin-4-yl-piperidin-4-yl)amine dihydrochloride (MDL No: MFCD06797043) commercially available from e.g. ABCR. **Amine F-33:** 4-Phenyl-2,4,8-triazaspiro[4.5]decan-1-one (MDL No: MFCD00005977) commercially available from e.g. ABCR.

Amine F-34: N-[[4-(4-Methylpiperazin-1-yl)-piperidin-4-yl]methyl] pyridine-4-carboxylic acid amide dihydrochloride

Stage 1: Water (1.2 ml), N-methylpiperazine (1 eq.), acetic acid (1 eq.) and KCN (1.1 eq.) were added to a methanolic solution (20 ml) of N-benzyl piperidone (52.9 mmol). The reaction mixture was stirred for 1 h at 25°C and a solid was precipitated. 35% ammonium hydroxide (300 ml) and ice (100 g) were then added to the batch. The solid was filtered off, washed repeatedly with water and then dried. Yield: 45%

Stage 2: A solution of concentrated H₂SO₄ (1.5 eq.) in THF (1 ml/mmol) was added dropwise to a cold (0°C) suspension of LiAlH (3 eq.) in THF (2 ml/mmol) under an argon atmosphere (very exothermic). The suspension was stirred for 90 min at 25°C and then cooled to 0°C. The cyano component (1 eq.) in THF (2 ml/mmol) was added dropwise to this cold reaction mixture and on completion of the addition the mixture was heated for 12 h at 50°C (DC control). The batch was carefully quenched with a saturated sodium sulfate solution and filtered through celite. The residue was washed with ethyl acetate, the organic phase was dried over sodium sulfate and concentrated to small volume under reduced pressure. The crude amine was obtained and was used directly in the next stage with no further purification. Yield: 79%

Stage 3: TEA (5 eq.) and trifluoroacetic acid anhydride (2 eq.) were added to a solution of the amine from the second stage (74.5 mmol) in dichloromethane (5 ml/mmol) at 0°C. The reaction mixture was stirred for 2 h at 25°C (DC control). It was diluted with dichloromethane, washed successively with water and saturated NaCl solution and dried over sodium sulfate. Concentration to small volume under reduced pressure resulted in the crude product, which was purified by column chromatography (10% methanol in dichloromethane). Yield: 64%

GRA3454-WO
22nd December 2009

Stage 4: A solution of the benzylated product from the third stage (19 g) in methanol (285 ml) was degassed under argon. This was done by adding Pd(OH)₂ 10% (9.5 g) and AcOH (7.6 ml) and hydrogenating the mixture for 16 h under normal pressure (DC and LCMS control). The mixture was filtered through celite, the residue washed with methanol and the combined organic phases evaporated to dryness under reduced pressure. The crude product that was obtained was used directly in the next stage with no further purification. Yield: 14.8 g (quantitative)

Stage 5: DIPEA (1.5 eq.) and Boc anhydride (1.2 eq.) were added to a solution of the amine from the fourth stage (14.8 g, 48 mmol) in dichloromethane (240 ml) at 0°C. The reaction mixture was stirred for 3 h at room temperature. It was diluted with dichloromethane, washed successively with water and saturated NaCl solution and dried over sodium sulfate. Concentration to small volume under reduced pressure resulted in the crude product, which was purified by column chromatography (10% methanol in dichloromethane). Yield: 12.5 g (63%)

Stage 6: 1N NaOH (120 ml) was added to a solution of the Boc-protected product from the fifth stage in methanol (80 ml) at 0°C and the reaction mixture was stirred for 2 h at 25°C (DC control). The mixture was diluted with ethyl acetate, the aqueous phase was extracted repeatedly with ethyl acetate and the combined organic phases were washed with saturated NaCl solution. After drying over sodium sulfate the organic phase was concentrated to small volume under reduced pressure and the crude product obtained was used directly in the next stage with no further purification. Yield: 7.7 g (83%)

Stage 7: Triethylamine (2.5 eq.) and isonicotinoyl chloride hydrochloride (1 eq.) were added to a cold (0°C) solution of the amino component from the sixth stage (1 eq.) in dichloromethane. The reaction mixture was stirred for 2 h at 25°C (DC control). The mixture was quenched with crushed ice, diluted with dichloromethane and the organic phase was washed successively with water and saturated NaCl solution. After drying over sodium sulfate the organic phase was concentrated to small volume under reduced pressure and the crude product obtained was purified by column chromatography (aluminium oxide neutral, methanol in dichloromethane 1:9). Yield: 70%

GRA3454-WO
22nd December 2009

Stage 8: HCl in dioxane (2M, 6 ml/mmol) was added to a solution of the Boc-protected product from the seventh stage in dioxane (2 ml/mmol) at 0°C and the reaction mixture was stirred for 3 h at 25°C (DC control). The precipitated solid was filtered off, washed with ether under inert gas (very hygroscopic) and then dried under vacuum. Yield: 80%

Amine F-35: 1-(Pyridin-2-yl-methyl)-[1,4]diazepan [247118-06-5] available commercially from ChemCollect, for example. **Amine F-36:** 4-Pyrrolidin-3-yl-pyridine [150281-47-3] available commercially from Interchim, for example. **Amine F-37:** Piperazin-1-yl-pyridin-3-yl-methanone [39640-08-9] available commercially from Fluorochem, for example.

Amine F-38: 8-(Pyridin-4-yl)-2,8-diazaspiro[4.5]decane dihydrochloride

The synthesis was carried out analogously to the synthesis of amine F-14.

To that end, tert-butyl 2,8-diazaspiro[4.5]decane-2-carboxylate was reacted with 4-chloropyridinium chloride in stage (i) (yield: 22%). Then, in stage (ii), the Boc protecting group was removed. When the reaction was complete and the methanol had been removed under vacuum, the residue was taken up in ethanol and cooled, and acetone was added. The resulting suspension was stirred for 30 min in an ice bath, and the precipitate was filtered off with suction, washed with acetone and dried under vacuum (yield: 92%).

Amine F-39: 3-(Pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene bis(2,2,2-trifluoroacetate)

Stage (i): tert-Butyl 4-methylenepiperidine-1-carboxylate

In a heated apparatus flushed with protecting gas, methyltriphenylphosphonium bromide (53.82 g, 150 mmol) was suspended in diethyl ether (300 ml) and cooled to 0°C. Potassium tert-butyrate (15.78 g, 140 mmol) was added in portions, and the suspension was stirred for 30 min. Boc-4-piperidone (20 g, 100 mmol), dissolved in diethyl ether (200 ml), was slowly added dropwise, and then the mixture was heated to room temperature and stirred for 15 h. The reaction mixture was cooled, and

GRA3454-WO
22nd December 2009

ammonium chloride solution (300 ml, 10%) was added. After phase separation, the aqueous phase was extracted with ether (3 x 200 ml), and the combined organic phases were dried (MgSO₄) and concentrated under vacuum. The crude product was purified by column chromatography (silica gel) with ether/hexane (1:1).

Yield: 18.57 g (93%)

Stage (ii): tert-Butyl 3-(pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate

(a): (Z)-N-Hydroxyisonicotinimidoyl chloride: Pyridine-4-carbaldoxime (1 g, 8.19 mmol) was dissolved in DMF (10 ml); a solution of N-chlorosuccinimide (1.31 g, 9.83 mmol) in DMF (5 ml) was slowly added dropwise, and the reaction mixture was stirred at room temperature. When the reaction was complete (monitoring by thin-layer chromatography, here 6 h), diethyl ether (50 ml) and water (20 ml) were added, phase separation, extraction of the aqueous phase with diethyl ether (5 x 30 ml). The combined organic phases were washed with water (50 ml) and saturated sodium chloride solution (50 ml), dried (MgSO₄) and concentrated under vacuum. The crude substance was reacted without being purified and analysed further.

Yield: 0.74 g (100%)

(b): tert-Butyl-4-methylenepiperidine-1-carboxylate (0.7 g, 3.55 mmol) was dissolved in dichloromethane (10 ml) and dissolved to 0°C under protecting gas. (Z)-N-Hydroxyisonicotinimidoyl chloride (1.67 g, 10.64 mmol), dissolved in dichloromethane (15 ml), was added, followed by triethylamine (1.2 ml, 8.5 mmol) in dichloromethane (10 ml). The reaction mixture was heated slowly to room temperature and stirred for 15 h. It was diluted with dichloromethane (50 ml) and washed with water, 10% citric acid and saturated sodium chloride solution (in each case 30 ml), dried (MgSO₄) and concentrated under vacuum. The crude product was purified by column chromatography (silica gel) with ethyl acetate/hexane 10/1.

Yield: 0.48 g (42%)

Stage (iii): 3-(Pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene bis(2,2,2-trifluoroacetate)

tert-Butyl 3-(pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (0.48 g, 1.5 mmol) was dissolved in dichloromethane (10 ml) and cooled, and trifluoroacetic

GRA3454-WO
22nd December 2009

acid (1.2 ml, 15 mmol) was added slowly. After refluxing for 2 h, the solvent was removed under vacuum and the residue was co-evaporated with in each case 30 ml of toluene and methanol.

Yield: 0.74 g (100%)

Amine F-40: 6-(Piperidin-1-ylmethyl)-2-(pyrrolidin-3-yl)-1,2,3,4-tetrahydroisoquinoline trihydrochloride

Stage (i): 2,2,2-Trifluoro-1-(6-(piperidin-1-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone

2-(2,2,2-Trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-carbaldehyde (2 g, 7.78 mmol) and piperidine (660 mg, 7.78 mmol) were dissolved in 1,2-dichloroethane (24 ml), and sodium triacetoxyborohydride (2.29 g, 10.89 mmol) was added. The reaction mixture was stirred for 15 h, then diluted with dichloromethane, and sat. sodium hydrogen carbonate solution (100 ml) was added. After phase separation, the aqueous phase was extracted with dichloromethane (3 x 100 ml). The combined organic phases were washed with sat. sodium chloride solution (50 ml), dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, ethyl acetate/dichloromethane/methanol 10:1:1 + ammonia solution (25% aq.)).

Yield: 1.88 g (74%)

Stage (ii): 6-(Piperidin-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride

2,2,2-Trifluoro-1-(6-(piperidin-1-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone (1.88 g, 5.76 mmol) was dissolved in methanol (23 ml); potassium carbonate (1.99 g, 14.4 mmol) was added and the reaction mixture was stirred for 15 h at RT. The solvent was then removed under vacuum, and the residue was taken up in dichloromethane and washed with water (15 ml). The aqueous phase was extracted with dichloromethane, and the combined organic phases were dried over sodium sulfate and concentrated under vacuum. The residue was taken up in an acetone/diethyl ether mixture, and the hydrochloride was precipitated with 2 M hydrogen chloride in diethyl ether (3 equiv.) and, after being filtered off with suction, was dried under vacuum.

GRA3454-WO
22nd December 2009

Yield: 1.62 g (93%)

Stage (i): tert-Butyl 3-(6-(piperidin-1-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl)pyrrolidine-1-carboxylate

6-(Piperidin-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride (0.5 g, 1.65 mmol), triethylamine (0.57 ml, 4.12 mmol) and tert-butyl 3-oxopyrrolidine-1-carboxylate (305 mg, 1.65 mmol) were dissolved in 1,2-dichloroethane (13 ml), and sodium triacetoxyborohydride (480 mg, 2.309 mmol) was added. The reaction mixture was stirred for 2 h, and then sat. sodium hydrogen carbonate solution was added. After phase separation, the aqueous phase was extracted with dichloromethane (2 x). The combined organic phases were washed with sat. sodium chloride solution (1 x), dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, ethyl acetate/methanol/ammonia (25% aq.) (200:20:1).

Yield: 0.55 g (83%)

Stage (ii): 6-(Piperidin-1-ylmethyl)-2-(pyrrolidin-3-yl)-1,2,3,4-tetrahydroisoquinoline trihydrochloride

1.25 M hydrogen chloride in methanol (11 ml) was added to tert-butyl 3-(6-(piperidin-1-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl)pyrrolidine-1-carboxylate (0.55 g, 1.38 mmol), and the mixture was refluxed for 3 h. The solvent was removed under vacuum and the residue was taken up in ethanol/acetone (5 ml). Diethyl ether (20 ml) was then added, and the resulting precipitate was filtered off and dried under vacuum.

Yield: 0.41 g (73%)

Amine F-41: 2-(Pyridin-4-yl)-2,7-diazaspiro[4.4]nonane dihydrochloride

The synthesis was carried out analogously to the synthesis of amine **F-14**.

To that end, tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate was reacted with 4-chloropyridinium chloride in stage (i) (yield: 50%). Then, in stage (ii), the Boc protecting group was removed. When the reaction was complete and the methanol had been removed under vacuum, the residue was taken up in ethanol and cooled,

GRA3454-WO
22nd December 2009

and acetone was added. The resulting suspension was stirred for 30 min in an ice bath, and the precipitate was filtered off with suction, washed with acetone and dried under vacuum. (Yield: 73%).

Amine F-42: 9-(Azetidin-1-yl)-3-azaspiro[5.5]undecane dihydrochloride

Stage (i): tert-Butyl 9-(azetidin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate

tert-Butyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate (stage (iv) Amine-F43) (1 g, 3.74 mmol) and azetidine (0.25 ml, 3.74 mmol) were placed in 1,2-dichloroethane (15 ml), and sodium triacetoxyborohydride (1.1 g, 5.23 mmol) was added. The reaction mixture was stirred for 3 d at room temperature, and then saturated sodium hydrogen carbonate solution was added. After phase separation, the aqueous phase was extracted with dichloromethane (2 x). The combined organic phases were washed with saturated sodium chloride solution (1 x), dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, ethyl acetate/methanol/ammonia (25% aq.), 100:10:1). Yield: 1 g (89%)

Stage (ii): 9-(Azetidin-1-yl)-3-azaspiro[5.5]undecane

Hydrogen chloride in methanol (1.25 mol/l, 15.5 ml) was added to tert-butyl 9-(azetidin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate (1 g, 3.24 mmol), and the mixture was refluxed for 45 min. The solvent was removed under vacuum and the residue was dissolved in a small amount of ethanol. A solid was then precipitated by addition of acetone, and finally diethyl ether was added and the resulting precipitate was filtered off with suction.

Yield: 0.87 g (95%)

Amine F-43: 9-(Pyridin-4-yloxy)-3-azaspiro[5.5]undecane dihydrochloride

Stage (i): 1-(Benzyloxycarbonyl)piperidine-4-carboxylic acid

To piperidine-4-carboxylic acid (25 g) in THF (75 ml) there was added water (75 ml), followed by sodium bicarbonate (30.8 g). The mixture was cooled to 0°C, and Cbz chloride (38.9 ml) was added dropwise. The reaction mixture was then stirred for 5 h at room temperature (TLC monitoring). When the reaction was complete, the organic

GRA3454-WO
22nd December 2009

solvent was distilled off and the residue was taken up in water (200 ml) and washed with ethyl acetate (2 x 150 ml). The aqueous phase was acidified with dilute aqueous HCl solution and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under vacuum.

Yield: 48.5 g (96%)

Stage (ii): 1-Benzyl 4-methylpiperidine-1,4-dicarboxylate

1-(Benzyloxycarbonyl)piperidine-4-carboxylic acid (48.5 g) in methanol (485 ml) was cooled to 0°C, and thionyl chloride (13.34 ml) was added dropwise. The mixture was then refluxed for 20 min (TLC monitoring). When the reaction was complete, the methanol was distilled off and the residue was taken up in water (15 ml) and with ethyl acetate (2 x 150 ml). The combined organic phases were extracted with water and sat. sodium chloride solution, dried (Na_2SO_4) and concentrated under vacuum.

Yield: 38 g (67%)

Stage (iii): Benzyl 4-formylpiperidine-1-carboxylate

A solution of 1-benzyl 4-methylpiperidine-1,4-dicarboxylate (10 g) in toluene (100 ml), under nitrogen, was cooled to -78°C. Then DIBAL-H (60.9 ml) was added dropwise at -78°C, and the mixture was stirred for 1 h at that temperature (TLC monitoring).

Because the reaction was incomplete, a further 0.2 eq. of DIBAL-H was added and stirring was carried out for a further 30 min (TLC monitoring: some starting material and the corresponding alcohol were detectable). Methanol (40 ml) followed by sat. sodium chloride solution (40 ml) were added slowly to the reaction mixture at -78°C. The mixture was filtered over celite, and the solvent was removed under vacuum. The residue was extracted with ethyl acetate (3 x 75 ml), dried (Na_2SO_4) and concentrated under vacuum. The crude product so obtained was purified by column chromatography (silica gel, 20% ethyl acetate/hexane).

Yield: 4.3 g (49%)

Stage (iv): Benzyl 9-oxo-3-azaspiro[5.5]undec-7-ene-3-carboxylate

Methyl vinyl ketone (1.64 ml), ethanol (5 ml) and water (5 ml) were added to benzyl 4-formylpiperidine-1-carboxylate (5 g). The mixture was then added to a boiling solution of potassium hydroxide (0.22 g) in ethanol (10 ml), and the resulting reaction mixture was refluxed for 1 h (TLC monitoring). When the reaction was complete, the

GRA3454-WO
22nd December 2009

mixture was added to water (25 ml) and extracted with ethyl acetate (2 x 50 ml). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The crude product so obtained was purified by column chromatography (silical gel, 25% ethyl acetate/hexane).

Yield: 2.8 g (46%)

Stage (v): tert-Butyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate

Boc anhydride (9.4 ml) and potassium carbonate (7.56 g) were added to benzyl 9-oxo-3-azaspiro[5.5]undec-7-ene-3-carboxylate (8.2 g) in EtOH/water (9:1) (200 ml). Pd/C (1 g) was then added, and the mixture was subjected to hydrogenolysis for 4 h at 80 psi (TLC monitoring). When the reaction was complete, the mixture was filtered over celite and then rinsed with ethanol and ethyl acetate. The filtrate was dried (Na_2SO_4) and concentrated under vacuum. The residue was taken up in ethyl acetate and water, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The crude product so obtained was purified by column chromatography (silica gel, 20% ethyl acetate/hexane).

Yield: 2.92 g, 40%

Stage (vi): tert-Butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate

tert-Butyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate (1.5 g) was dissolved in THF (7.5 ml) and cooled to -5°C . NaBH_4 (0.212 g) was then added and the mixture was stirred for 1 h at room temperature (TLC monitoring). When the reaction was complete, acetic acid was added to the mixture, and the methanol was then distilled off. The residue was taken up in water (50 ml) and extracted with ethyl acetate (2 x 50 ml). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The crude product so obtained was purified by column chromatography (silica gel, 30% ethyl acetate/hexane).

Yield: 1.2 g (80%)

Stage (vii): tert-Butyl 9-(pyridin-4-yloxy)-3-azaspiro[5.5]undecane-3-carboxylate

4-Chloropyridine hydrochloride (1.3 g) was added to sodium hydride (0.89 g) in DMSO (20 ml), and the mixture was stirred for 10 min. tert-Butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (2.0 g) in DMSO (20 ml) was then added

GRA3454-WO
22nd December 2009

slowly, and the mixture was stirred overnight (TLC monitoring: conversion about 30-35%). A catalytic amount of sodium iodide was added, and the reaction mixture was stirred for 8 h at 80°C (TLC monitoring). Methanol and NaHCO₃ solution were added to the reaction mixture, and stirring was carried out for 20 min. Extraction with ethyl acetate was then carried out, followed by washing with NaHCO₃ solution and cold water. The organic phase was dried (Na₂SO₄) and concentrated under vacuum. The crude product so obtained was purified by column chromatography (silica gel, 70% ethyl acetate/hexane).

Yield: 1.0 g (40%)

Stage (viii): 9-(Pyridin-4-yloxy)-3-azaspiro[5.5]undecane dihydrochloride

tert-Butyl 9-(pyridin-4-yloxy)-3-azaspiro[5.5]undecane-3-carboxylate (1 g, 2.886 mmol) was dissolved in methanol (2 ml); hydrogen chloride in methanol (1.25 mol/l, 11.5 ml) was added, and the mixture was refluxed for 30 min. The solvent was removed under vacuum and the residue was dissolved in a small amount of ethanol. Acetone (about 25 ml) was then added, the mixture was stirred for 30 min at 0°C, and finally the resulting solid was filtered off with suction.

Yield: 0.96 g (>99%)

Amine F-44: 9-(3,3-Difluoroazetidin-1-yl)-3-azaspiro[5.5]undecane dihydrochloride

Stage (i): tert-Butyl 9-(3,3-difluoroazetidin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate

tert-Butyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate (stage (iv) Amine-F43) (1 g, 3.74 mmol) was added to 3,3-difluoroazetidine hydrochloride (0.484 g, 3.74 mmol) and triethylamine (0.52 ml, 3.74 mmol) in 1,2-dichloroethane (15 ml). The mixture was stirred for 5 min, and then sodium triacetoxyborohydride (1.1 g, 5.23 mmol) was added and stirring was carried out for 3 d at room temperature. Saturated sodium hydrogen carbonate solution was added and, after phase separation, the aqueous phase was extracted with dichloromethane (2 x). The combined organic phases were washed with saturated sodium chloride solution (1 x), dried over magnesium sulfate and concentrated under vacuum.

Yield: 1.26 g (98%)

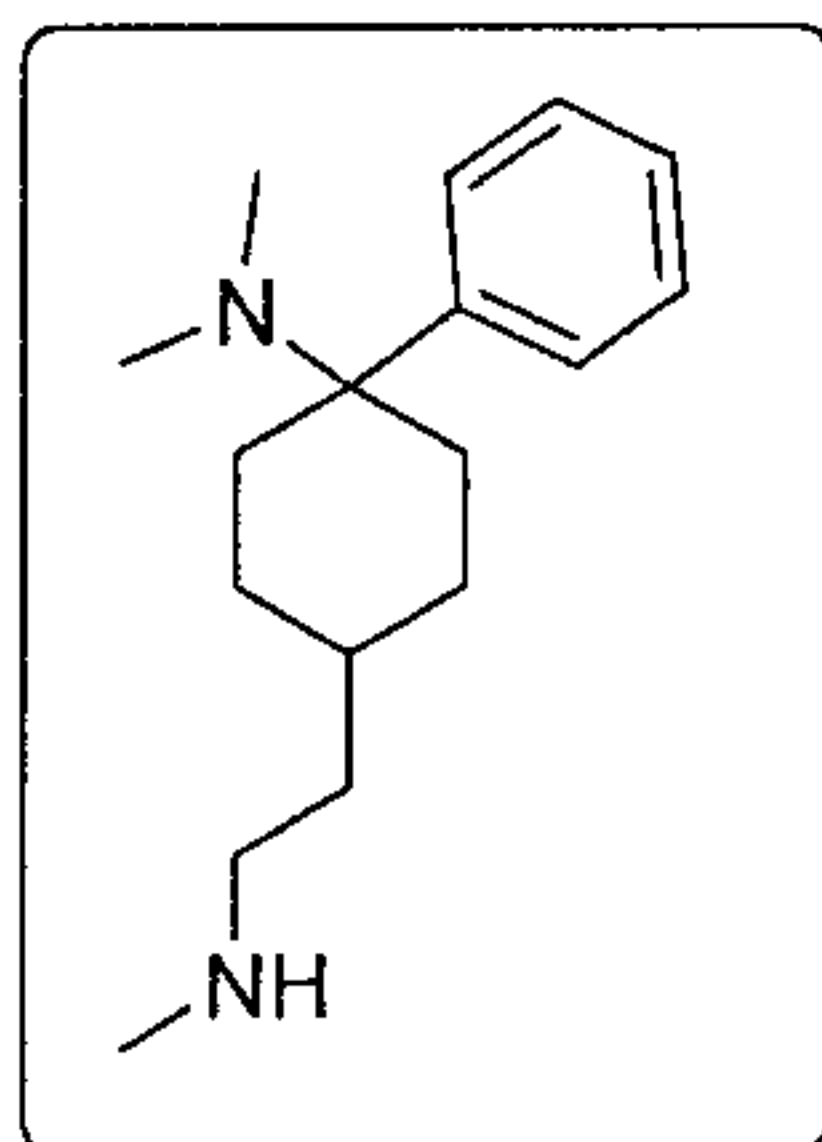
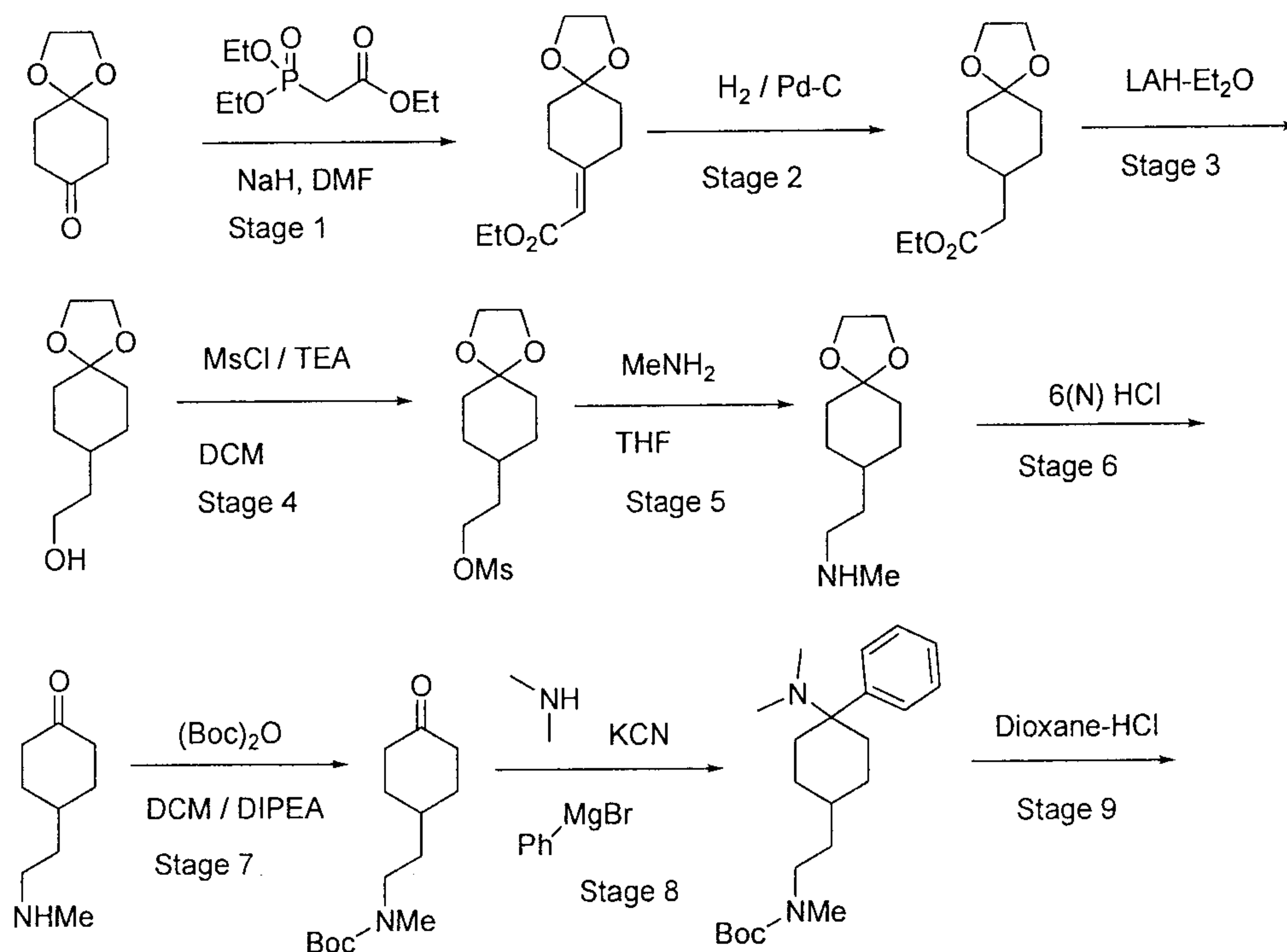
GRA3454-WO
22nd December 2009

Stage (ii): 9-(3,3-Difluoroazetidin-1-yl)-3-azaspiro[5.5]undecane dihydrochloride
tert-Butyl 9-(3,3-difluoroazetidin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate (1.26 g, 3.66 mmol) was dissolved in hydrogen chloride in methanol (1.25 mol/l, 29 ml) and refluxed for 45 min. The solvent was removed under vacuum and the residue was dissolved in a small amount of ethanol. A solid was then precipitated by addition of acetone. The mixture was stirred for 10 min at room temperature, then diethyl ether was added and stirring was carried out for a further 30 min at room temperature. The resulting precipitate was filtered off with suction, washed with diethyl ether and dried under vacuum.

Yield: 1.1 g (95%)

GRA3454-WO
22nd December 2009

Amine F-45: Dimethyl-[4-(2-methylamino-ethyl)-1-phenyl-cyclohexyl]-amine dihydrochloride (F-45)



Stage 1:

A solution of triethyl phosphonoacetate (1.1 eq.) in THF (5 ml/mmol) was added slowly to a suspension, at 0°C, of 60% NaH (1 eq.) in dry THF (5 ml/mmol). The resulting reaction mixture was stirred for 30 min at RT. It was then cooled to 0°C, and 1,4-dioxaspiro[4.5]decan-8-one (1 eq.) in dry THF (5 ml/mmol) was added slowly at a constant temperature. The reaction mixture was stirred for 16 h at 25°C. Quenching

GRA3454-WO
22nd December 2009

with ice and sat. sodium chloride solution was carried out, the aqueous phase was extracted with ethyl acetate, and the organic phase was washed successively with water and sodium chloride solution. The combined org. phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate in n-hexane).

Yield: 90 %

Stage 2:

A solution of the ester (1 eq.) obtained above in stage 1 in methanol (3 ml/mmol) was deoxygenated with argon for 15 minutes, and then 10% Pd/C (50% by weight) was added. The resulting reaction mixture was hydrogenated for 16 h under normal pressure and then filtered off over filtering earth (celite). The residue was washed with methanol, and the combined organic phases were concentrated completely. The crude product was used immediately in the next stage without being purified further.

Yield: 90% (crude product)

Stage 3:

A solution of the ester obtained in stage 2 (1 eq.) in THF (5 ml/mmol) was added slowly in the course of 30 minutes to a suspension, at 0°C, of LAH (1 eq.) in dry THF (3 ml/mmol). When the addition was complete, the reaction mixture was stirred for 1 h at 25°C, cooled to 0°C and quenched with sat. sodium sulfate solution and then filtered over celite. After concentrating the solvent completely, the resulting crude product was used in the next stage without being purified further.

Yield: 80% (crude product)

Stage 4:

Methanesulfonyl chloride (1.1 eq.) was added at 0°C, under a nitrogen atmosphere, to a solution of the alcohol obtained in stage 1 (1 eq.) in DCM (5 ml/mmol). When the addition was complete, the reaction mixture was stirred for 2 h at 25°C and diluted with dichloromethane, and the organic phase was washed successively with water and sat. sodium chloride solution and then dried over sodium sulfate. The organic phase was concentrated under reduced pressure and the crude product was used immediately in the next stage.

Yield: 80% (crude product)

GRA3454-WO
22nd December 2009

Stage 5:

2M methylamine solution in THF (10 ml) was added to a solution of the compound obtained in stage 4 (5 mmol) in THF. The resulting reaction mixture was heated for 16 h at 100°C in a firmly closed vessel. The solvent was then removed completely under reduced pressure and the resulting crude product, which could not be purified, was used in the next stage.

Yield: 90% (crude product)

Stage 6:

Aqueous hydrochloric acid solution (6N, 2 ml/mmol) was added at 0°C to the amine obtained in stage 5 (1 eq.). The resulting reaction mixture was stirred for 20 h at RT. Then the aqueous phase was washed with ethyl acetate and subsequently adjusted to pH 14 with 6 N aqueous sodium hydroxide solution. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed successively with water and sat. sodium chloride solution. The combined org. phases were dried over sodium sulfate, the solvent was concentrated under reduced pressure, and the resulting crude product was used in the next stage without being purified further.

Yield: 80% (crude product)

Stage 7:

Diisopropylethylamine (2.5 eq.) and $\text{Boc}_2(\text{O})$ (1.2 eq.) were added at 0°C to a solution of the amine obtained in stage 6 (1 eq.) in dichloromethane (3 ml/mmol). When the addition was complete, the mixture was stirred for 16 h at 25°C. The mixture was then diluted with dichloromethane, and the org. phase was washed successively with water and sat. sodium chloride solution and finally dried over sodium sulfate. The org. phase was concentrated under reduced pressure, and the crude product was purified by column chromatography (5% methanol in dichloromethane).

Yield: 60%

Stage 8:

40% aqueous dimethylamine solution (71 ml) and acetic acid (26.5 ml) and KCN (1.5 eq.) were added at 0°C to a solution of the Boc amine obtained in stage 7

GRA3454-WO
22nd December 2009

(84.3 mmol) in methanol (45 ml). The resulting reaction mixture was stirred for 16 h at RT. Then 35% ammonium hydroxide solution (300 ml) and ice (300 g) were added, the aqueous phase was extracted with ethyl acetate, and the combined org. phases were washed successively with water, sat. sodium chloride solution and aqueous iron sulfate solution. After drying over sodium sulfate, the org. phase was concentrated under reduced pressure. The crude product (25 g) was taken up in THF (50 ml), and phenylmagnesium bromide (337 ml, 1M in THF) was added at 0°C. When the addition was complete, the reaction mixture was stirred for 16 h at 25°C. For working up, the reaction mixture was quenched with sat. ammonium chloride solution and diluted with ethyl acetate, and the org. phase was washed with sat. sodium chloride solution. After drying over sodium sulfate, the org. phase was concentrated under reduced pressure and the resulting crude product was purified by column chromatography (5% methanol in dichloromethane).

Yield: 40%

Stage 9:

HCl in dioxane (2M, 6 ml/mmol) was added at 0°C to a dioxane solution (2 ml/mmol) of the Boc amine obtained in stage 8. The resulting reaction mixture was stirred for 3 h at 25°C, and the solid was filtered off under protecting gas (very hygroscopic), washed with diethyl ether and finally dried under a high vacuum.

Yield: 80%

Amine F-46: 1-[4-(3-Fluorophenyl)-piperidin-4-yl]-4-methyl-piperazine dihydrochloride (F-46)

1-[4-(3-Fluorophenyl)-piperidin-4-yl]-4-methyl-piperazine dihydrochloride (F-46) was prepared analogously to dimethyl-(4-phenyl-piperidin-4-yl)-amine dihydrochloride (F-07) using methylpiperazine and 3-fluorophenyl-magnesium bromide.

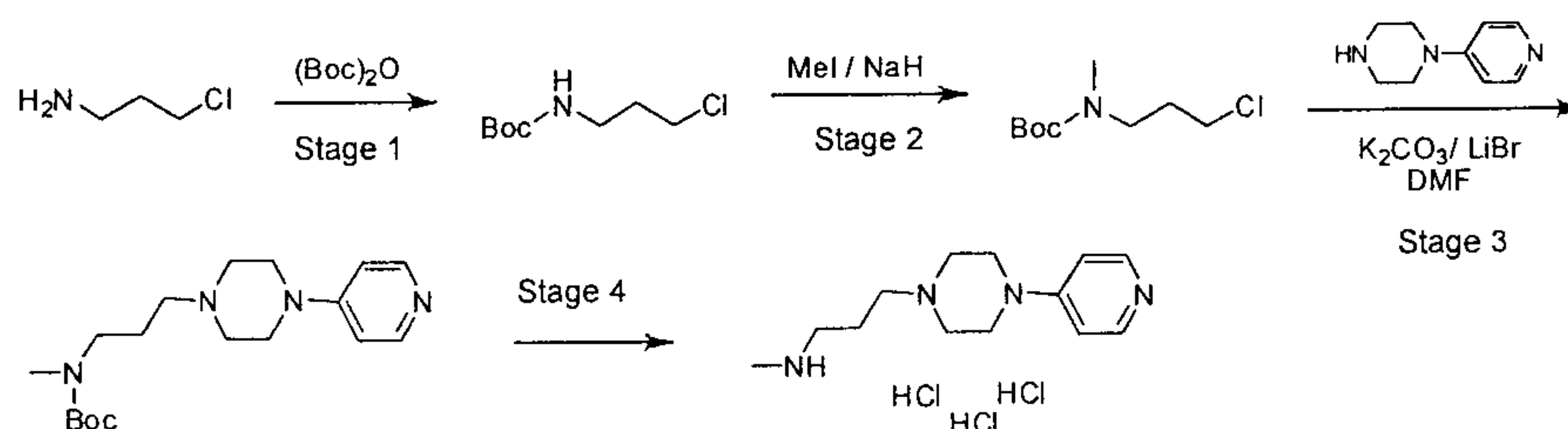
Amine F-47: 2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl-methyl-amine tetrahydrochloride (F-47)

2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl-methyl-amine tetrahydrochloride (F-47) was prepared analogously to dimethyl-[1-(3-methylamino-

GRA3454-WO
22nd December 2009

propyl)-4-phenyl-piperidin-4-yl]-amine trihydrochloride (F-11) using methylpiperazine and 3-fluorophenylmagnesium bromide.

Amine F-48: Methyl-[3-(4-pyridin-4-yl)-piperazin-1-yl]-propyl]-amine trihydrochloride (F-48)



Stage 1:

An aqueous sodium dicarbonate solution (3.5 g in 57 ml of water) and solid sodium chloride (7.5 g) were added at 0°C to a suspension of 3-chloropropylamine hydrochloride (38 mmol) in DCM (77 ml), and the mixture was stirred for 30 minutes. A solution of Boc anhydride (1.2 eq.) in dichloromethane (20 ml) was then slowly added dropwise. The reaction mixture was stirred overnight at RT. The reaction mixture was extracted with dichloromethane, and the org. phase was washed with water and sat. sodium chloride solution, dried over sodium sulfate (anhydrous) and concentrated. The desired product was used in the next stage without being purified further.

Yield: 83.7%

Stage 2:

Methyl iodide (3 eq.) was added at 0°C to a solution of the Boc amine obtained in stage 1 (155 mmol) in DMF (600 ml). Sodium hydride (2 eq.) was then added in portions. The reaction mixture was stirred for 15 h at RT. For working up, the reaction mixture was quenched with water and extracted with n-hexane. The combined org. phases were washed with water and sat. sodium chloride solution, dried over sodium sulfate (anhydrous) and concentrated. The desired product was used in the next stage without being purified further.

Yield: quantitative

GRA3454-WO
22nd December 2009

Stage 3:

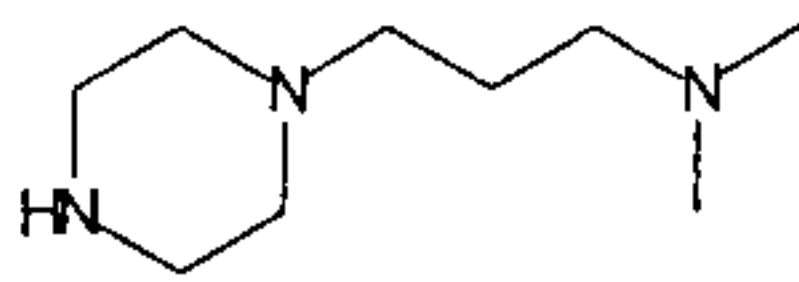
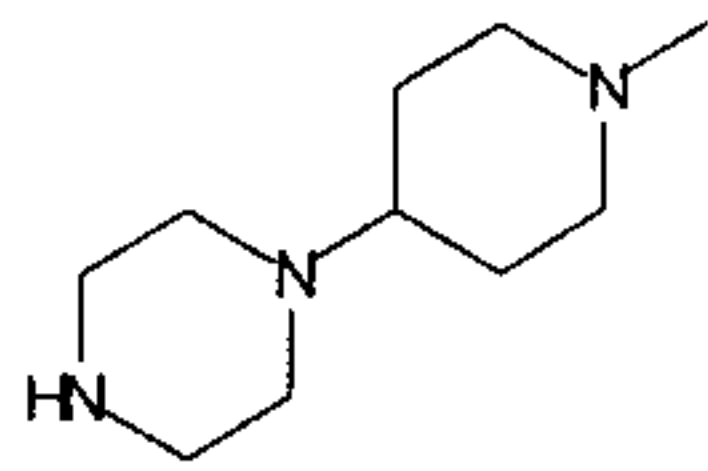
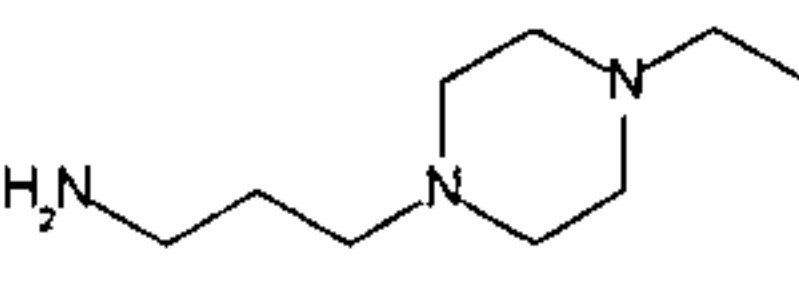
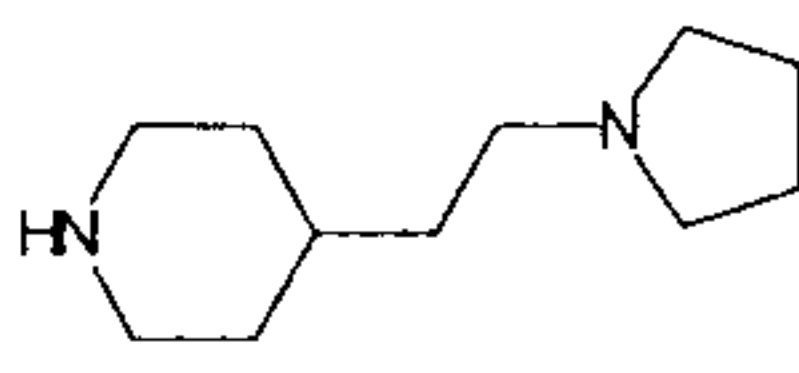
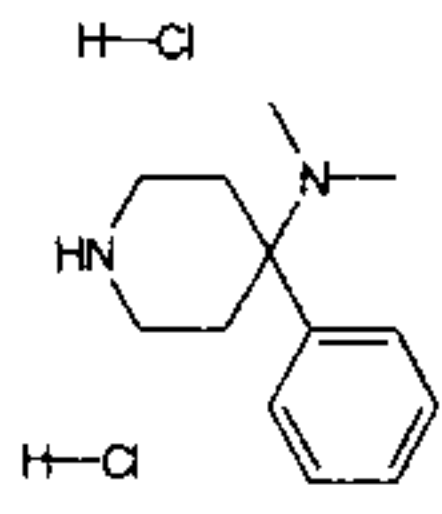
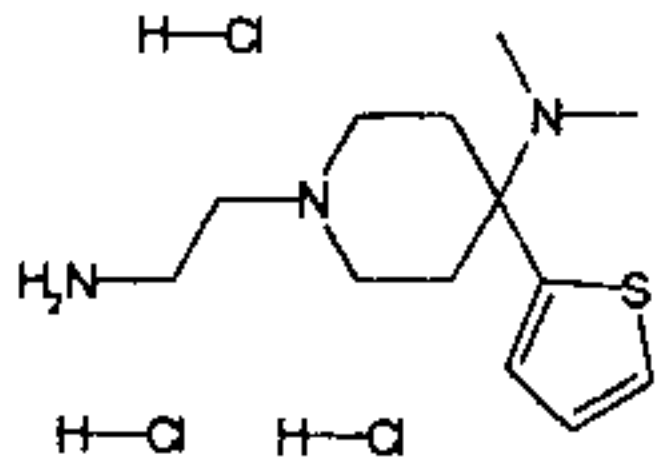
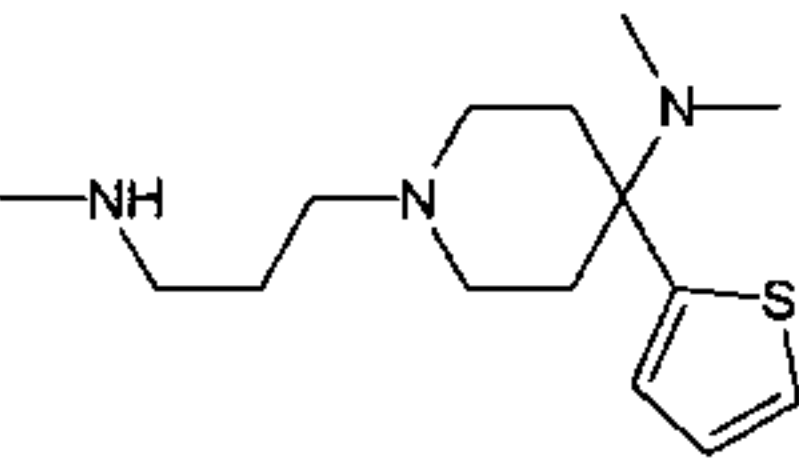
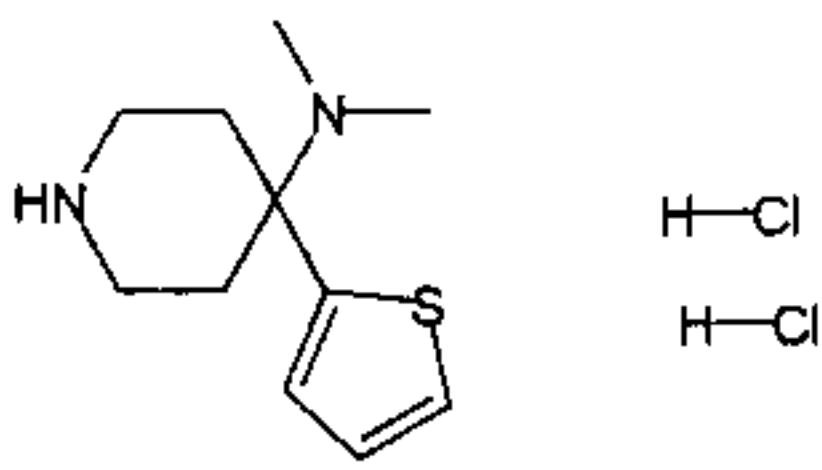
DIPEA (2 eq.) and LiBr (1 eq.) were added to a solution of 4-(4-pyridyl)-piperazine (30.64 mmol) and the Boc amine obtained in stage 2 (1.5 eq.) in ethanol (150 ml). The reaction mixture was heated for 15 h at reflux and was then concentrated and diluted with dichloromethane and water. The org. phase was washed successively with water and sat. sodium chloride solution, dried over sodium sulfate (anhydrous) and concentrated under reduced pressure. The residue was purified by column chromatography over neutral alumina (eluant: DCM/MeOH) to yield the desired pure product.

Yield: 60%

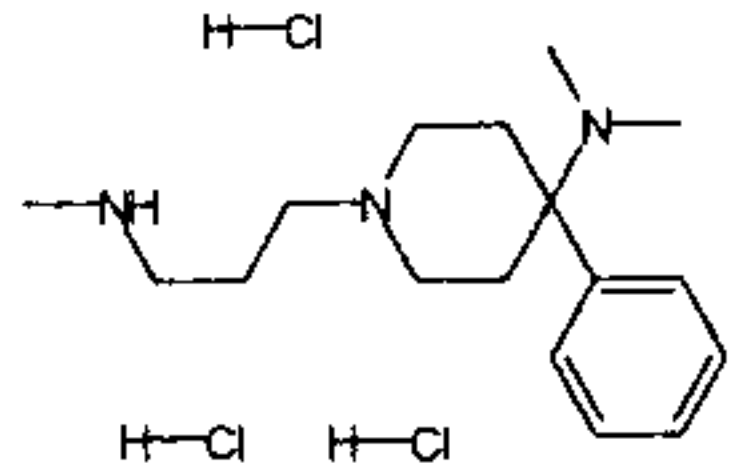
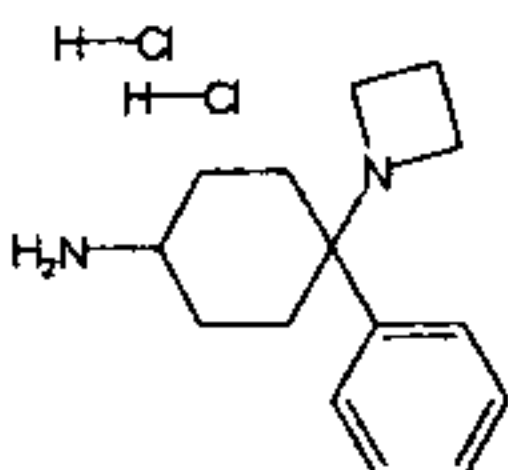
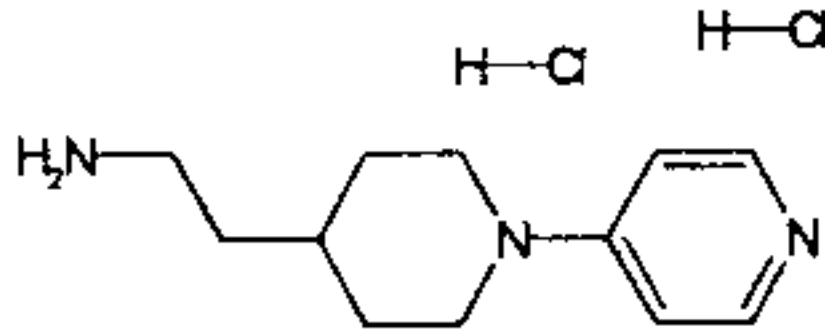
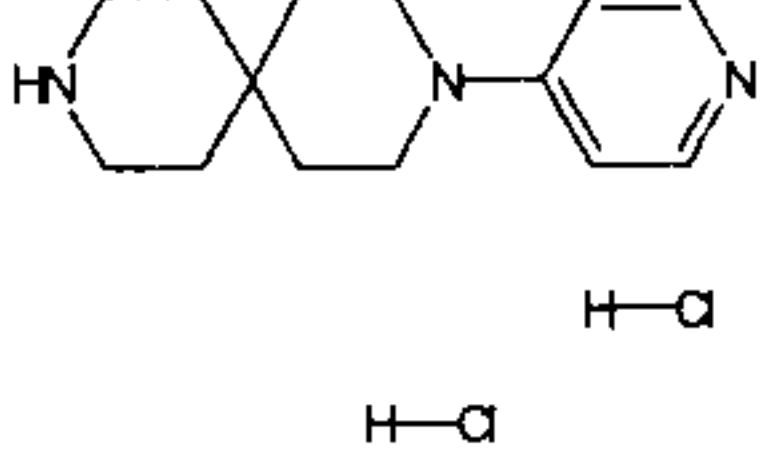
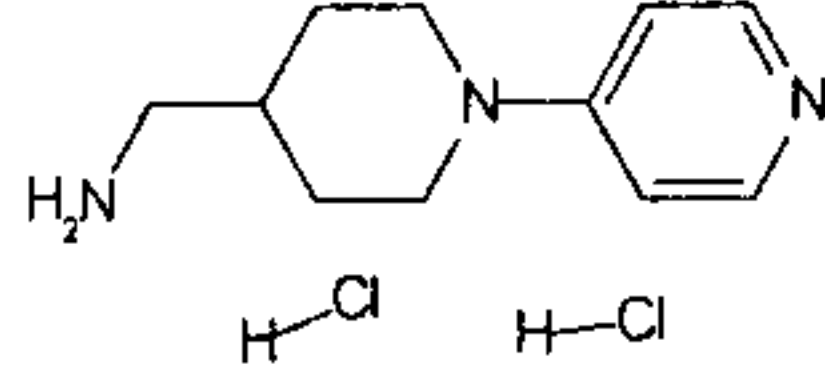
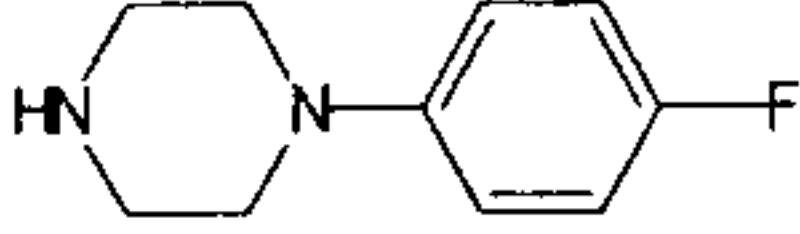
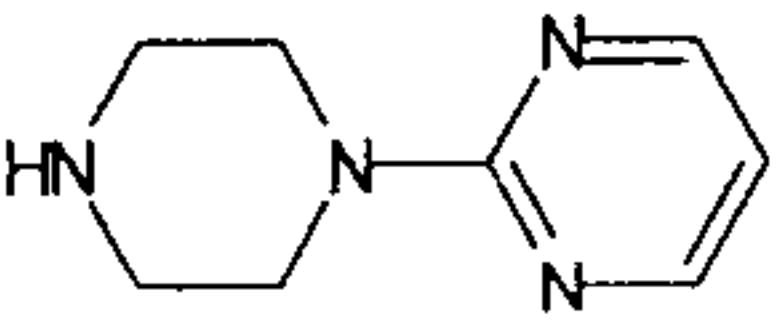
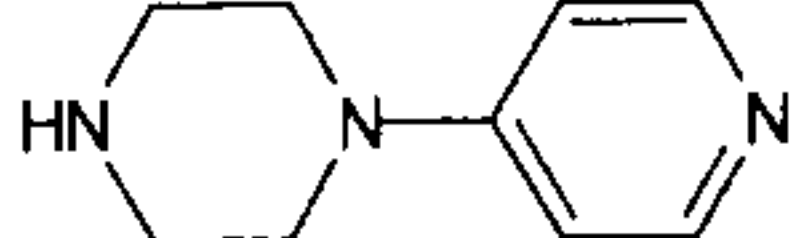
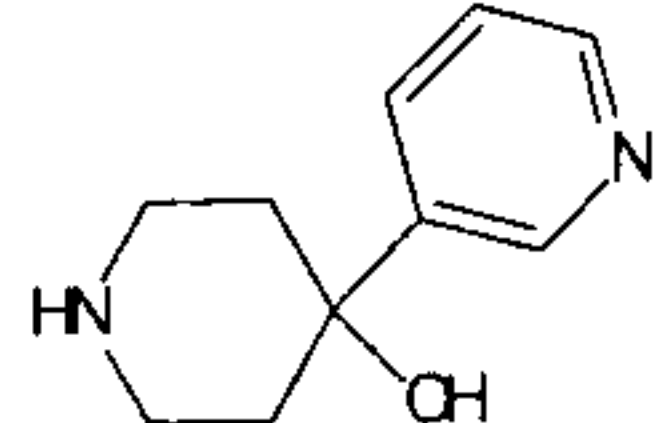
Stage 4:

10 eq. of acetyl chloride were added at 0°C to a solution of the Boc amine obtained in stage 3 in methanol. The progress of the reaction was monitored by means of thin-layer chromatography (10% MeOH/CHCl₃). When the reaction was complete, the solvent was removed under reduced pressure and the product was obtained in the form of a solid.

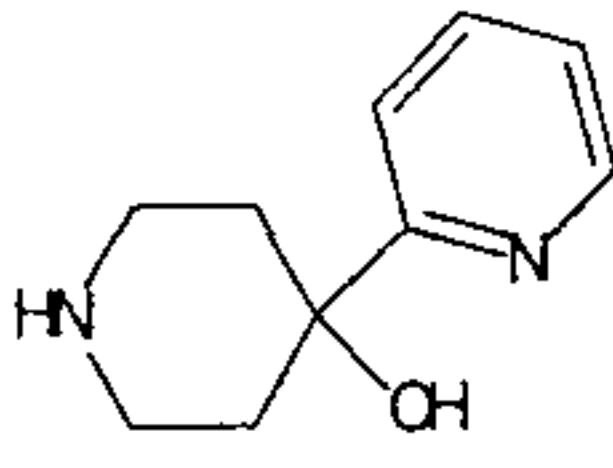
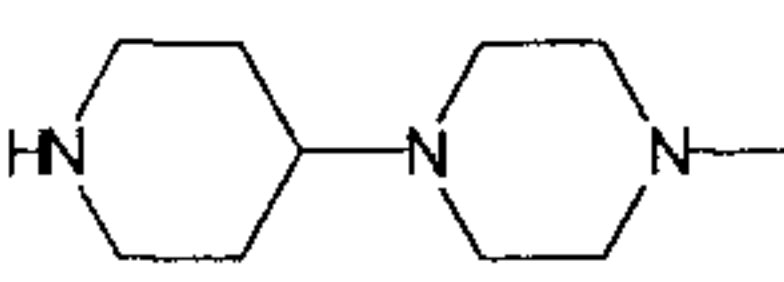
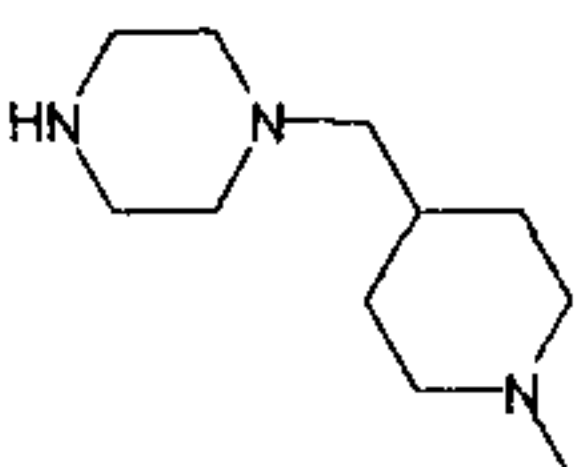
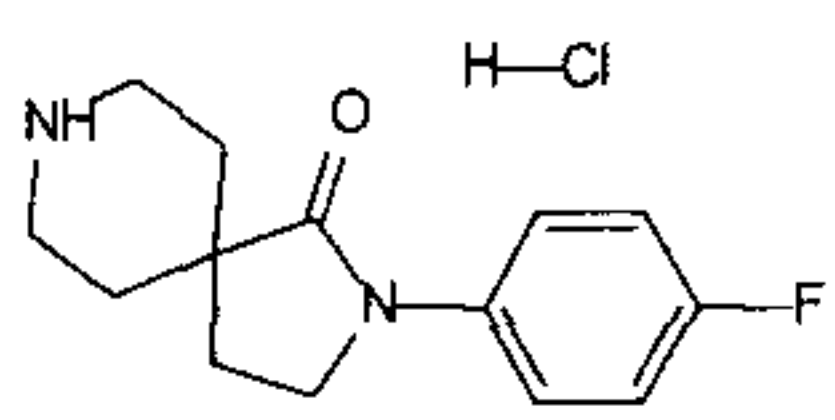
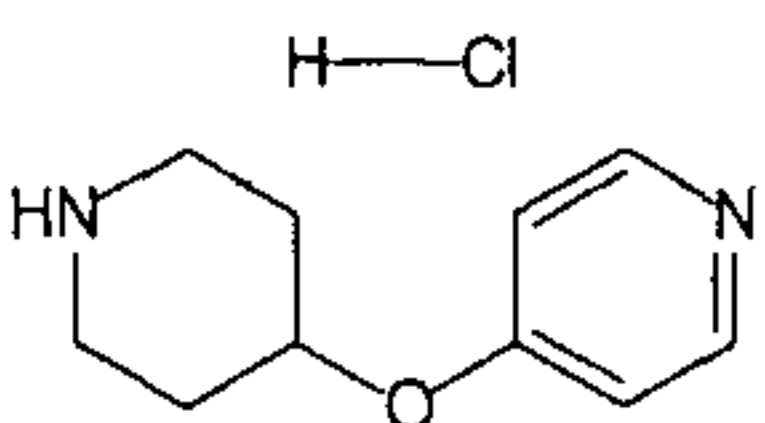
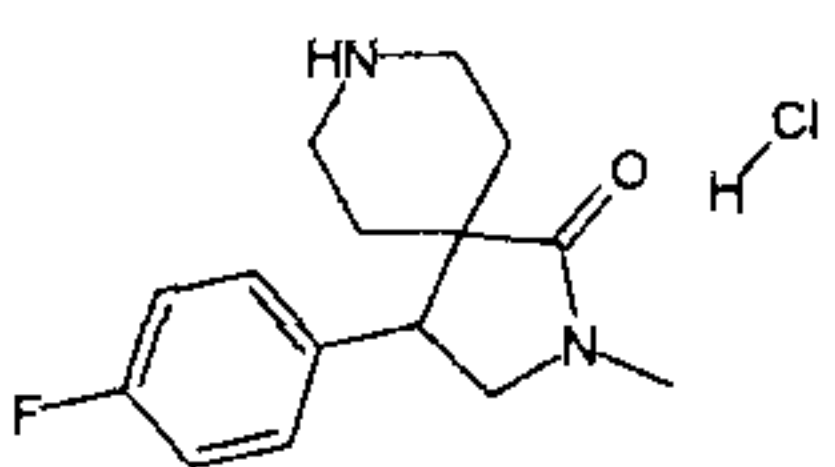
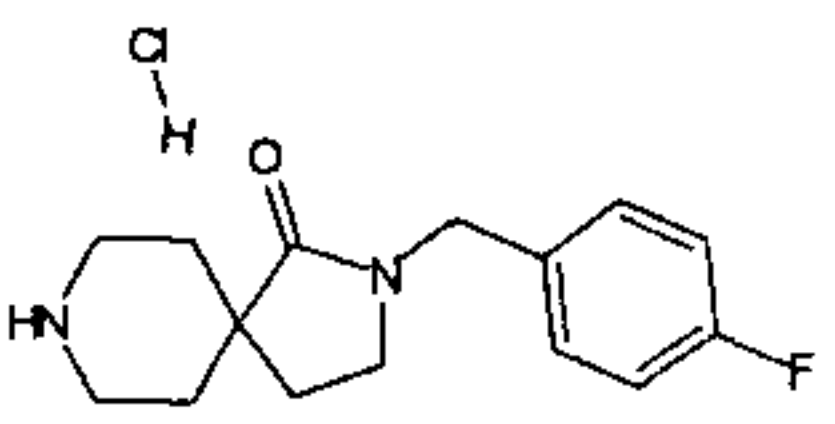
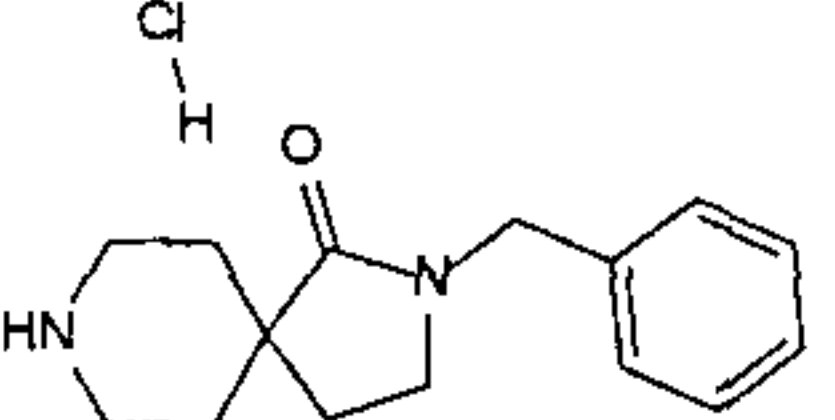
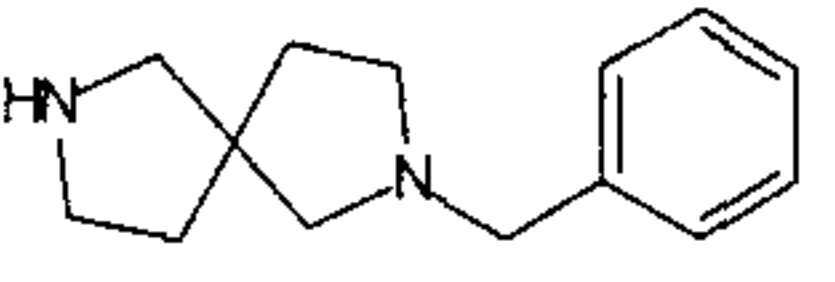
GRA3454-WO
22nd December 2009

Amine	Structure	Name
F-01		Dimethyl-(3-piperazin-1-yl-propyl)amine (F-01)
F-02		1-(1-Methyl-piperidin-4-yl) piperazine (F-02)
F-03		3-(4-Ethyl-piperazin-1-yl)-propylamine (F-03)
F-05		4-(2-Pyrrolidin-1-yl-ethyl) piperidine (F-05)
F-07		Dimethyl-(4-phenyl-piperidin-4-yl)amine dihydrochloride (F-07)
F-08		[1-(2-Aminoethyl)-4-thiophen-2-yl-piperidin-4-yl]-dimethylamine trihydrochloride (F-08)
F-09		Dimethyl-[1-(3-methylaminopropyl)-4-thiophen-2-yl-piperidin-4-yl]amine (F-09)
F-10		Dimethyl-(4-thiophen-2-yl piperidin-4-yl)amine dihydrochloride (F-10)

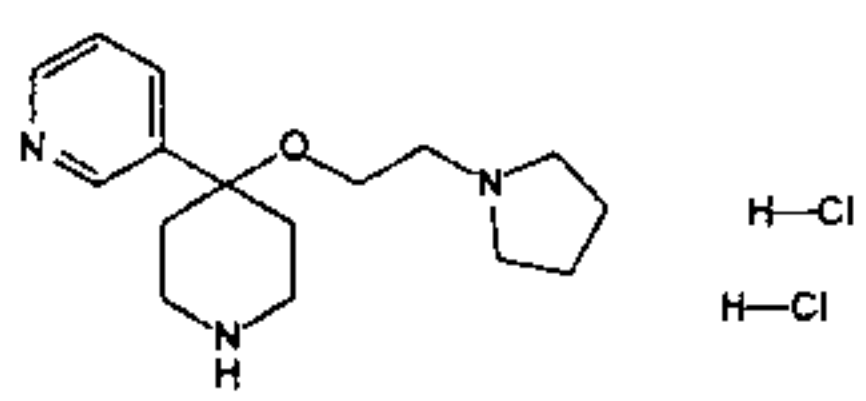
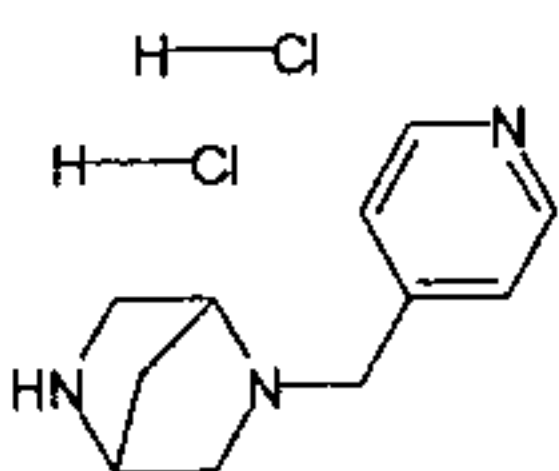
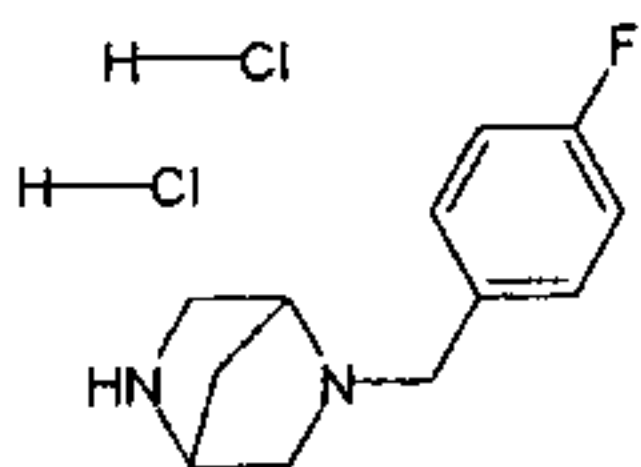
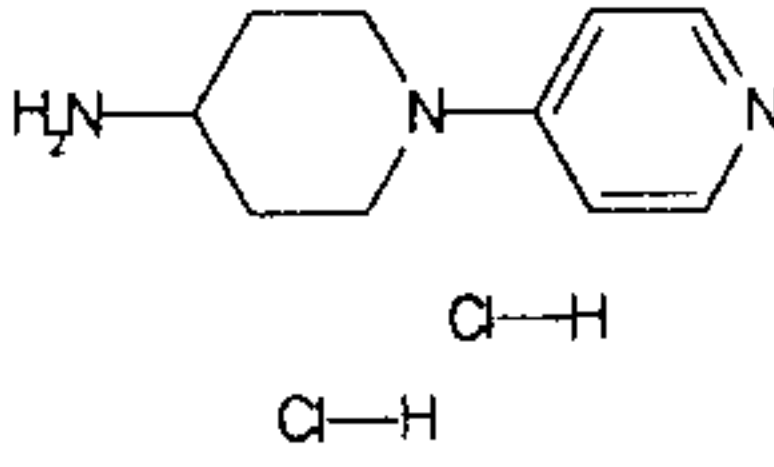
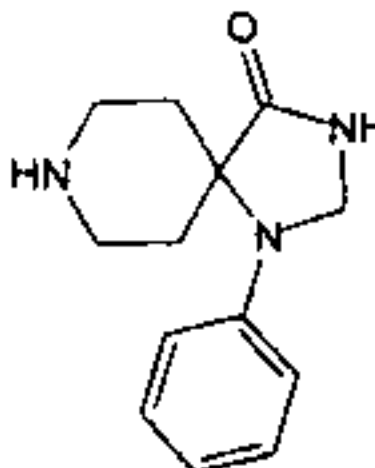
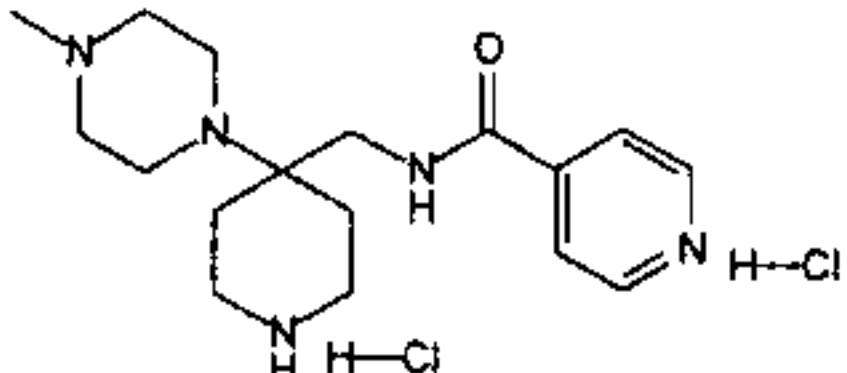
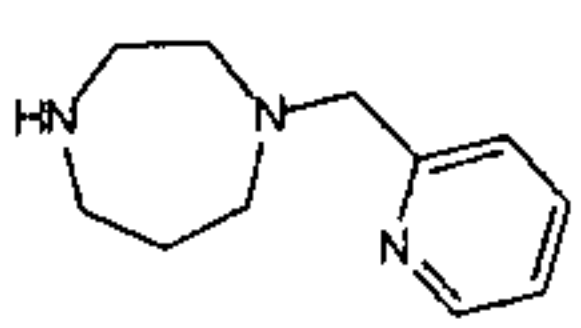
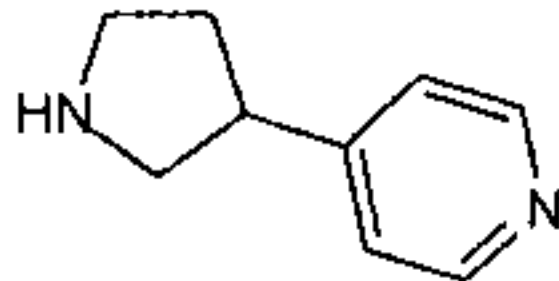
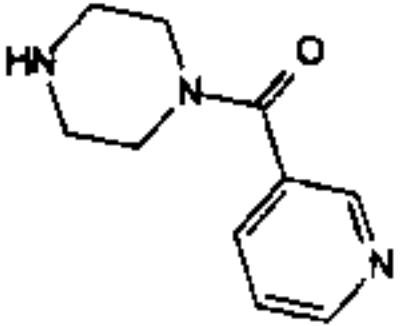
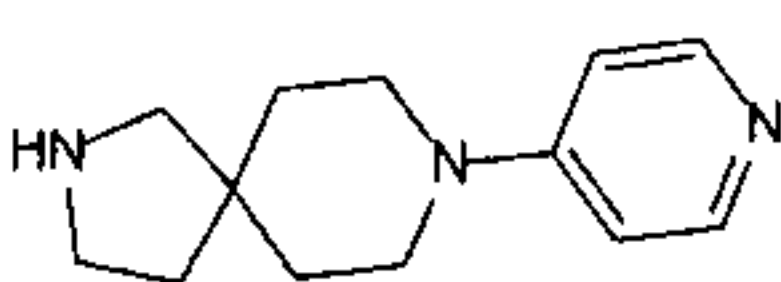
GRA3454-WO
22nd December 2009

F-11		Dimethyl-[1-(3-methylaminopropyl)-4-phenyl piperidin-4-yl]amine trihydrochloride (F-11)
F-12		[4-(Azetidin-1-yl)-4-phenyl-cyclohexyl]amine dihydrochloride (F-12)
F-13		2-(1-Pyridin-4-yl-piperidin-4-yl)ethylamine dihydrochloride (F-13)
F-14		3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
F-15		(1-Pyridin-4-yl-piperidin-4-yl)methylamine dihydrochloride (F-15)
F-16		1-(4-Fluorophenyl)piperazine (F-16)
F-17		2-Piperazin-1-yl pyrimidine (F-17)
F-18		1-Pyridin-4-yl piperazine (F-18)
F-19		4-Pyridin-3-yl piperidin-4-ol (F-19)

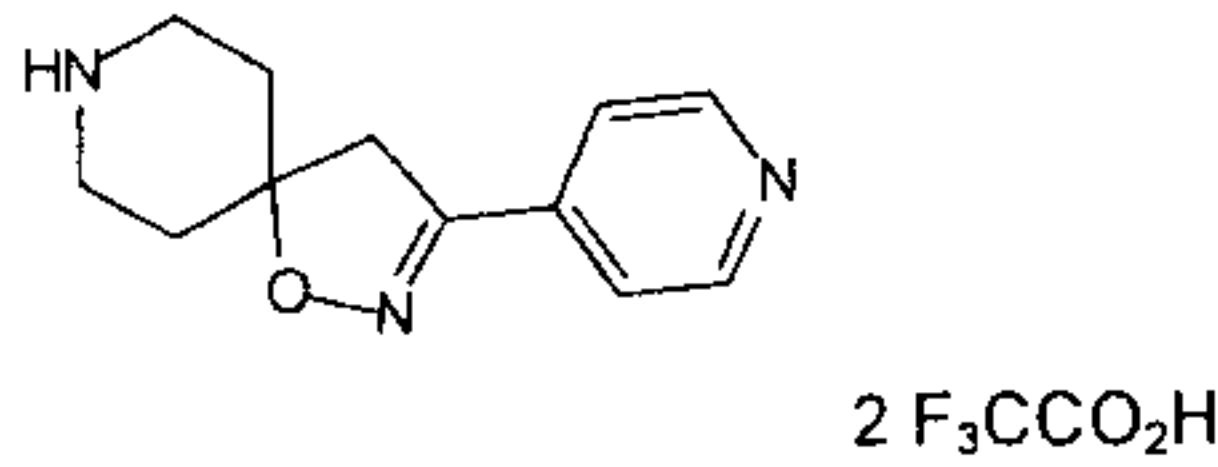
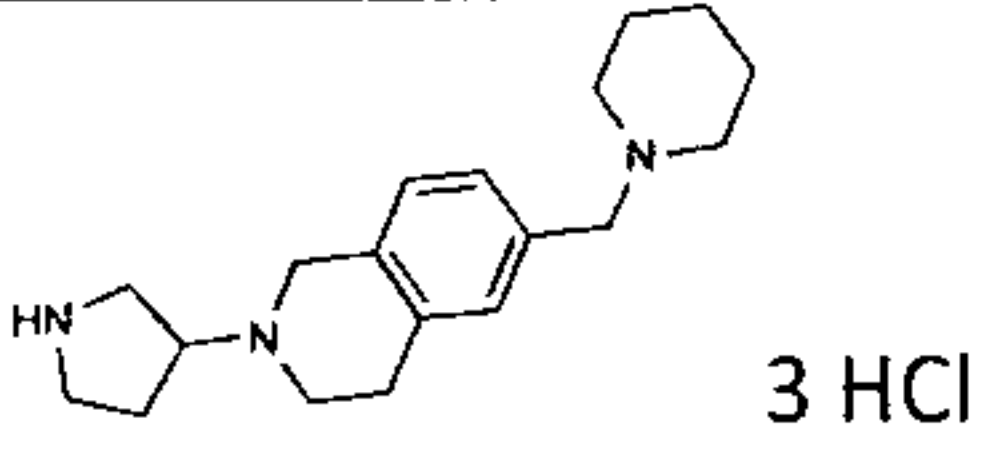
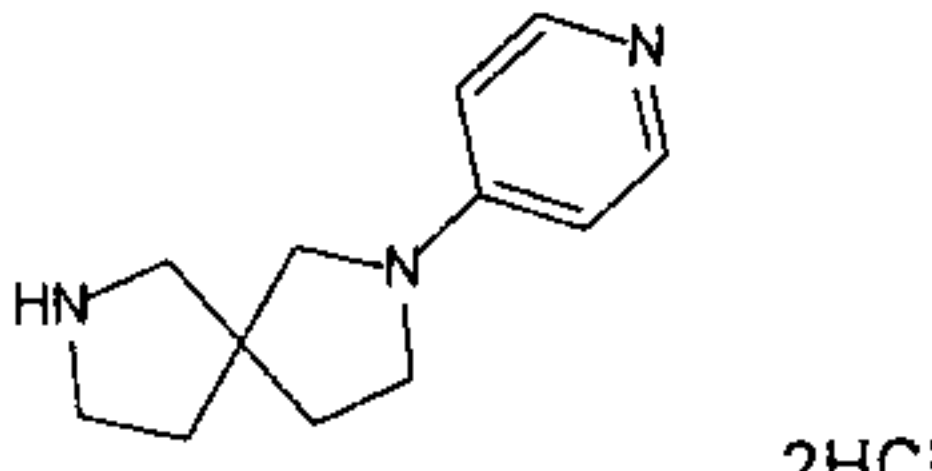
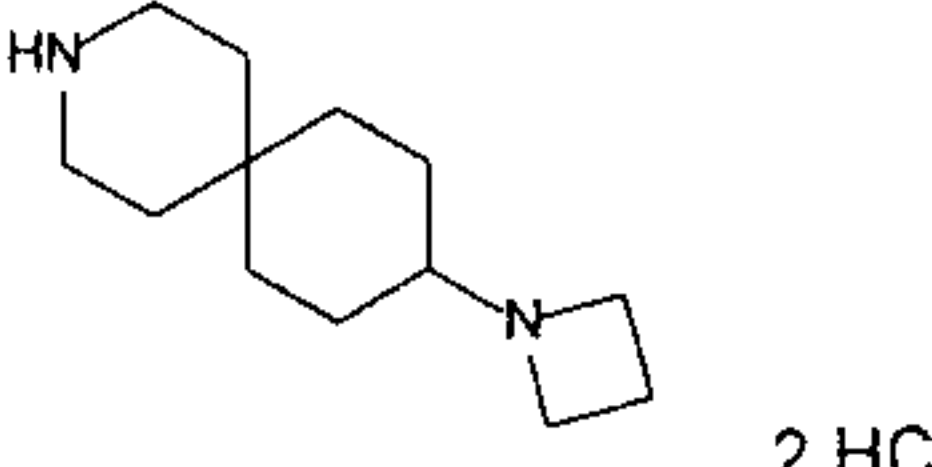
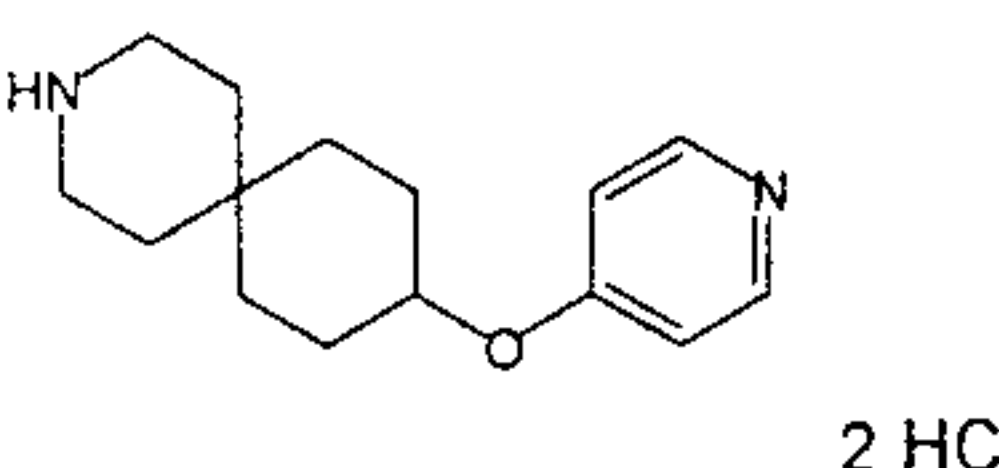
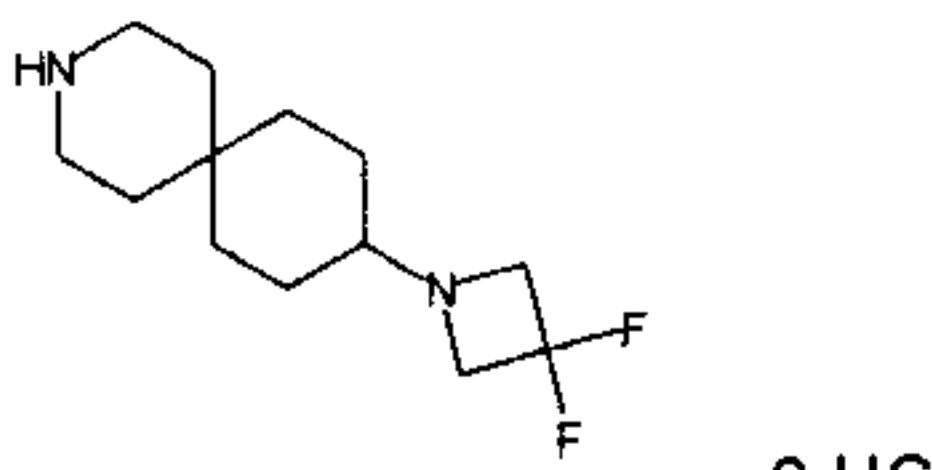
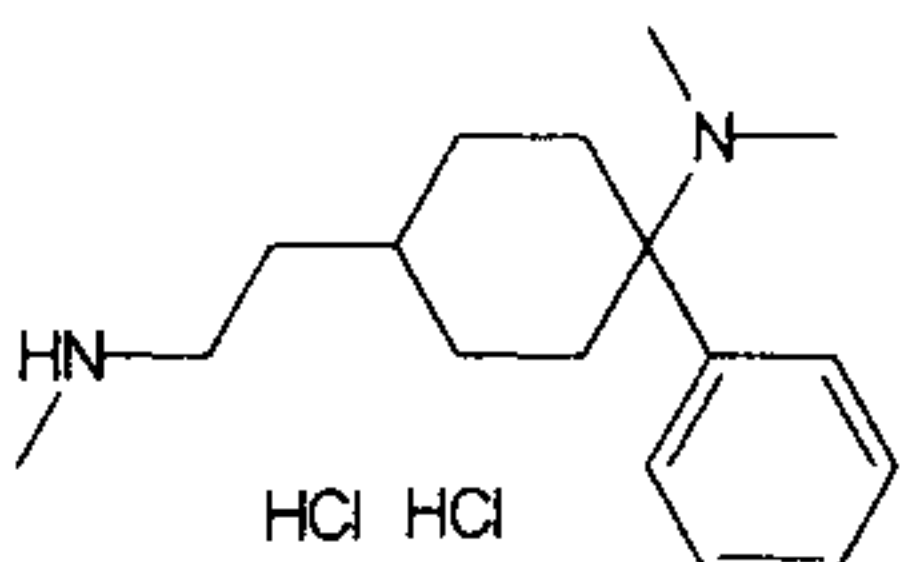
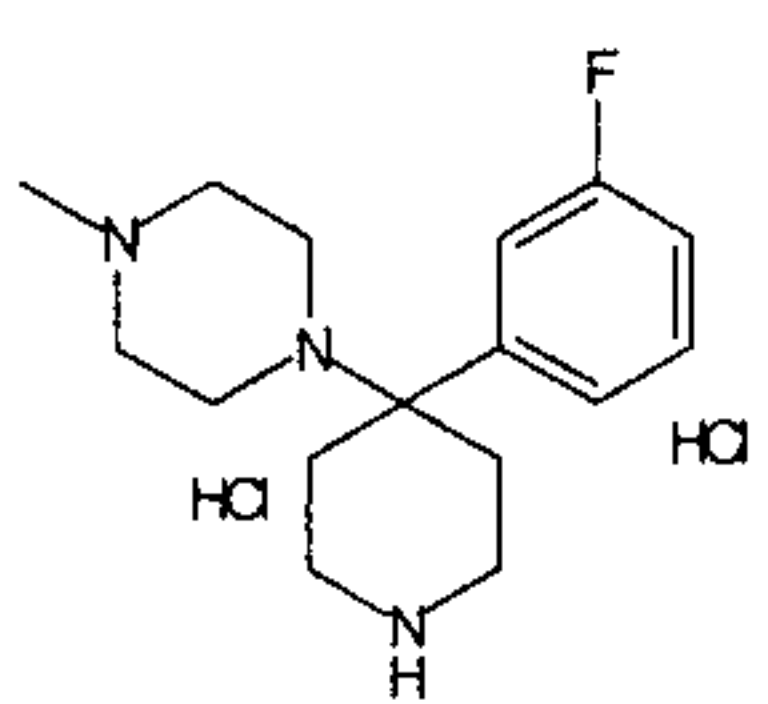
GRA3454-WO
22nd December 2009

F-20		4-Pyridin-2-yl piperidin-4-ol (F-20)
F-21		1-Methyl-4-piperidin-4-yl piperazine (F-21)
F-22		1-[(1-Methyl-piperidin-4-yl) methyl] piperazine (F-22)
F-23		3-(4-Fluorophenyl)-3,8-diazaspiro[4.5]decan-4-one hydrochloride (F-23)
F-24		4-Piperidin-4-yloxy pyridine hydrochloride (F-24)
F-25		1-(4-Fluorophenyl)-3-methyl-3,8-diazaspiro[4.5]decan-4-one hydrochloride (F-25)
F-26		3-[(4-Fluorophenyl)-methyl]-3,8-diazaspiro[4.5]decan-4-one hydrochloride (F-26)
F-27		3-Benzyl-3,8-diazaspiro[4.5]decan-4-one hydrochloride (F-27)
F-28		3-Benzyl-3,7-diazaspiro[4.4]nonane (F-28)

GRA3454-WO
22nd December 2009

F-29		3-[4-(2-Pyrrolidin-1-yl-ethoxy)piperidin-4-yl] pyridine dihydrochloride (F-29)
F-30		2-(Pyridin-4-yl-methyl)-2,5-diazabicyclo[2.2.1]heptane dihydrochloride (F-30)
F-31		2-[(4-Fluorophenyl)methyl]-2,5-diazabicyclo[2.2.1]heptane dihydrochloride (F-31)
F-32		(1-Pyridin-4-yl-piperidin-4-yl)amine dihydrochloride (F-32)
F-33		4-Phenyl-2,4,8-triazaspiro[4.5]decan-1-one (F-33)
F-34		N-[[4-(4-Methylpiperazin-1-yl)-piperidin-4-yl]methyl]pyridine-4-carboxylic acid amide dihydrochloride (F-34)
F-35		1-(Pyridin-2-yl-methyl)-[1,4]diazepan (F-35)
F-36		4-Pyrrolidin-3-yl-pyridine (F-36)
F-37		Piperazin-1-yl-pyridin-3-yl-methanone (F-37)
F-38		8-(Pyridin-4-yl)-2,8-diazaspiro[4.5]decane dihydrochloride (F-38)

GRA3454-WO
22nd December 2009

F-39	 2 F ₃ CCO ₂ H	3-(Pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene bis(trifluoroacetate) (F-39)
F-40	 3 HCl	6-(Piperidin-1-ylmethyl)-2-(pyrrolidin-3-yl)-1,2,3,4-tetrahydroisoquinoline trihydrochloride (F-40)
F-41	 2 HCl	2-(Pyridin-4-yl)-2,7-diazaspiro[4.4]nonane dihydrochloride (F-41)
F-42	 2 HCl	9-(Azetidin-1-yl)-3-azaspiro[5.5]undecane dihydrochloride (F-42)
F-43	 2 HCl	9-(Pyridin-4-yloxy)-3-azaspiro[5.5]undecane dihydrochloride (F-43)
F-44	 2 HCl	9-(3,3-Difluoroazetidin-1-yl)-3-azaspiro[5.5]undecane dihydrochloride (F-44)
F-45	 HCl HCl	Dimethyl-[4-(2-methylamino-ethyl)-1-phenyl-cyclohexyl]-amine dihydrochloride (F-45)
F-46	 HCl HCl	1-[4-(3-Fluorophenyl)-piperidin-4-yl]-4-methyl-piperazine dihydrochloride (F-46)

GRA3454-WO
22nd December 2009

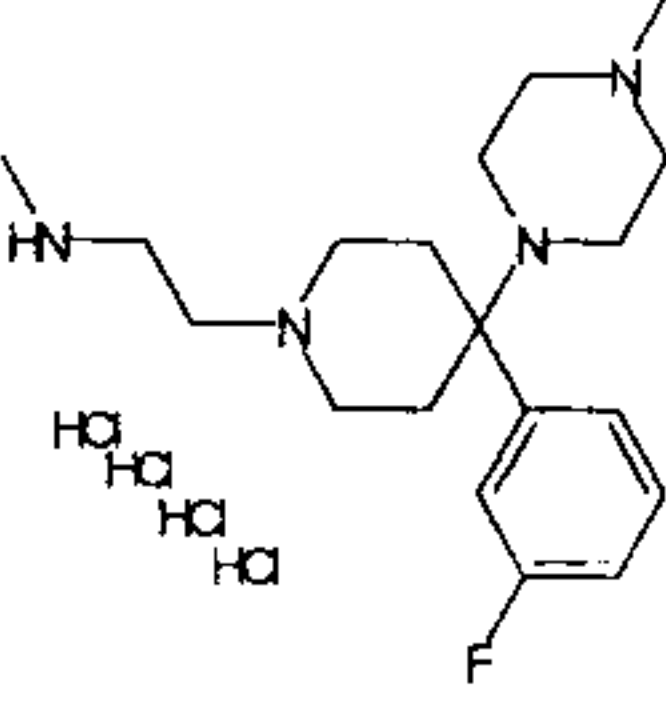
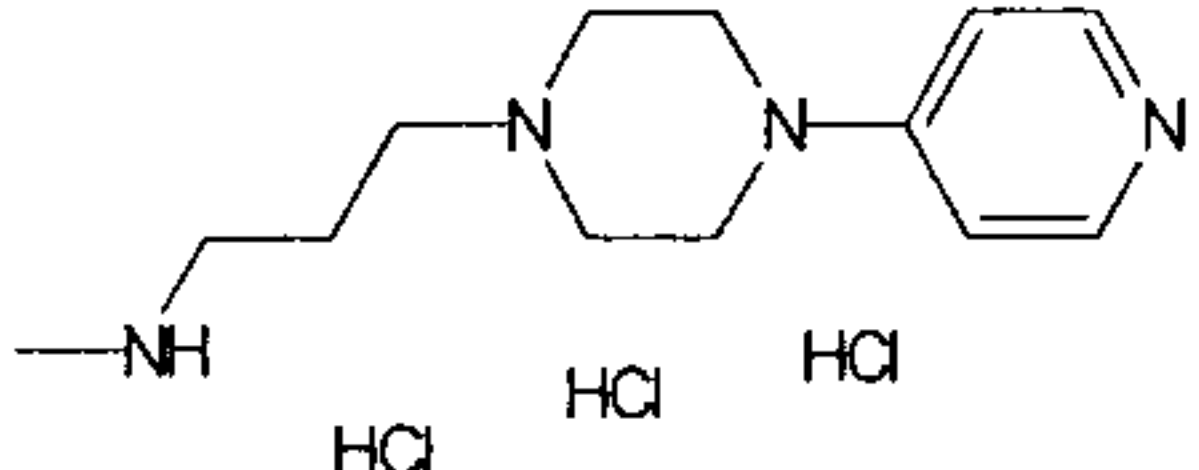
F-47		2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl-methyl-amine tetrahydrochloride (F-47)
F-48		Methyl-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-amine trihydrochloride (F-48)

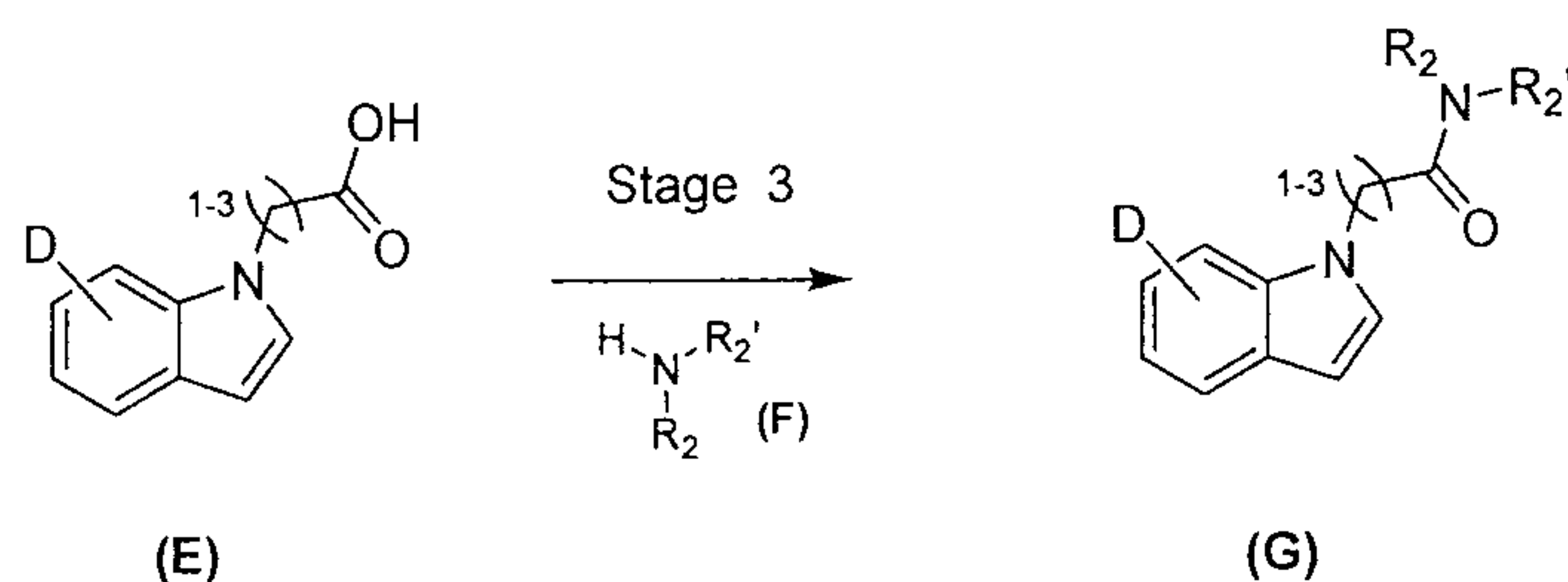
Table 3 Amine overview

GRA3454-WO
22nd December 2009

Syntheses of individual substances

6) Synthesis of indolamides G

General method for the synthesis of indolamides G



wherein $N(H)(R^2)(R^{2'})$ stands for $N(H)(R^8)-[CR^{9a}R^{9b}]_t-A(R^{10})(R^{11})$.

Figure 2: Synthesis of indolamides G

General procedure GP V – CDI coupling: A solution of acid **E** (1 eq.) and carbonyldiimidazole (2 eq.) in dichloromethane/dimethyl formamide was stirred for 1 h at room temperature, then mixed with amine **F** (3 eq.) dissolved in dichloromethane and stirred for 12 h at room temperature. The reaction solution was washed 3 times with saturated sodium hydrogen carbonate solution, dried over magnesium sulfate and concentrated under reduced pressure. The desired product was obtained after purification by column chromatography (alox neutral, ethyl acetate/hexane or silica, DCM/MeOH optionally NEt_3).

General procedure GP VI – EDCI coupling: A cold solution ($0^\circ C$) of acid **E** (1.5 eq.), HOBt (0.3 eq.) and diisopropylethylamine (4 eq.) in dichloromethane was mixed with EDCI (1.5 eq.) and stirred for 15 min. Amine **F** (1 eq.) was then added and the mixture was stirred for 12 h at room temperature. The reaction solution was washed 3 times with 0.5N potassium hydroxide solution, dried over magnesium sulfate and concentrated under reduced pressure. The desired product was obtained after

GRA3454-WO
22nd December 2009

purification by column chromatography (alox neutral, ethyl acetate/hexane or silica, DCM/MeOH optionally NEt_3).

General procedure GP VII – CDI coupling: 1,1'-Carbonyldiimidazole (1.05 eq.) and carboxylic acid **E** (1 eq.) were dissolved in dichloromethane or a dichloromethane/*N,N*-dimethyl formamide (3:2) mixture and stirred for 1 h at room temperature. Then amine **F** (optionally in the form of the corresponding hydrochloride (xHCl)) (1.5 eq.) dissolved in a mixture of dichloromethane/*N,N*-dimethyl formamide (3:2) and triethylamine (2 - 3 eq.) was added dropwise and the reaction mixture was stirred for 1 to 3 days at room temperature (DC control). The mixture was mixed with a little water and concentrated to small volume under vacuum. Then the residue was taken up in dichloromethane and washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution. The aqueous phase was extracted with dichloromethane (twice) and the combined organic phases were washed again with saturated sodium chloride solution. Then the mixture was dried over sodium sulfate or magnesium sulfate and concentrated to small volume under vacuum. The crude product was purified by column chromatography (silica gel).

General procedure GP Va – TBTU coupling: The carboxylic acid **E** (1 equiv.), *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1 equiv.) and 1-hydroxybenzotriazole hydrate (1 equiv.) were placed in tetrahydrofuran, under protecting gas, and the mixture was stirred for 30 min at room temperature. A solution of the amine **F** (optionally in the form of the corresponding hydrochloride (xHCl)) (1 equiv.) and diisopropylethylamine (DIPEA) (3-5 equiv.) in tetrahydrofuran was added, and the reaction mixture was stirred for 15 h to 3 d at room temperature. Tetrahydrofuran was then removed under vacuum, the residue was taken up in ethyl acetate or DCM and saturated sodium hydrogen carbonate solution, and the phases were separated. The aqueous phase was extracted with ethyl acetate (or DCM), and the combined organic phases were in turn washed with sat. sodium chloride solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (silica gel) or by crystallisation (from ethyl acetate).

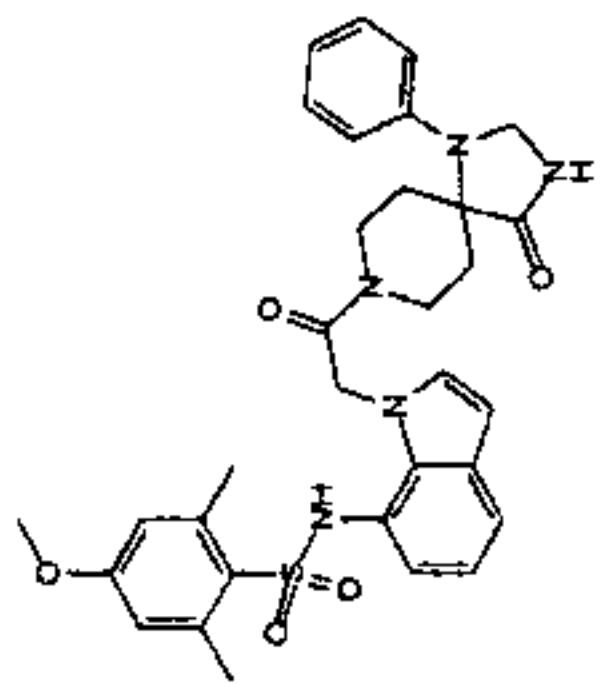
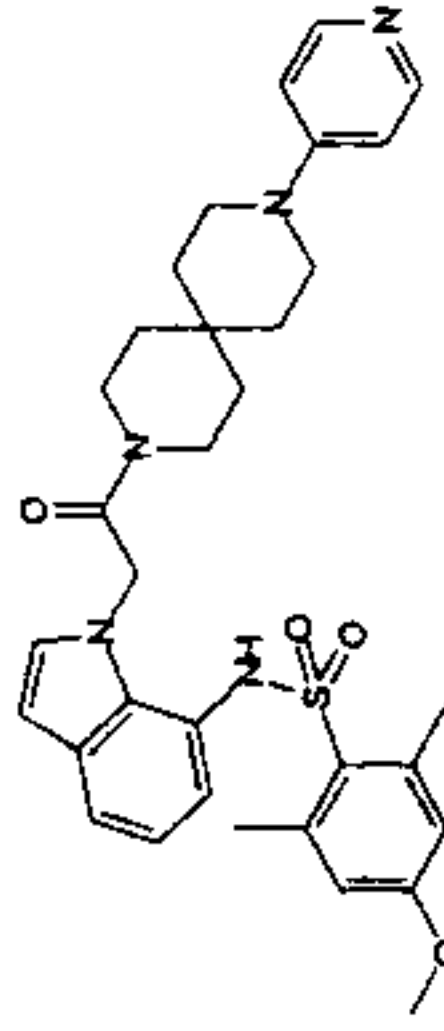
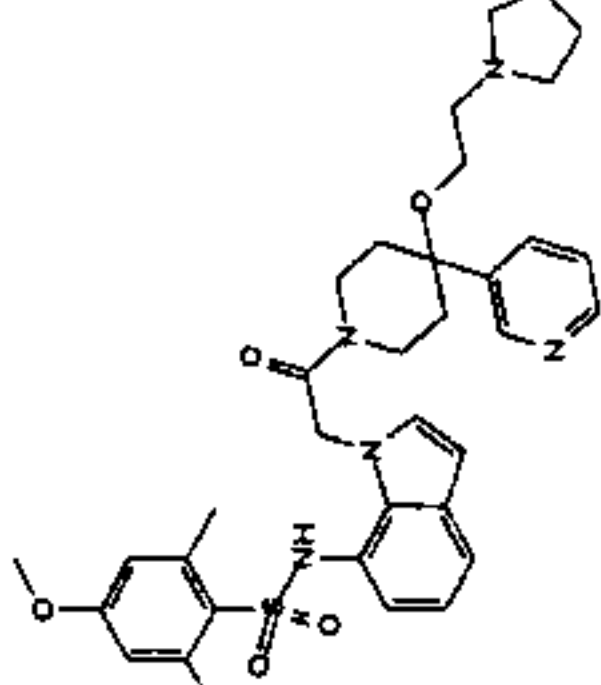
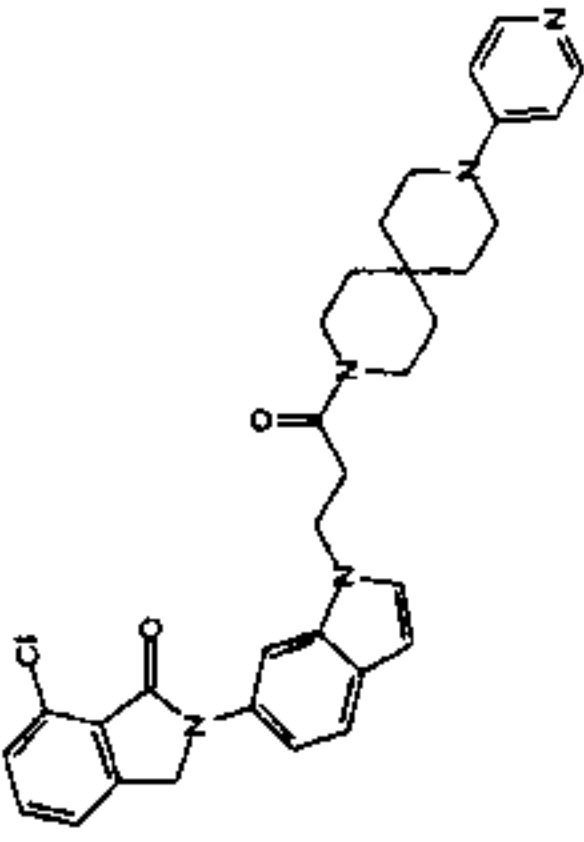
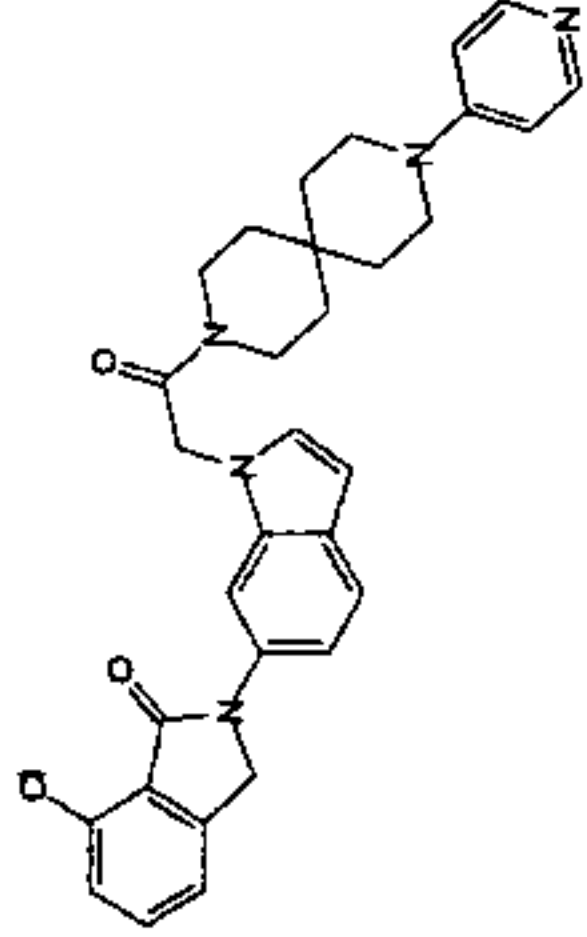
GRA3454-WO
22nd December 2009

General procedure GP Vb – HATU coupling: HATU (1.1 equiv.) was added to a solution of carboxylic acid **E** (1 equiv.) in THF, and the mixture was cooled to 0°C. DIPEA (2.5 equiv.) was added, and the reaction mixture was stirred for 10 min. A solution of the amine **F** in THF was then added dropwise, and the mixture was stirred for 16 h. Water was added and extraction with ethyl acetate was carried out (3 x). The combined organic phases were extracted with water and sat. NaCl solution, dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by column chromatography (silica gel).

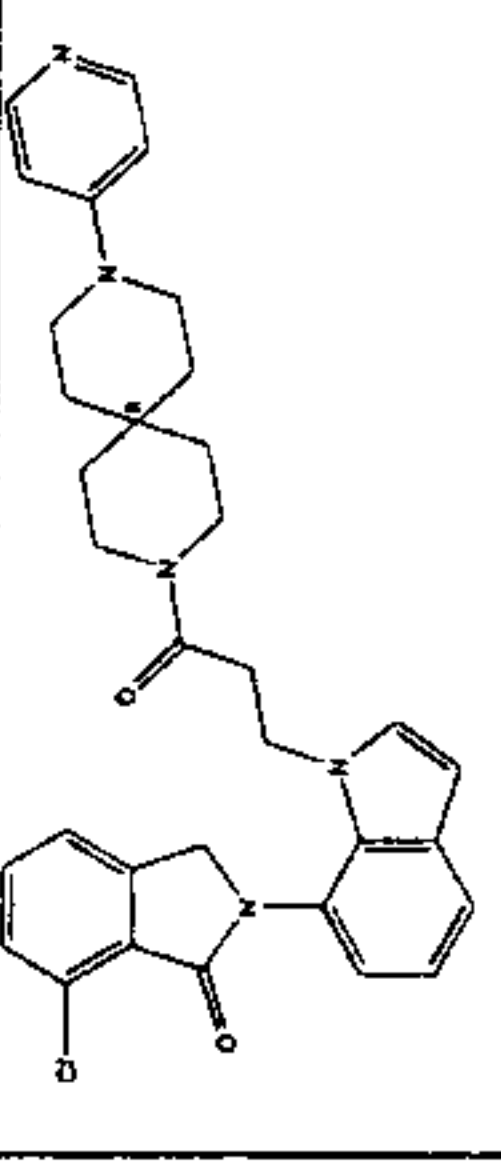
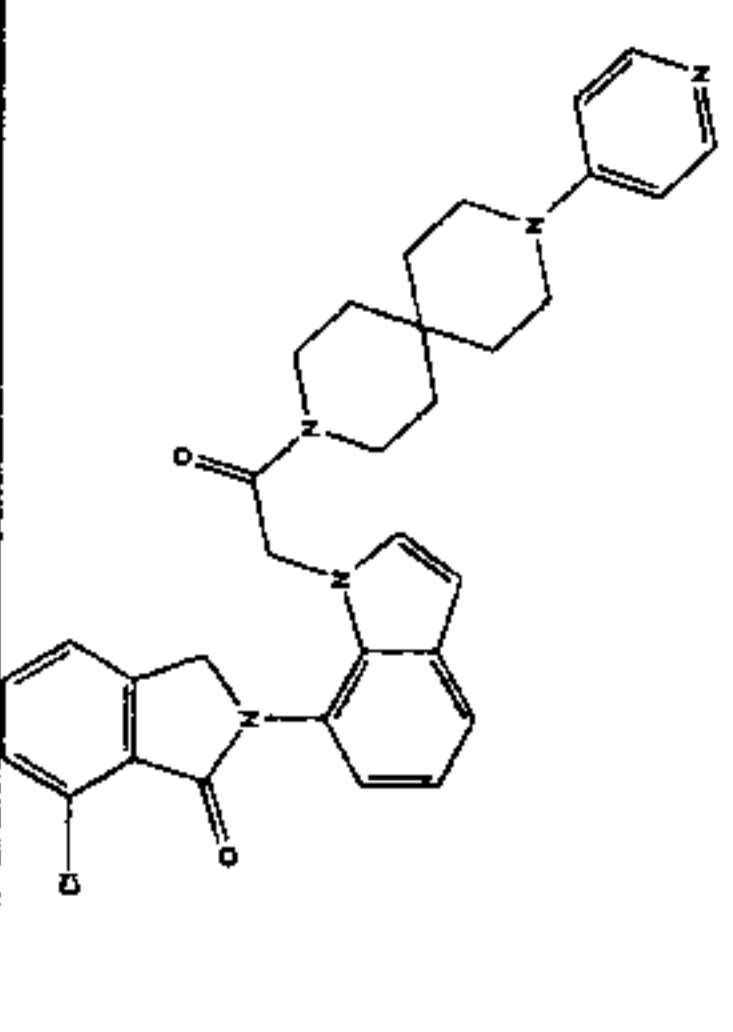
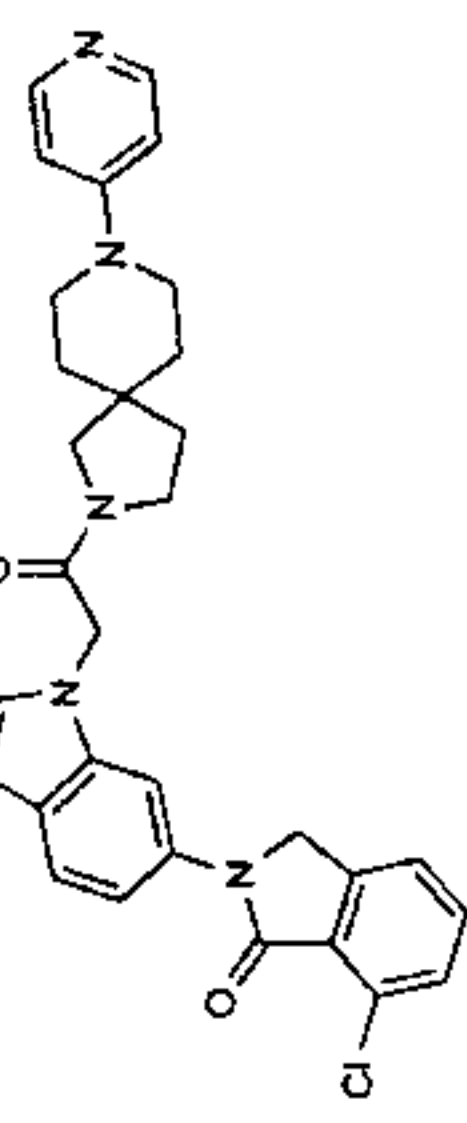
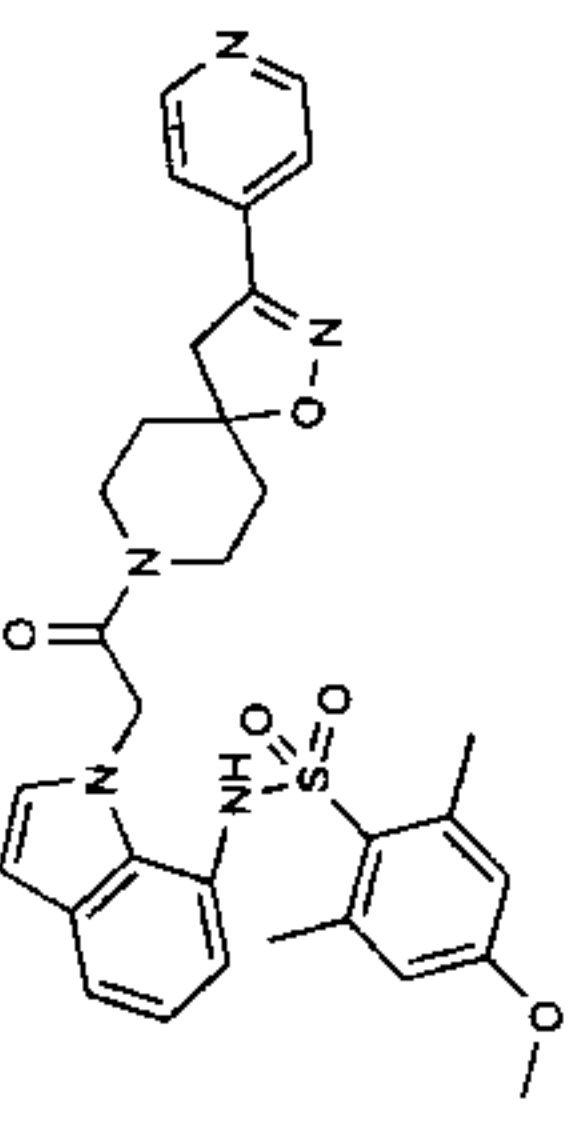
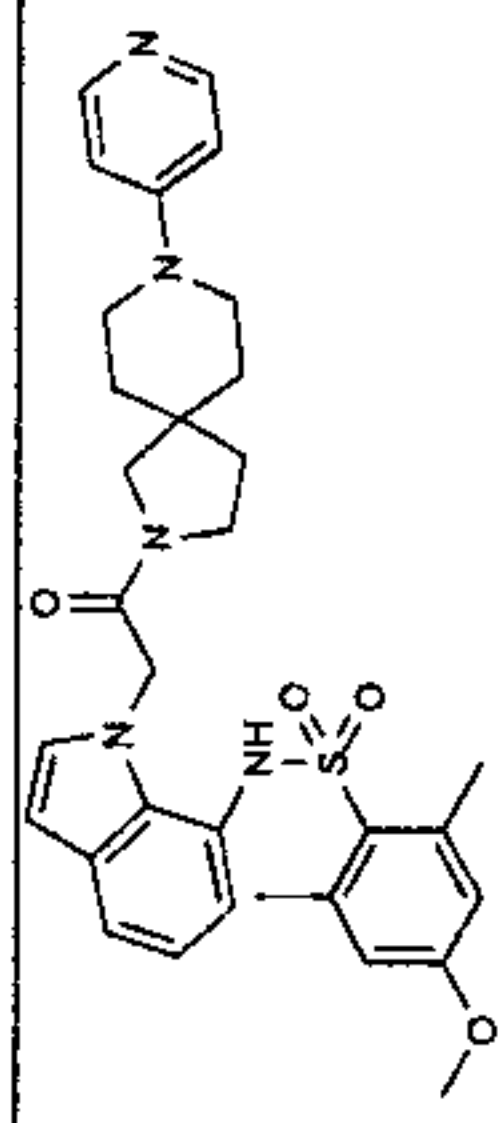
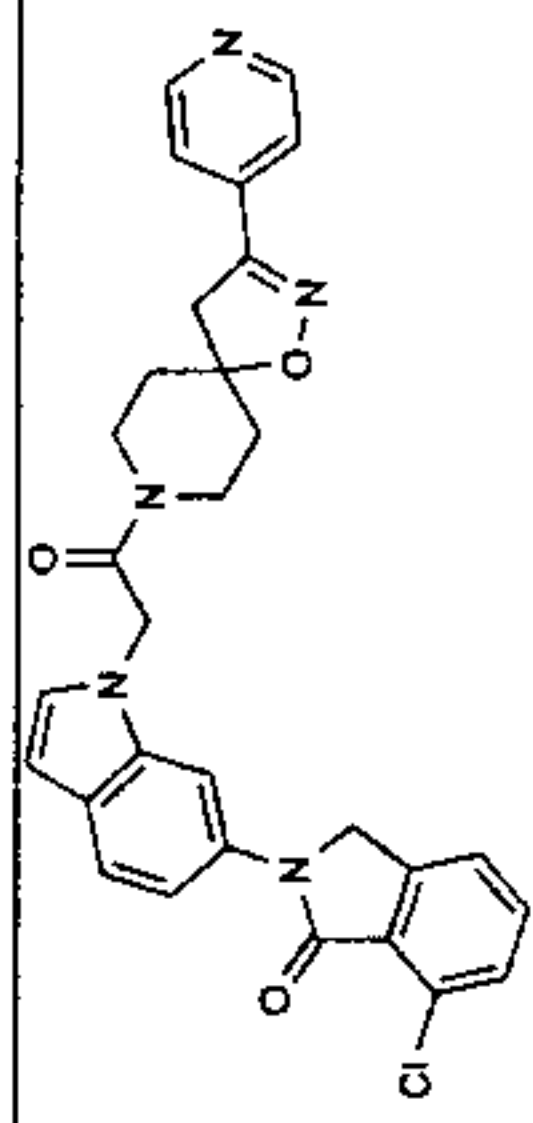
General procedure GP Vc – EDCI coupling: DIPEA (2.4 - 4 equiv.), EDCI (1.2 - 1.5 equiv.) and HOBt (1.0 – 1.2 equiv.) were added to a solution, at 0°C, of carboxylic acid **E** (1.0 equiv.) in DCM, and the resulting mixture was stirred for 15 min at 25°C. It was then cooled to 0°C again, and the amine **F** (1 equiv.) in DCM (optionally plus DMF) was added. The reaction mixture was stirred for 16 h at 25°C. DCM was added, and the mixture was extracted with sodium bicarbonate solution, NH₄Cl solution, water and sat. NaCl solution, dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by column chromatography (silica gel).

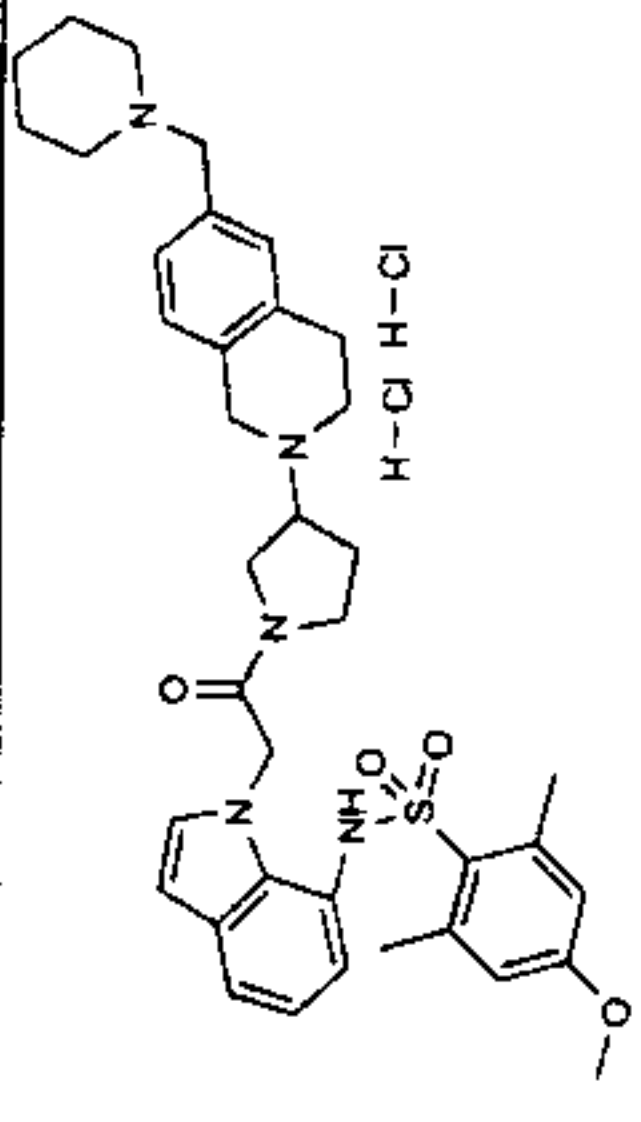
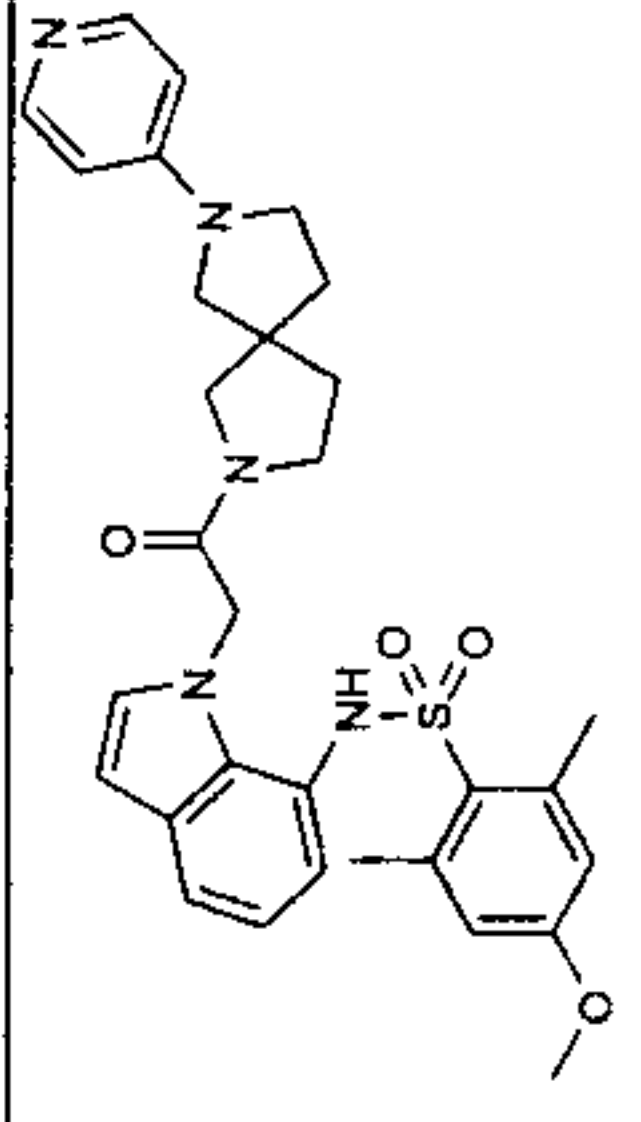
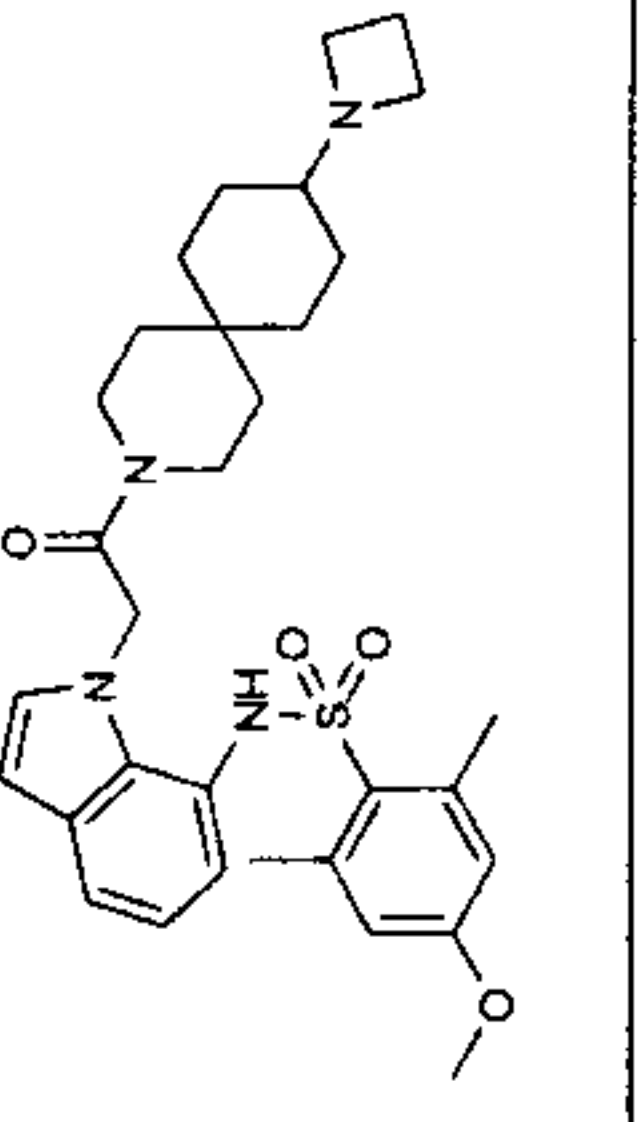
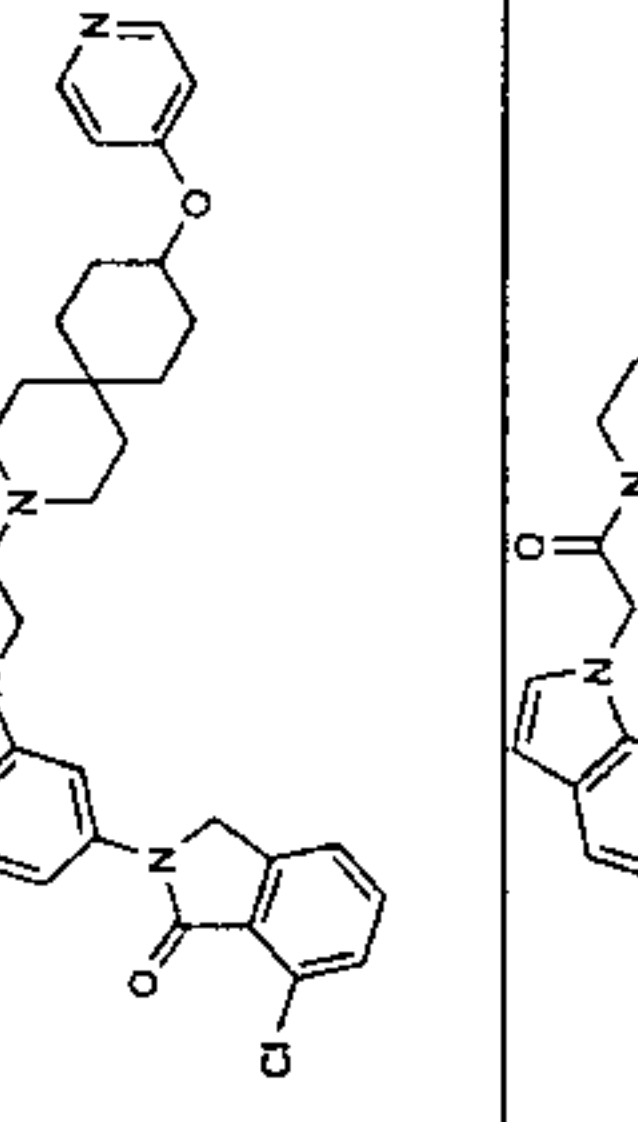
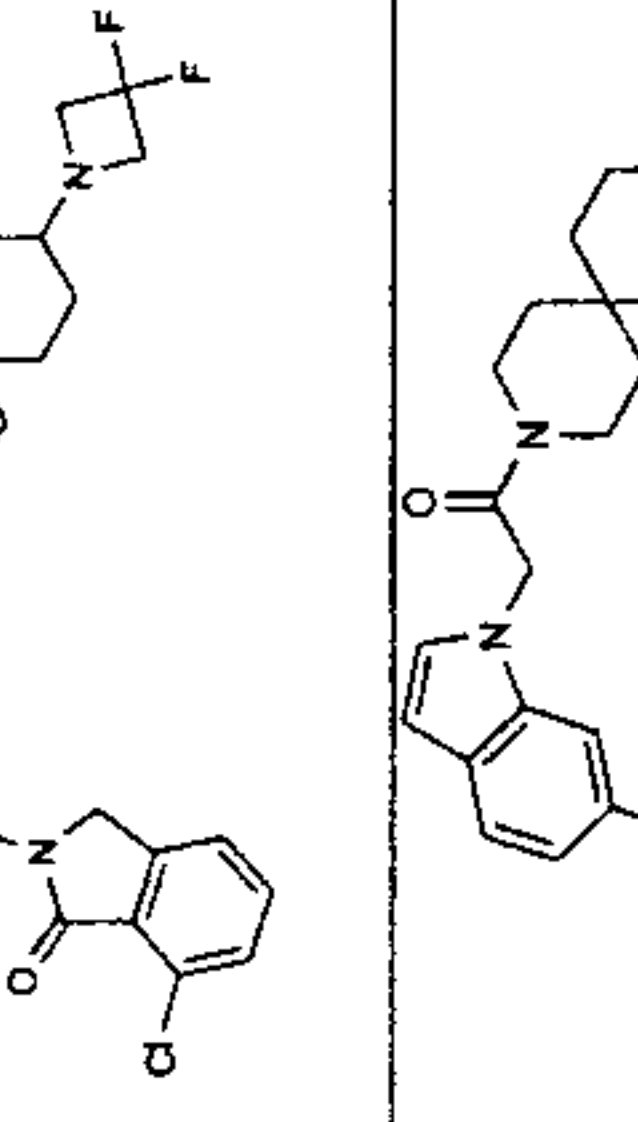
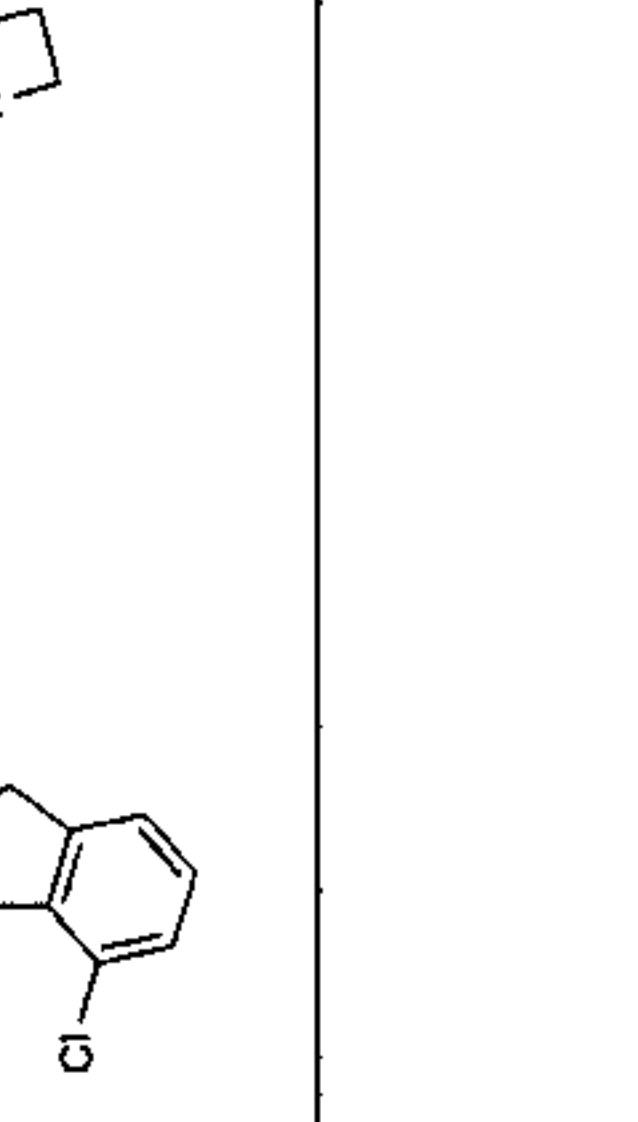
Example no.	Structure	Name	Indole acid (E)	Amine (F)	Yield	Analysis (LC/MS) ^[1]	Synthesised by / Comment
G-01		4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G-01)	2-[6-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]] acetic acid (E-03)	4-(2-Pyrrolidin-1-yl-ethyl) piperidine (F-05)	43% (0.17 mmol)	R _t = 3.0 min; m/z = 553.2 [MH] ⁺	GP V
G-02		4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G-02)	2-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]] acetic acid (E-02)	4-(2-Pyrrolidin-1-yl-ethyl) piperidine (F-05)	30% (0.11 mmol)	R _t = 3.3 min; m/z = 553.2 [MH] ⁺	GP V
G-03		4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyridin-4-yloxy-piperidin-1-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G-03)	2-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]] acetic acid (E-02)	4-Piperidin-4-yloxy-pyridine hydrochloride (F-24)	6% (10 mg)		GP VII

[¹] Equipment and methods for HPLC-MS analysis: HPLC: Waters Alliance 2795 with PDA Waters 2998; MS: Micromass Quattro MicroTM API; column: Waters Atlantis[®] T3, 3 µm, 100 Å, 2.1 x 30 mm; column temp: 40°C; Eluent A: purified water + 0.1% formic acid; Eluent B: acetonitrile (gradient grade) + 0.1% formic acid; Gradient: 0% B to 100% B in 8.8 min, 100% B for 0.4 min, 100% B to 0% B in 0.01 min, 0% B for 0.8 min; Flow: 1.0 ml/min; Ionisation: ES⁺, 25 V; make up: 100 µl/min 70% methanol + 0.2% formic acid; UV: 200 – 400 nm.

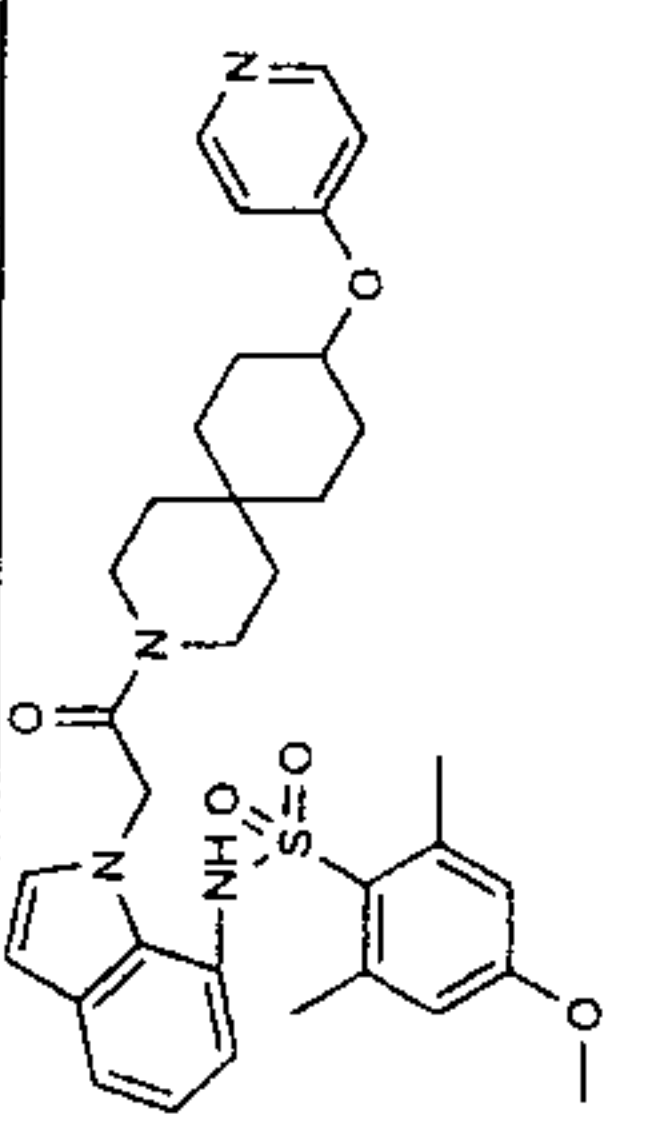
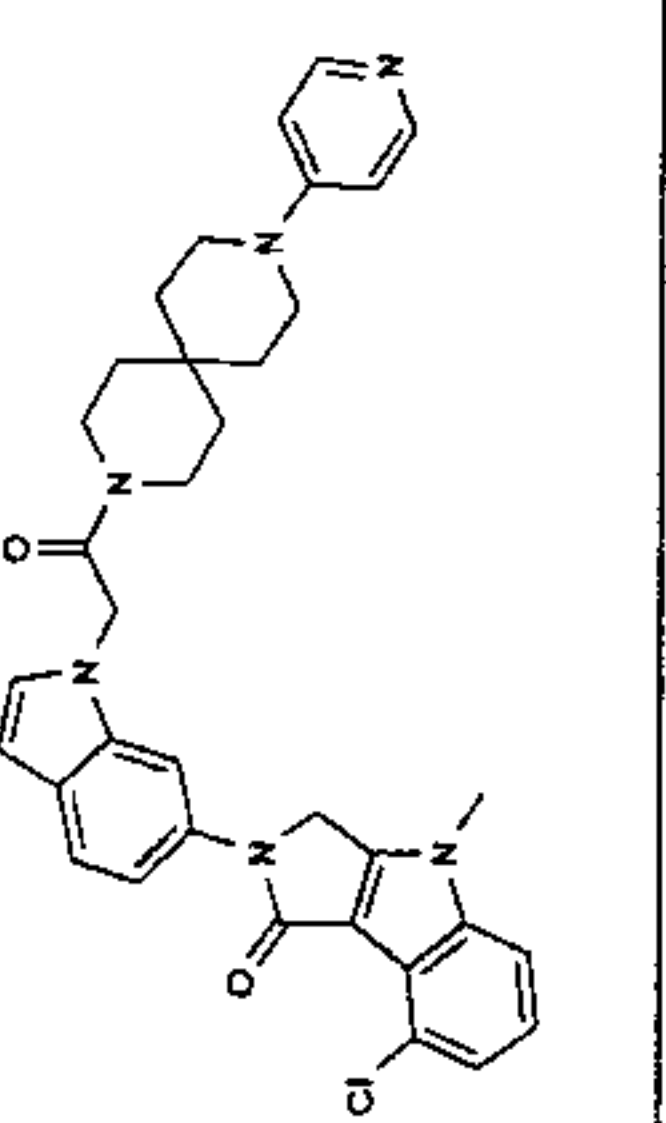
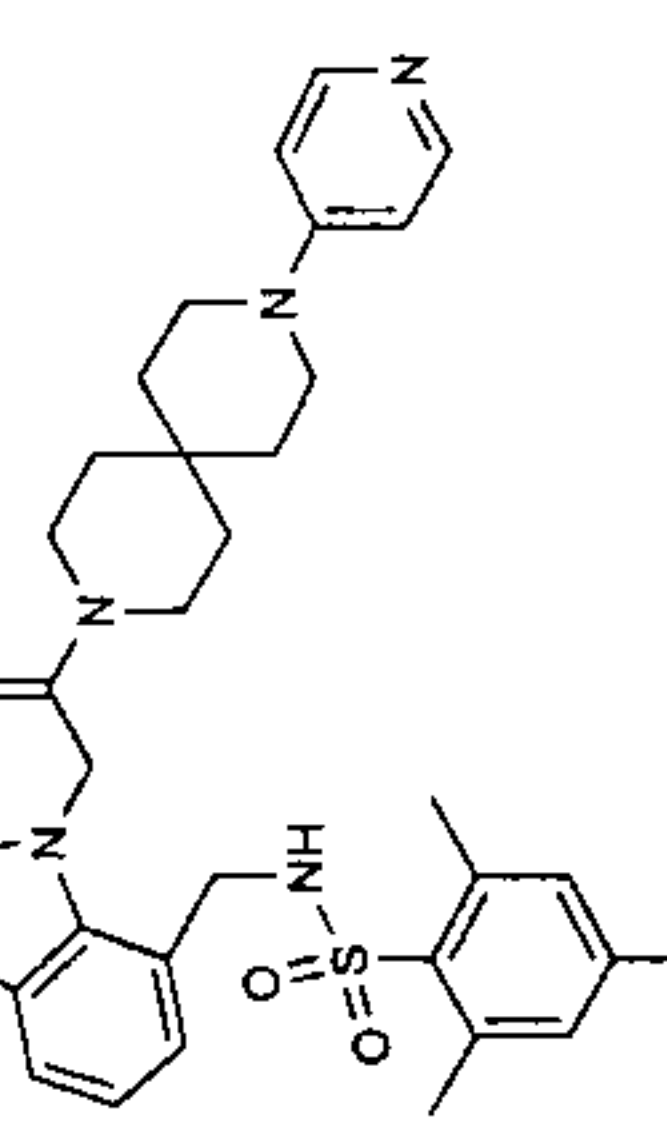
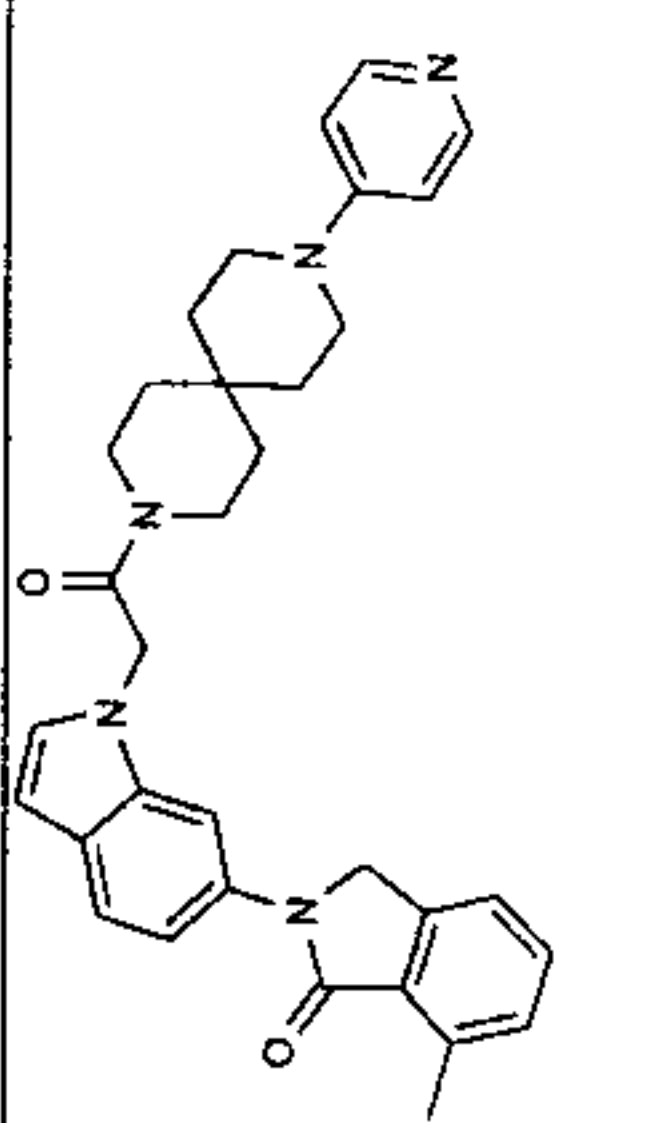
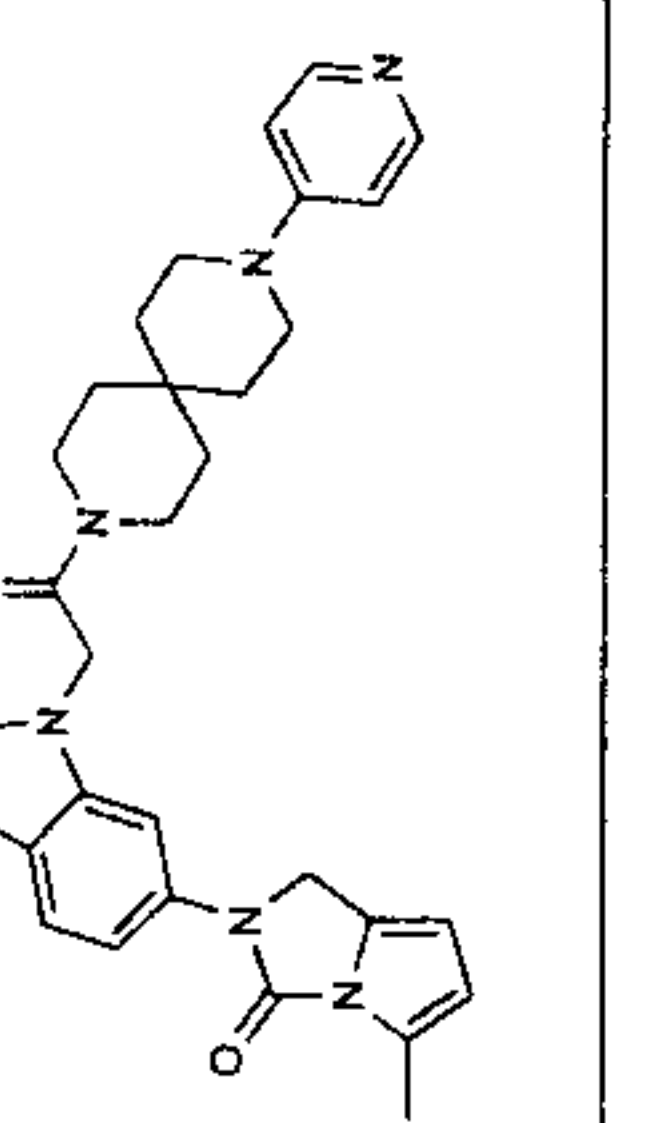
G-04		4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(1-oxo-4-phenyl-2,4,8-triazaspiro[4.5]decan-8-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G-04)	2-[7-[[4-Methoxy-2,6-dimethylphenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	4-Phenyl-2,4,8-triazaspiro[4.5]decan-1-one (F-33)	38% (2.0 mmol)	R _t = 5.2 min; m/z = 602.1 [MH] ⁺	GP V
G-05		4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G-05)	2-[7-[[4-Methoxy-2,6-dimethylphenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)	14% (160 mg)	R _t = 3.6 min; m/z = 602.1 [MH] ⁺	GP VII
G-06		4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-pyridin-3-yl-4-(2-pyrrolidin-1-ylethoxy)-piperidin-1-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G-06)	2-[7-[[4-Methoxy-2,6-dimethylphenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	3-[4-(2-Pyrrolidin-1-ylethoxy)piperidin-4-yl]pyridine dihydrochloride (F-29)	16% (0.08 mmol)	R _t = 2.8 min; m/z = 646.1 [MH] ⁺	GP VI
G-07		7-Chloro-2-[1-[3-oxo-3-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-propyl]-1H-indol-6-yl]-2,3-dihydroisindol-1-one (G-07)	3-[6-(4-Chloro-3-oxo-1,2-dihydroisindol-2-yl)-1H-indol-1-yl] propionic acid (E-15)	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)	44% (0.16 mmol)	R _t = 3.2 min; m/z = 568.3 [MH] ⁺	GP VI
G-08		7-Chloro-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-2,3-dihydroisindol-1-one (G-08)	2-[6-(4-Chloro-3-oxo-1,2-dihydroisindol-2-yl)-1H-indol-1-yl] acetic acid (E-16)	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)	54% (0.21 mmol)	R _t = 3.2 min; m/z = 554.3 [MH] ⁺	GP VI

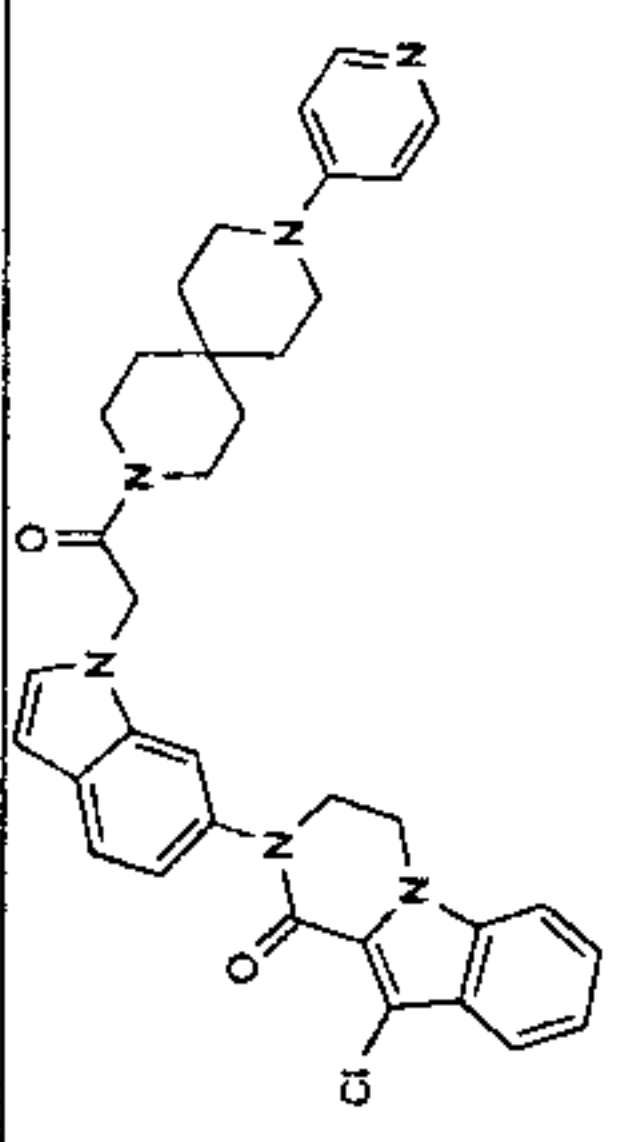
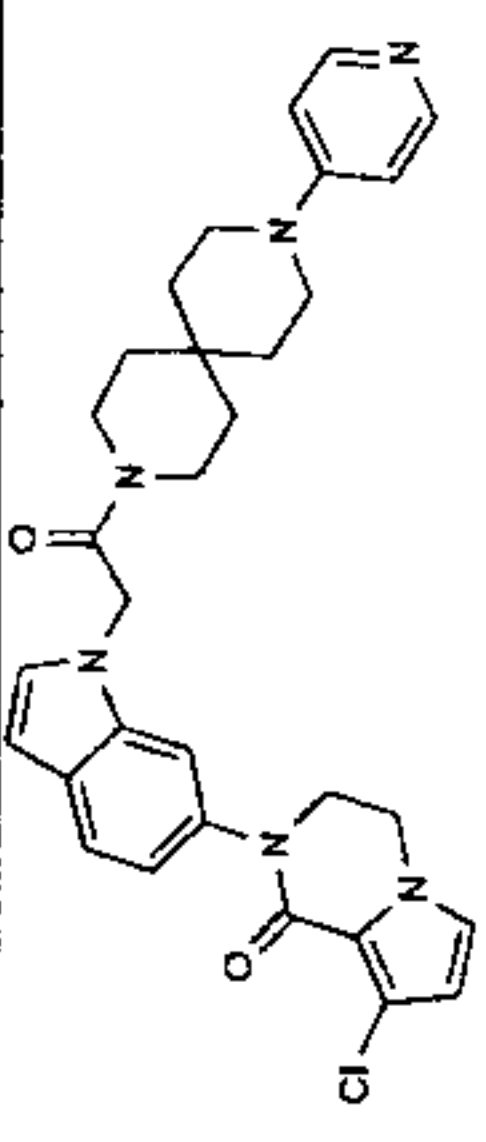
GRA3454-WO
22nd December 2009

G-10		7-Chloro-2-[1-[3-oxo-3-(9-pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl]-1H-indol-7-yl]-2,3-dihydroisoindol-1-one (G-10)	3-[7-(4-Chloro-3-oxo-1,2-dihydroisoindol-2-yl)-1H-indol-1-yl]-propionic acid (E-17)	3-(Pyridin-4-yl)-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)	57 % (0.24 mmol)	$R_t = 3.2 \text{ min};$ $m/z = 568.4$ [MH] ⁺	GP VI
G-11		7-Chloro-2-[1-[2-oxo-2-(9-pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl]-1H-indol-7-yl]-2,3-dihydroisoindol-1-one (G-11)	2-[7-(4-Chloro-3-oxo-1,2-dihydroisoindol-2-yl)-1H-indol-1-yl]-acetic acid (E-19)	3-(Pyridin-4-yl)-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)	63 % (0.27 mmol)	$R_t = 2.9 \text{ min};$ $m/z = 554.4$ [MH] ⁺	GP VI
G-12		7-Chloro-2-[1-[2-oxo-2-(8-pyridin-4-yl)-3,8-diazaspiro[4.5]decan-3-yl)ethyl]-1H-indol-6-yl]-2,3-dihydroisoindol-1-one (G-12)	2-[6-(4-Chloro-3-oxo-1,2-dihydroisoindol-2-yl)-1H-indol-1-yl]-acetic acid (E-16)	8-(Pyridin-4-yl)-2,8-diazaspiro[4.5]decan-2-ene dihydrochloride (F-38)	34 % (0.08 g)	$R_t = 3.1 \text{ min};$ $m/z = 540.2$ [MH] ⁺	GP Va
G-13		4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(3-pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-8-yl)ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G-13)	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	3-(Pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene bis(trifluoroacetate) (F-39)	44 % (0.1 g)	$R_t = 34.2 \text{ min};$ $m/z = 588.3$ [MH] ⁺	GP Va
G-14		4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(8-pyridin-4-yl)-3,8-diazaspiro[4.5]decan-3-yl)ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G-14)	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	8-(Pyridin-4-yl)-2,8-diazaspiro[4.5]decan-2-ene dihydrochloride (F-38)	53 % (0.12 g)	$R_t = 3.5 \text{ min};$ $m/z = 588.3$ [MH] ⁺	GP Va
G-15		7-Chloro-2-[1-[2-oxo-2-(3-pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-8-yl)ethyl]-1H-indol-6-yl]-2,3-dihydroisoindol-1-one (G-15)	2-[6-(4-Chloro-3-oxo-1,2-dihydroisoindol-2-yl)-1H-indol-1-yl]-acetic acid (E-16)	3-(Pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene bis(trifluoroacetate) (F-39)	39 % (0.08 g)	$R_t = 3.7 \text{ min};$ $m/z = 540.2$ [MH] ⁺	GP Va

G-16		4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[3-[6-(piperidin-1-yl-methyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]-pyrrolidin-1-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide dihydrochloride (G-16)	2-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	6-(Piperidin-1-ylmethyl)-2-(pyrrolidin-3-yl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride (F-40)	74 % (0.14 g)	$R_t = 2.7$ min; $m/z = 670.4$ [MH] ⁺	GP Va
G-17		4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(8-pyridin-4-yl-3,8-diazaspiro[4.4]nonan-3-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G-17)	2-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	2-(Pyridin-4-yl)-2,7-diazaspiro[4.4]nonane dihydrochloride (F-41)	34 % (0.1 g)	$R_t = 3.5$ min; $m/z = 574.3$ [MH] ⁺	GP Va
G-18		N-[1-[2-[9-(Azetidin-1-yl)-3-azaspiro[5.5]undecan-3-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G-18)	2-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	9-(Azetidin-1-yl)-3-azaspiro[5.5]undecane dihydrochloride (F-42)	29 % (0.08 g)	$R_t = 3.6$ min; $m/z = 579.4$ [MH] ⁺	GP Va
G-19		7-Chloro-2-[1-[2-oxo-2-(9-pyridin-4-yloxy-3-azaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-2,3-dihydroisindol-1-one (G-19)	2-[6-(4-Chloro-3-oxo-1,2-dihydroisindol-2-yl)-1H-indol-1-yl]-acetic acid (E-16)	9-(Pyridin-4-yloxy)-3-azaspiro[5.5]undecane dihydrochloride (F-43)	72 % (0.3 g)	$R_t = 3.5$ min; $m/z = 569.3$ [MH] ⁺	GP Va
G-20		7-Chloro-2-[1-[2-[9-(3,3-difluoroazetidin-1-yl)-3-azaspiro[5.5]undecan-3-yl]-2-oxo-ethyl]-1H-indol-6-yl]-2,3-dihydroisindol-1-one (G-20)	2-[6-(4-Chloro-3-oxo-1,2-dihydroisindol-2-yl)-1H-indol-1-yl]-acetic acid (E-16)	9-(3,3-Difluoroazetidin-1-yl)-3-azaspiro[5.5]undecane dihydrochloride (F-44)	39 % (0.13 g)	$R_t = 3.3$ min; $m/z = 567.3$ [MH] ⁺	GP Va
G-21		2-[1-[2-[9-(Azetidin-1-yl)-3-azaspiro[5.5]undecan-3-yl]-2-oxo-ethyl]-1H-indol-6-yl]-7-chloro-2,3-dihydroisindol-1-one (G-21)	2-[6-(4-Chloro-3-oxo-1,2-dihydroisindol-2-yl)-1H-indol-1-yl]-acetic acid (E-16)	9-(Azetidin-1-yl)-3-azaspiro[5.5]undecane dihydrochloride (F-42)	51 % (0.15 g)	$R_t = 3.2$ min; $m/z = 531.3$ [MH] ⁺	GP Va

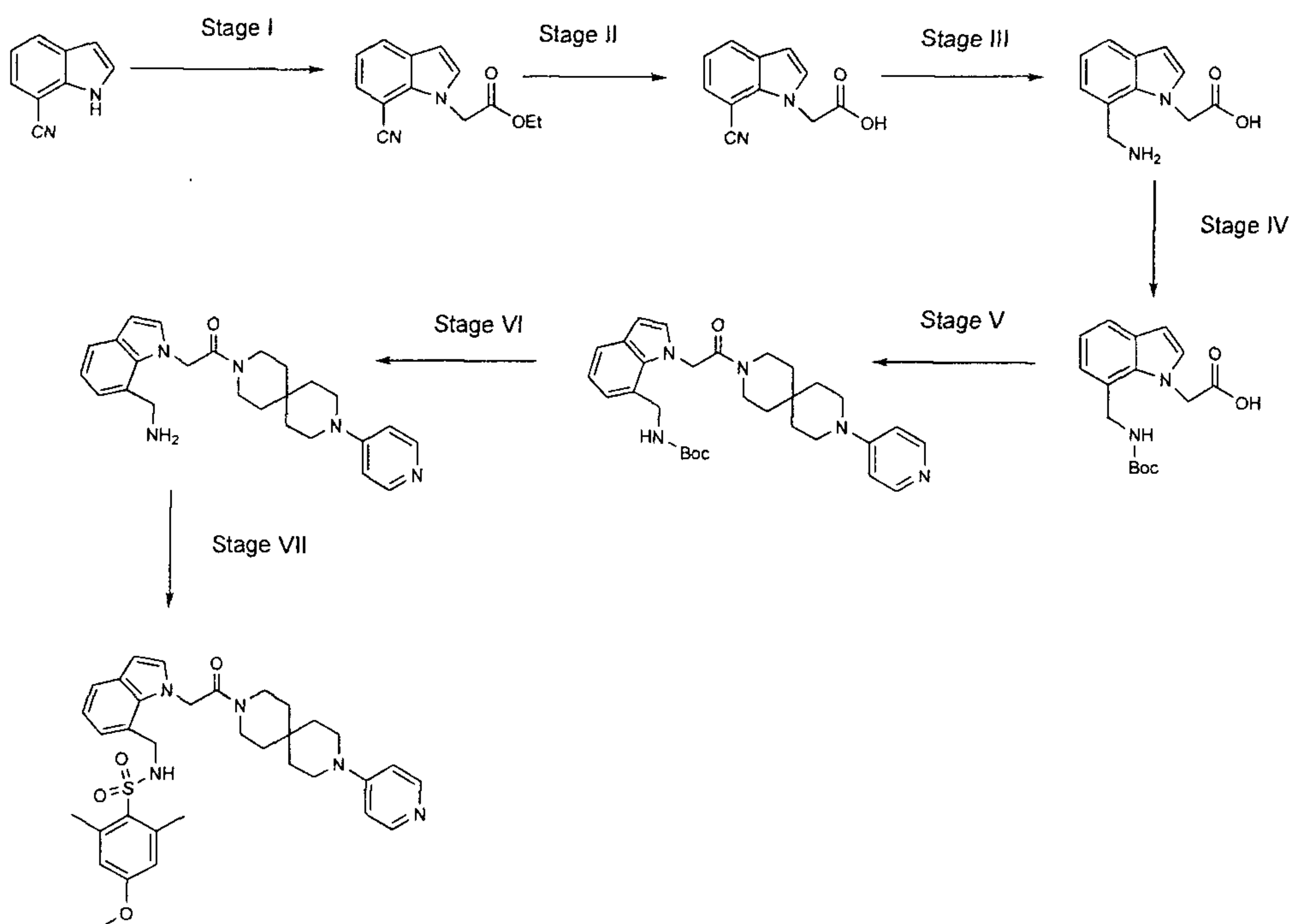
GRA3454-WO
22nd December 2009

G-22		4-Methoxy-2,6-dimethyl-N-[[1-[2-oxo-2-(9-pyridin-4-yloxy-3-azaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G-22)	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	9-(Pyridin-4-yloxy)-3-azaspiro[5.5]undecane dihydrochloride (F-43)	81 % (0.32 g)	$R_t = 3.8 \text{ min};$ $m/z = 617.3$ [MH] ⁺	GP Va
G-23		8-Chloro-4-methyl-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-3,4-dihydro-2H-pyrrolo[3,4-b]indol-1-one (G-23)	2-(6-(8-Chloro-4-methyl-1-oxopyrrolo[3,4-b]indol-2(1H,3H,4H)-yl)-1H-indol-1-yl)acetic acid (E-20)	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane trifluoroacetate (F-14)	40 %	$R_t = 3.6 \text{ min};$ $m/z = 607.3$ [MH] ⁺	GP Vb
G-24		4-Methoxy-2,6-dimethyl-N-[[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-7-yl]-methyl]-benzenesulfonic acid amide (G-24)				$R_t = 3.7 \text{ min};$ $m/z = 616.5$ [MH] ⁺	for synthesis see below
G-26		7-Methyl-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-2,3-dihydroisindol-1-one (G-26)	2-(6-(7-Methyl-1-oxoisindolin-2-yl)-1H-indol-1-yl)acetic acid (E-21)	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane (F-14)	24 %	$R_t = 3.6 \text{ min};$ $m/z = 534.4$ [MH] ⁺	GP Vc
G-27		5-Methyl-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-1,2-dihydropyrrolo[2,1-e]imidazol-3-one (G-27)	2-(6-(5-Methyl-3-oxo-1H-pyrrolo[1,2-c]imidazol-2(3H)-yl)-1H-indol-1-yl)acetic acid (E-22)	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane (F-14)	30 %	$R_t = 3.7 \text{ min};$ $m/z = 523.4$ [MH] ⁺	GP Vc

G-31		10-Chloro-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one (G-31)	2-(6-(10-Chloro-1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-1H-indol-1-yl)acetic acid (E-23)	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane (F-14)	12 %	$R_t = 3.7 \text{ min};$ $m/z = 607.3$ [MH] ⁺	GP Vc
G-33		8-Chloro-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-3,4-dihydro-2H-pyrrolo[1,2-a]pyrazin-1-one (G-33)	2-(6-(8-Chloro-1-oxo-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-1H-indol-1-yl)acetic acid (E-24)	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane (F-14)	25 %	$R_t = 3.0 \text{ min};$ $m/z = 557.3$ [MH] ⁺	GP Vc

GRA3454-WO
22nd December 2009

Exemplary compound G-24: 4-Methoxy-2,6-dimethyl-N-[[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-7-yl]-methyl]-benzenesulfonic acid amide



Stage I: Ethyl 2-(7-cyano-1H-indol-1-yl)acetate

A solution of 1H-indole-7-carbonitrile (2.0 g, 14.08 mmol, 1.0 equiv.) in dry DMF (10 ml) was added at 0°C to a suspension of NaH (0.845 g, 21.12 mmol, 1.5 equiv. 60% in mineral oil) in DMF (10 ml), and the mixture was stirred for 30 min. Ethyl bromoacetate (1.9 ml, 16.9 mmol, 1.2 equiv.) was added at 0°C, and stirring was carried out for 1 h at RT. When the reaction was complete (TLC monitoring), the mixture was cooled and diluted with water (60 ml). Extraction with ethyl acetate (3 x 80 ml) was carried out, and the combined organic phases were washed with sat. NaCl solution (2 x 100 ml), dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, 8-10% ethyl acetate/hexane) and the desired product was isolated in the form of a yellow solid. Yield: 80% (2.6 g, 11.37 mmol)

GRA3454-WO
22nd December 2009

Stage II: 2-(7-Cyano-1H-indol-1-yl)acetic acid

A solution of LiOH.H₂O (1.4 g, 34.06 mmol, 3.0 equiv.) in water (10 ml) was added at 0°C to a solution of ethyl 2-(7-cyano-1H-indol-1-yl)acetate (2.6 g, 11.37 mmol, 1.0 equiv.) in THF, and the mixture was stirred for 2 h at RT. When the reaction was complete (TLC monitoring), the mixture was concentrated under vacuum and the residue was taken up in water (50 ml). Extraction with ethyl acetate (50 ml) was carried out, and then the aqueous phase was adjusted to pH $\approx$ 3-4 with 10% HCl solution. Extraction with DCM (2 x 50 ml) was then carried out, and the combined organic phases were washed with sat. NaCl solution, dried over Na₂SO₄ and concentrated under vacuum. The desired product was isolated in the form of a light-yellow solid.

Yield: 92% (2.1 g, 10.5 mmol)

Stage III: 2-(7-(Aminomethyl)-1H-indol-1-yl)acetic acid

Raney Ni (7.0 g) was added to a solution of 2-(7-cyano-1H-indol-1-yl)acetic acid (700 mg, 3.5 mmol) in MeOH (15 ml), and the mixture was hydrogenated for 6 h at RT and 60 psi hydrogen in a Parr apparatus. The reaction mixture was filtered over celite and the filtrate was concentrated under vacuum. The crude product so obtained was used directly in the following stage without being purified further.

Yield: 96% (692 mg, 3.36 mmol)

Stage IV: 2-(7-((tert-Butoxycarbonylamino)methyl)-1H-indol-1-yl)acetic acid

1 N NaOH (6 ml) was added at 0°C to a solution of 2-(7-(aminomethyl)-1H-indol-1-yl)acetic acid (692 mg, 3.36 mmol, 1.0 equiv.) in dioxane, followed by (Boc)₂O (1.1 ml, 5.08 mmol, 1.5 equiv.). The resulting reaction mixture was stirred for 16 h at RT and then the solvent was removed under vacuum. The residue was taken up in water (25 ml) and extracted with ethyl acetate (2 x 20 ml). The aqueous phase was then adjusted to an acidic pH value with KHSO₄ solution at 0°C. Extraction with DCM (3 x 30 ml) was then carried out, and the combined organic phases were washed with sat. NaCl solution (40 ml), dried over Na₂SO₄ and concentrated under vacuum. The crude product so obtained was used directly in the following stage without being purified further.

Yield: 36% (372 mg, 1.22 mmol)

GRA3454-WO
22nd December 2009

Stage V: tert-Butyl (1-(2-oxo-2-(9-(pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-1H-indol-7-yl)methylcarbamate

HATU (464 mg, 1.22 mmol, 1.0 equiv.) and DIPEA (0.8 ml, 4.88 mmol, 4.0 equiv.) were added at 0°C to a suspension of 2-(7-((tert-butoxycarbonylamino)methyl)-1H-indol-1-yl)acetic acid (372 mg, 1.22 mmol, 1.0 equiv.) in THF (8 ml), and the mixture was stirred for 15 min. A solution of 3-pyridin-4-yl-3,9-diazaspiro[5.5]undecane (F-14) (283 mg, 1.22 mmol, 1.0 equiv.), dissolved in a mixture of THF (4 ml) and DMF (0.5 ml), was added, and stirring was carried out for 14 h at RT. The reaction mixture was diluted with ethyl acetate (30 ml) and extracted with sodium bicarbonate solution (2 x 20 ml), NH₄Cl solution (2 x 20 ml), water (20 ml) and sat. NaCl solution (20 ml) and dried over Na₂SO₄. The solvent was removed under vacuum and the crude product was purified by column chromatography (Alox neutral; 0.5% MeOH/DCM), and the desired product was thus obtained in the form of a white solid.

Yield: 95% (600 mg, 1.16 mmol)

Stage VI: 2-(7-(Aminomethyl)-1H-indol-1-yl)-1-(9-(pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethanone

Dioxane-HCl (6 ml) was added to a solution of tert-butyl (1-(2-oxo-2-(9-(pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-1H-indol-7-yl)methylcarbamate (600 mg, 1.16 mmol, 1.0 equiv.) in dioxane (6 ml), and the mixture was stirred for 1 h at RT. When the reaction was complete (TLC monitoring), the solvent was removed under vacuum and the residue was adjusted to a basic pH value with TEA and was concentrated again. The crude product was purified by column chromatography (Alox neutral; 5-10% MeOH/DCM), and the desired product was thus obtained in the form of a white solid.

Yield: 45% (220 mg, 0.53 mmol)

Stage VII: 4-Methoxy-2,6-dimethyl-N-((1-(2-oxo-2-(9-(pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-1H-indol-7-yl)methyl)benzenesulfonamide

A mixture of 2-(7-(aminomethyl)-1H-indol-1-yl)-1-(9-(pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethanone (220 mg, 0.53 mmol, 1.0 equiv.) and NaHCO₃ (134 mg, 1.59 mmol, 3.0 equiv.) in THF-water(1:1, 20 ml) was added at 0°C to a solution of 2,6-dimethyl-4-methoxyphenylsulfonyl chloride (136 mg, 0.58 mmol, 1.1 equiv.) in THF (5 ml), and the mixture was stirred for 16 h at RT. The reaction mixture was

GRA3454-WO
22nd December 2009

diluted with water (15 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organic phases were washed with sat. NaCl solution (40 ml) and dried over Na₂SO₄. The solvent was removed under vacuum and the crude product was purified by column chromatography (silica gel; 6-8% MeOH/DCM), and the desired product was thus obtained in the form of a white solid.

Yield: 38% (64 mg, 0.104 mmol)

Library syntheses

Parallel method for the synthesis of indolamides G_CC

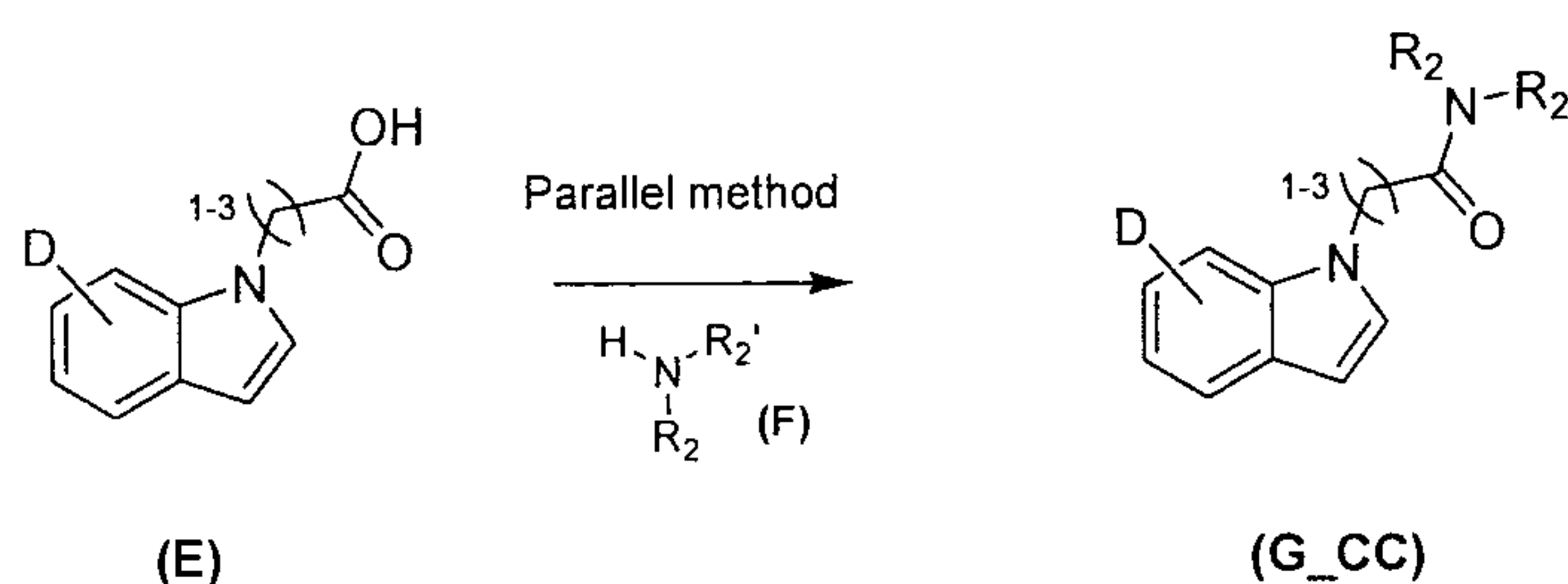


Figure 5: Parallel synthesis of indolamides G_CC

The acid structural units **E** were reacted in a parallel synthesis with the amines **F** to form the amides **G_CC**, as illustrated in the figure above. The correlation between product and reagent, structural unit and method is shown in the synthesis matrix.

The crude products from the parallel synthesis were analysed by HPLC-MS^[2] and then purified by Reverse Phase HPLC-MS^[2]. The products were able to be identified by means of analytical HPLC-MS measurements^[3].

[2] Equipment and methods for HPLC-MS analysis:

Parallel synthesis method: HPLC: Waters Alliance 2795 with PDA Waters 2996; MS: ZQ 2000

MassLynx Single Quadrupol MS Detector; Column: Atlantis dC18 30 x 2.1 mm, 3 µm; Column

temperature: 40 °C, Eluent A: purified water + 0.1% formic acid; Eluent B: acetonitrile (gradient grade)

+ 0.1% formic acid; Gradient: 0% B to 100% B in 2.3 min, 100% B for 0.4 min, 100% B to 0% B in 0.01

min, 0% B for 0.8 min; Flow: 1.0 ml/min; Ionisation: ES+, 25V; make up: 100 µl/min 70% methanol +

0.2% formic acid; UV: 200 – 400 nm.

GRA3454-WO
22nd December 2009

[3] Equipment and methods for HPLC-MS purification: *Prep Pump:* Waters 2525; *Make Up Pump:* Waters 515; *Auxiliary Detector:* Waters DAD 2487; *MS Detector:* Waters Micromass ZQ; *Injector/Fraction Collector:* Waters Sample Manager 2767; *Gradient: Initial:* 60% Water 40% Methanol -> 12-14.5 min: 0% Water 100% Methanol -> 14.5-15 min: 60% Water 40% Methanol; *Flow:* 35 ml/min
Column: Macherey-Nagel, C18 Gravity, 100x21 mm, 5 μ .

Parallel synthesis: Synthesis instructions for the preparation of indolamides

G_CC

A solution of 1,1'-carbonyldiimidazole (200 μ M) in 0.5 ml dichloromethane was added to a solution of acid **E** (100 μ M) in a mixture of 1.8 ml dichloromethane and 0.2 ml DMF and the mixture is shaken for 1 hour at room temperature.

Then a solution^[4] of amine **F** (200 μ M) was added. The reaction mixture was shaken for 18 hours at room temperature.

3 ml of semi-saturated sodium hydrogen carbonate solution were added to the reaction mixture and it was mixed intensively. The organic phase was removed and transferred to a tared vessel. Then the aqueous phase was extracted once again with 3 ml dichloromethane. The combined organic phases were concentrated under reduced pressure in vacuum centrifuges (GeneVac). The final purification was performed by HPLC-MS^[3]. The final analysis was performed by LC-MS^[2].

[4] The amines in the form of hydrochloride were mixed with a 0.5 M excess (relative to the hydrochloride) of Hünig's base and with 500 μ l N,N-dimethyl formamide, then topped up to a total volume of 2 ml with dichloromethane, causing them to be dissolved or suspended. The amines in the form of the free base were dissolved or suspended in dichloromethane and/or N,N-dimethyl formamide.

GRA3454-WO
22nd December 2009

Example no.	Example name	Indole acid no.	Indole acid name	Amine no.	Amine name
G_CC-1	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G_CC-1)	E-03	2-[6-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-03)	F-02	1-(1-Methyl-piperidin-4-yl) piperazine (F-02)
G_CC-2	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G_CC-2)	E-03	2-[6-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-03)	F-21	1-Methyl-4-piperidin-4-yl piperazine (F-21)
G_CC-3	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G_CC-3)	E-03	2-[6-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-03)	F-17	2-Piperazin-1-yl pyrimidine (F-17)
G_CC-4	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G_CC-4)	E-03	2-[6-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-03)	F-22	1-[(1-Methyl-piperidin-4-yl) methyl] piperazine (F-22)
G_CC-5	N-[1-[2-[4-(4-fluorophenyl)-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-5)	E-02	2-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-16	1-(4-Fluorophenyl)piperazine (F-16)
G_CC-6	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-6)	E-02	2-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-17	2-Piperazin-1-yl pyrimidine (F-17)
G_CC-7	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-7)	E-02	2-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-22	1-[(1-Methyl-piperidin-4-yl) methyl] piperazine (F-22)
G_CC-8	4-Chloro-2,5-dimethyl-N-[1-[2-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G_CC-8)	E-04	2-[6-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-04)	F-22	1-[(1-Methyl-piperidin-4-yl) methyl] piperazine (F-22)
G_CC-9	2-[6-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[(1-pyridin-4-yl-piperidin-4-yl)-methyl]-acetamide (G_CC-9)	E-03	2-[6-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-03)	F-15	(1-Pyridin-4-yl-piperidin-4-yl)methylamine dihydrochloride (F-15)
G_CC-10	N-[1-[2-(3-Benzyl-3,7-diazaspiro[4.4]nonan-7-yl)-2-oxo-ethyl]-1H-indol-6-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-10)	E-03	2-[6-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-03)	F-28	3-Benzyl-3,7-diazaspiro[4.4]nonane (F-28)

GRA3454-WO
22nd December 2009

G_CC-11	N-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-2-[6-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-11)	E-03	2-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-03)	F-11	Dimethyl-[1-(3-methylaminopropyl)-4-phenyl piperidin-4-yl]amine trihydrochloride (F-11)
G_CC-12	N-[1-[2-[3-(4-Fluorophenyl)-4-oxo-3,8-diazaspiro[4.5]decan-8-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-12)	E-02	2-[7-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-23	3-(4-Fluorophenyl)-3,8-diazaspiro[4.5]decan-4-one hydrochloride (F-23)
G_CC-13	N-[1-[2-(3-Benzyl-3,7-diazaspiro[4.4]nonan-7-yl)-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-13)	E-02	2-[7-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-28	3-Benzyl-3,7-diazaspiro[4.4]nonane (F-28)
G_CC-14	N-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-2-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-14)	E-02	2-[7-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-11	Dimethyl-[1-(3-methylaminopropyl)-4-phenyl piperidin-4-yl]amine trihydrochloride (F-11)
G_CC-15	2-[6-[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[3-(4-dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-N-methyl-acetamide (G_CC-15)	E-04	2-[6-[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-04)	F-11	Dimethyl-[1-(3-methylaminopropyl)-4-phenyl piperidin-4-yl]amine trihydrochloride (F-11)
G_CC-16	N-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-N-methyl-2-[7-[[naphthalen-1-ylsulfonyl]amino]-1H-indol-1-yl]-acetamide (G_CC-16)	E-07	2-[7-[[Naphthalen-1-ylsulfonyl]amino]-1H-indol-1-yl] acetic acid (E-07)	F-11	Dimethyl-[1-(3-methylaminopropyl)-4-phenyl piperidin-4-yl]amine trihydrochloride (F-11)
G_CC-17	N-[4-(Azetidin-1-yl)-4-phenyl-cyclohexyl]-2-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetamide (G_CC-17)	E-02	2-[7-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-12	[4-(Azetidin-1-yl)-4-phenyl-cyclohexyl]amine dihydrochloride (F-12)
G_CC-18	N-[3-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-2-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-18)	E-02	2-[7-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-09	Dimethyl-[1-(3-methylaminopropyl)-4-thiophen-2-yl-piperidin-4-yl]amine (F-09)
G_CC-19	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-2-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetamide (G_CC-19)	E-02	2-[7-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-08	[1-(2-Aminoethyl)-4-thiophen-2-yl-piperidin-4-yl]-dimethylamine trihydrochloride (F-08)
G_CC-20	N-[1-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-20)	E-02	2-[7-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-10	Dimethyl-(4-thiophen-2-yl piperidin-4-yl)amine dihydrochloride (F-10)

GRA3454-WO
22nd December 2009

G_CC-21	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide (G_CC-21)	E-02	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-13	2-(1-Pyridin-4-yl-piperidin-4-yl)ethylamine dihydrochloride (F-13)
G_CC-22	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-3-[6-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionamide (G_CC-22)	E-05	3-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-05)	F-08	[1-(2-Aminoethyl)-4-thiophen-2-yl-piperidin-4-yl]-dimethylamine trihydrochloride (F-08)
G_CC-23	3-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide (G_CC-23)	E-05	3-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-05)	F-13	2-(1-Pyridin-4-yl-piperidin-4-yl)ethylamine dihydrochloride (F-13)
G_CC-24	2-[6-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide (G_CC-24)	E-04	2-[6-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-04)	F-13	2-(1-Pyridin-4-yl-piperidin-4-yl)ethylamine dihydrochloride (F-13)
G_CC-25	N-[3-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-N-methyl-2-[7-[[[naphthalen-1-yl)sulfonyl]amino]-1H-indol-1-yl]-acetamide (G_CC-25)	E-07	2-[7-[[[Naphthalen-1-yl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-07)	F-09	Dimethyl-[1-(3-methylaminopropyl)-4-thiophen-2-yl-piperidin-4-yl]amine (F-09)
G_CC-26	2-[7-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[3-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-N-methyl-acetamide (G_CC-26)	E-08	2-[7-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-08)	F-09	Dimethyl-[1-(3-methylaminopropyl)-4-thiophen-2-yl-piperidin-4-yl]amine (F-09)
G_CC-27	2-[7-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-acetamide (G_CC-27)	E-08	2-[7-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-08)	F-08	[1-(2-Aminoethyl)-4-thiophen-2-yl-piperidin-4-yl]-dimethylamine trihydrochloride (F-08)
G_CC-28	2-[7-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide (G_CC-28)	E-08	2-[7-[[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-08)	F-13	2-(1-Pyridin-4-yl-piperidin-4-yl)ethylamine dihydrochloride (F-13)
G_CC-29	N-[3-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-2-[6-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-29)	E-03	2-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-03)	F-09	Dimethyl-[1-(3-methylaminopropyl)-4-thiophen-2-yl-piperidin-4-yl]amine (F-09)
G_CC-30	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-2-[6-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetamide (G_CC-30)	E-03	2-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-03)	F-08	[1-(2-Aminoethyl)-4-thiophen-2-yl-piperidin-4-yl]-dimethylamine trihydrochloride (F-08)

GRA3454-WO
22nd December 2009

G_CC-31	N-[1-[2-[1-(4-Fluorophenyl)-3-methyl-4-oxo-3,8-diazaspiro[4.5]decan-8-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-31)	E-02	2-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-25	1-(4-Fluorophenyl)-3-methyl-3,8-diazaspiro[4.5]decan-4-one hydrochloride (F-25)
G_CC-32	N-[1-[2-(3-Benzyl-4-oxo-3,8-diazaspiro[4.5]decan-8-yl)-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-32)	E-02	2-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-27	3-Benzyl-3,8-diazaspiro[4.5]decan-4-one hydrochloride (F-27)
G_CC-33	N-[1-[2-[2-[(4-Fluorophenyl)-methyl]-2,5-diazabicyclo[2.2.1]heptan-5-yl]-2-oxo-ethyl]-1H-indol-6-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-33)	E-03	2-[6-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-03)	F-31	2-[(4-Fluorophenyl)methyl]-2,5-diazabicyclo[2.2.1]heptane dihydrochloride (F-31)
G_CC-34	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[2-(pyridin-4-yl-methyl)-2,5-diazabicyclo[2.2.1]heptan-5-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-34)	E-02	2-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-02)	F-30	2-(Pyridin-4-yl-methyl)-2,5-diazabicyclo[2.2.1]heptane dihydrochloride (F-30)
G_CC-35	4-Methoxy-2,6-dimethyl-N-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G_CC-35)	E-05	3-[6-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-05)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-36	4-Chloro-2,5-dimethyl-N-[1-[2-oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G_CC-36)	E-04	2-[6-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-04)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-37	N-[1-[2-Oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-6-yl]-2-(trifluoromethyl)-benzenesulfonic acid amide (G_CC-37)	E-06	2-[6-[[[2-(Trifluoromethyl)-phenyl]sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-06)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-38	N-[1-[2-Oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-naphthalene-1-sulfonic acid amide (G_CC-38)	E-07	2-[7-[(Naphthalen-1-ylsulfonyl)amino]-1H-indol-1-yl] acetic acid (E-07)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-39	4-Chloro-2,5-dimethyl-N-[1-[2-oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-39)	E-08	2-[7-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-08)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-40	4-Methoxy-2,6-dimethyl-N-[1-[3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-40)	E-14	3-[7-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-02	1-(1-Methyl-piperidin-4-yl)piperazine (F-02)

GRA3454-WO

22nd December 2009

G_CC-41	4-Methoxy-2,6-dimethyl-N-[1-[3-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-41)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-05	4-(2-Pyrrolidin-1-yl-ethyl) piperidine (F-05)
G_CC-42	4-Methoxy-2,6-dimethyl-N-[1-[3-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-42)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-21	1-Methyl-4-piperidin-4-yl piperazine (F-21)
G_CC-43	4-Methoxy-2,6-dimethyl-N-[1-[3-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-43)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-22	1-[(1-Methyl-piperidin-4-yl)methyl] piperazine (F-22)
G_CC-44	N-[1-[3-[4-(3-Dimethylamino-propyl)-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-44)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-01	Dimethyl-(3-piperazin-1-yl-propyl)amine (F-01)
G_CC-45	N-[1-[3-[4-(4-Hydroxy-4-pyridin-2-yl-piperidin-1-yl)-3-oxo-propyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-45)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-20	4-Pyridin-2-yl piperidin-4-ol (F-20)
G_CC-46	N-[3-[4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-3-[7-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide (G_CC-46)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-09	Dimethyl-[1-(3-methylaminopropyl)-4-thiophen-2-yl-piperidin-4-yl]amine (F-09)
G_CC-47	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide (G_CC-47)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-13	2-(1-Pyridin-4-yl-piperidin-4-yl)ethylamine dihydrochloride (F-13)
G_CC-48	N-[1-[3-[4-Dimethylamino-4-phenyl-piperidin-1-yl)-3-oxo-propyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-48)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-07	Dimethyl-(4-phenyl-piperidin-4-yl)amine dihydrochloride (F-07)
G_CC-49	N-[3-[4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-3-[7-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide (G_CC-49)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-11	Dimethyl-[1-(3-methylaminopropyl)-4-phenyl piperidin-4-yl]amine trihydrochloride (F-11)
G_CC-50	N-[4-(Azetidin-1-yl)-4-phenyl-cyclohexyl]-3-[7-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionamide (G_CC-50)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-12	[4-(Azetidin-1-yl)-4-phenyl-cyclohexyl]amine dihydrochloride (F-12)
G_CC-51	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-3-[7-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic	F-08	[1-(2-Aminoethyl)-4-thiophen-2-yl-piperidin-4-yl]-dimethylamine

GRA3454-WO
22nd December 2009

	yl]-propionamide (G_CC-51)		acid (E-14)		trihydrochloride (F-08)
G_CC-52	N-[1-[3-Oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-7-yl]-2-(trifluoromethyl)-benzenesulfonic acid amide (G_CC-52)	E-09	3-[7-[[[2-(Trifluoromethyl)-phenyl]sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-09)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-53	N-[1-[2-Oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-2-(trifluoromethyl)-benzenesulfonic acid amide (G_CC-53)	E-13	2-[7-[[[2-(Trifluoromethyl)-phenyl]sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-13)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-54	4-Methoxy-2,6-dimethyl-N-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-54)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl]sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-56	N-[3-(4-Ethyl-piperazin-1-yl)-propyl]-3-[7-[[[4-methoxy-2,6-dimethyl-phenyl]sulfonyl]amino]-1H-indol-1-yl]-propionamide (G_CC-56)	E-14	3-[7-[[[4-Methoxy-2,6-dimethyl-phenyl]sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-14)	F-03	3-(4-Ethyl-piperazin-1-yl)-propylamine (F-03)
G_CC-57	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-pyridin-3-yl-4-(2-pyrrolidin-1-yl-ethoxy)-piperidin-1-yl]-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G-CC-57)	E-03	2-[6-[[[4-Methoxy-2,6-dimethyl-phenyl]sulfonyl]amino]-1H-indol-1-yl] acetic acid (E-03)	F-29	3-[4-(2-Pyrrolidin-1-yl-ethoxy)piperidin-4-yl] pyridine dihydrochloride (F-29)
G_CC-59	4-Chloro-2,5-dimethyl-N-[1-[3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-59)	E-10	3-[7-[[[4-Chloro-2,5-dimethyl-phenyl]sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-10)	F-02	1-(1-Methyl-piperidin-4-yl) piperazine (F-02)
G_CC-60	4-Chloro-2,5-dimethyl-N-[1-[3-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-60)	E-10	3-[7-[[[4-Chloro-2,5-dimethyl-phenyl]sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-10)	F-05	4-(2-Pyrrolidin-1-yl-ethyl) piperidine (F-05)
G_CC-61	4-Chloro-2,5-dimethyl-N-[1-[3-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-61)	E-10	3-[7-[[[4-Chloro-2,5-dimethyl-phenyl]sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-10)	F-21	1-Methyl-4-piperidin-4-yl piperazine (F-21)
G_CC-62	4-Chloro-2,5-dimethyl-N-[1-[3-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-62)	E-10	3-[7-[[[4-Chloro-2,5-dimethyl-phenyl]sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-10)	F-22	1-[(1-Methyl-piperidin-4-yl)methyl] piperazine (F-22)
G_CC-63	7-Chloro-2-[1-[3-oxo-3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one (G_CC-63)	E-15	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl] propionic acid (E-15)	F-18	1-Pyridin-4-yl piperazine (F-18)

GRA3454-WO
22nd December 2009

G_CC-64	7-Chloro-2-[1-[3-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-3-oxo-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one (G_CC-64)	E-15	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl] propionic acid (E-15)	F-22	1-[(1-Methyl-piperidin-4-yl)methyl] piperazine (F-22)
G_CC-65	4-Chloro-2,5-dimethyl-N-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G_CC-65)	E-12	3-[6-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-12)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-66	8-[3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-propanoyl]-3-[(4-fluorophenyl)-methyl]-3,8-diazaspiro[4.5]decan-4-one (G_CC-66)	E-15	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl] propionic acid (E-15)	F-26	3-[(4-Fluorophenyl)-methyl]-3,8-diazaspiro[4.5]decan-4-one hydrochloride (F-26)
G_CC-67	7-Chloro-2-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one (G_CC-67)	E-15	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl] propionic acid (E-15)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-68	7-Chloro-2-[1-[3-oxo-3-(4-pyridin-4-yloxy-piperidin-1-yl)-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one (G_CC-68)	E-15	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl] propionic acid (E-15)	F-24	4-Piperidin-4-yloxy-pyridine hydrochloride (F-24)
G_CC-69	7-Chloro-2-[1-[3-(4-hydroxy-4-pyridin-3-yl-piperidin-1-yl)-3-oxo-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one (G_CC-69)	E-15	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl] propionic acid (E-15)	F-19	4-Pyridin-3-yl piperidin-4-ol (F-19)
G_CC-70	3-[7-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide (G_CC-70)	E-10	3-[7-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-10)	F-13	2-(1-Pyridin-4-yl-piperidin-4-yl)ethylamine dihydrochloride (F-13)
G_CC-71	3-[6-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide (G_CC-71)	E-12	3-[6-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-12)	F-13	2-(1-Pyridin-4-yl-piperidin-4-yl)ethylamine dihydrochloride (F-13)
G_CC-72	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide (G_CC-72)	E-15	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl] propionic acid (E-15)	F-13	2-(1-Pyridin-4-yl-piperidin-4-yl)ethylamine dihydrochloride (F-13)
G_CC-73	3-[7-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-propionamide (G_CC-73)	E-10	3-[7-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-10)	F-08	[1-(2-Aminoethyl)-4-thiophen-2-yl-piperidin-4-yl]-dimethylamine trihydrochloride (F-08)
G_CC-74	3-[6-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-propionamide (G_CC-74)	E-12	3-[6-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl] propionic acid (E-12)	F-08	[1-(2-Aminoethyl)-4-thiophen-2-yl-piperidin-4-yl]-dimethylamine trihydrochloride (F-08)

GRA3454-WO
22nd December 2009

G_CC-76	2-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl)-piperazin-1-yl]-propyl]-acetamide (G_CC-76)	E-03	2-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-03)	F-48	Methyl-[3-(4-pyridin-4-yl)-piperazin-1-yl]-propyl]-amine trihydrochloride (F-48)
G_CC-77	N-[2-(4-Dimethylamino-4-phenyl-cyclohexyl)-ethyl]-2-[7-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-77)	E-02	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	F-45	Dimethyl-[4-(2-methylamino-ethyl)-1-phenyl-cyclohexyl]-amine dihydrochloride (F-45)
G_CC-81	N-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-3-[6-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide (G_CC-81)	E-05	3-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionic acid (E-05)	F-47	2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl-methyl-amine tetrahydrochloride (F-47)
G_CC-84	N-[1-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-84)	E-02	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	F-46	1-[4-(3-Fluorophenyl)-piperidin-4-yl]-4-methyl-piperazine dihydrochloride (F-46)
G_CC-88	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl)-piperazin-1-yl]-propyl]-acetamide (G_CC-88)	E-02	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	F-48	Methyl-[3-(4-pyridin-4-yl)-piperazin-1-yl]-propyl]-amine trihydrochloride (F-48)
G_CC-91	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-91)	E-02	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-92	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyridin-4-yloxy-piperidin-1-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-92)	E-02	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	F-24	4-Piperidin-4-yloxy-pyridine hydrochloride (F-24)
G_CC-95	N-[2-(4-Dimethylamino-4-phenyl-cyclohexyl)-ethyl]-2-[6-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-95)	E-03	2-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-03)	F-45	Dimethyl-[4-(2-methylamino-ethyl)-1-phenyl-cyclohexyl]-amine dihydrochloride (F-45)
G_CC-99	N-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-2-[6-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-99)	E-03	2-[6-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-03)	F-47	2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl-methyl-amine tetrahydrochloride (F-47)
G_CC-102	N-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-2-[7-[[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide	E-02	2-[7-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	F-47	2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl-methyl-amine tetrahydrochloride

GRA3454-WO
22nd December 2009

(G_CC-102)			(F-47)		
G_CC-103	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide (G_CC-103)	E-16	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-acetic acid (E-16)	F-13	2-(1-Pyridin-4-yl-piperidin-4-yl)-ethyl-amine dihydrochloride (F-13)
G_CC-106	7-Chloro-2-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-7-yl]-2,3-dihydro-isoindol-1-one (G_CC-106)	E-17	3-[7-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-propionic acid (E-17)	F-14	3-Pyridin-4-yl-3,9-diazaspiro[5.5]undecane dihydrochloride (F-14)
G_CC-108	N-[[1-[2-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetyl]-4-(4-methyl-piperazin-1-yl)-piperidin-4-yl]-methyl]-pyridine-4-carboxylic acid amide (G_CC-108)	E-03	2-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-03)	F-34	N-[[4-(4-Methyl-piperazin-1-yl)-piperidin-4-yl]-methyl]-pyridine-4-carboxylic acid amide dihydrochloride (F-34)
G_CC-111	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[(1-pyridin-4-yl-piperidin-4-yl)-methyl]-acetamide (G_CC-111)	E-16	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-acetic acid (E-16)	F-15	(1-Pyridin-4-yl-piperidin-4-yl)-methyl-amine dihydrochloride (F-15)
G_CC-113	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-[4-(3-fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-N-methyl-acetamide (G_CC-113)	E-16	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-acetic acid (E-16)	F-47	2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl-methyl-amine tetrahydrochloride (F-47)
G_CC-116	3-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-propionamide (G_CC-116)	E-05	3-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionic acid (E-05)	F-48	Methyl-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-amine trihydrochloride (F-48)
G_CC-117	N-[2-(4-Dimethylamino-4-phenyl-cyclohexyl)-ethyl]-3-[6-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide (G_CC-117)	E-05	3-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionic acid (E-05)	F-45	Dimethyl-[4-(2-methylamino-ethyl)-1-phenyl-cyclohexyl]-amine dihydrochloride (F-45)
G_CC-119	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-propionamide (G_CC-119)	E-15	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-propionic acid (E-15)	F-48	Methyl-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-amine trihydrochloride (F-48)
G_CC-120	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G_CC-120)	E-03	2-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-03)	F-05	4-(2-Pyrrolidin-1-yl-ethyl)-piperidine (F-05)

GRA3454-WO
22nd December 2009

G_CC-123	3-[7-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[(1-pyridin-4-yl-piperidin-4-yl)-methyl]-propionamide (G_CC-123)	E-17	3-[7-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-propionic acid (E-17)	F-15	(1-Pyridin-4-yl-piperidin-4-yl)-methyl-amine dihydrochloride (F-15)
G_CC-127	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-phenyl-cyclohexyl)-ethyl]-N-methyl-propionamide (G_CC-127)	E-15	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-propionic acid (E-15)	F-45	Dimethyl-[4-(2-methylamino-ethyl)-1-phenyl-cyclohexyl]-amine dihydrochloride (F-45)
G_CC-128	7-Chloro-2-[1-[2-[4-(3-fluoro-phenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one (G_CC-128)	E-16	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-acetic acid (E-16)	F-46	1-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-4-methyl-piperazine dihydrochloride (F-46)
G_CC-138	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-acetamide (G_CC-138)	E-16	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-acetic acid (E-16)	F-48	Methyl-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-amine trihydrochloride (F-48)
G_CC-139	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(pyridine-3-carbonyl)-piperazin-1-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-139)	E-02	2-[7-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetic acid (E-02)	F-37	Piperazin-1-yl-pyridin-3-yl-methanone (F-37)

GRA3454-WO
22nd December 2009

Pharmacological data

The pharmacological data was determined as described above. The following data is provided in the table below by way of example:

Compound	B1R antagonism, rat [10 μ M] % inhibition	B1R antagonism, human [10 μ M] % inhibition
G-01	78	98
G-02	100	95
G-03	90	
G-04	62	68
G-05	96	100
G-06	70	83
G-07	100	96
G-08	97	98
G-10	76	100
G-11	-21	46
G-12	92	98
G-13	96	73
G-14	96	99
G-15	54	81
G-16	96	100
G-17	95	100
G-18	99	99
G-19	94	97
G-20	13	43
G-21	43	99

GRA3454-WO
22nd December 2009

G-22	99	100
G-23	106	100
G-24	103	98
G-26	102	98
G-27	99	96
G-31	54	80
G-33	46	93
G_CC-1	62	
G_CC-2	70	46
G_CC-3	82	
G_CC-4	99	
G_CC-5	59	
G_CC-6	73	
G_CC-7	100	
G_CC-8	100	26
G_CC-9	65	
G_CC-10	69	
G_CC-11	87	
G_CC-12	58	
G_CC-13	58	
G_CC-14	86	
G_CC-15	65	
G_CC-16	67	
G_CC-17	52	

GRA3454-WO
22nd December 2009

G_CC-18	87	
G_CC-19	68	
G_CC-20	86	
G_CC-21	97	
G_CC-22	59	
G_CC-23	63	
G_CC-24	89	
G_CC-25	58	
G_CC-26	81	
G_CC-27	56	
G_CC-28	82	
G_CC-29	92	
G_CC-30	53	
G_CC-31	91	
G_CC-32	101	73
G_CC-33	71	
G_CC-34	58	
G_CC-35	72	
G_CC-36	63	
G_CC-37	91	
G_CC-38	96	
G_CC-39	95	
G_CC-40	86	
G_CC-41	76	

GRA3454-WO
22nd December 2009

G_CC-42	66	
G_CC-43	103	100
G_CC-44	73	
G_CC-45	59	
G_CC-46	94	
G_CC-47	102	100
G_CC-48	59	
G_CC-49	92	
G_CC-50	62	
G_CC-51	93	
G_CC-52	100	
G_CC-53	101	
G_CC-54	96	99
G_CC-56	54	
G_CC-57	100	
G_CC-59	87	
G_CC-60	87	
G_CC-61	79	
G_CC-62	99	94
G_CC-63	100	
G_CC-64	89	
G_CC-65	53	
G_CC-66	52	
G_CC-67	95	99

GRA3454-WO
22nd December 2009

G_CC-68	69	
G_CC-69	65	
G_CC-70	100	
G_CC-71	54	
G_CC-72	71	
G_CC-73	55	
G_CC-74	51	
G_CC-76	104	92
G_CC-77	104	
G_CC-81	103	
G_CC-84	102	
G_CC-88	101	100
G_CC-91	100	100
G_CC-92	98	
G_CC-95	96	
G_CC-99	93	
G_CC-102	89	
G_CC-103	88	
G_CC-106	86	
G_CC-108	84	
G_CC-111	81	
G_CC-113	78	
G_CC-116	74	
G_CC-117	74	

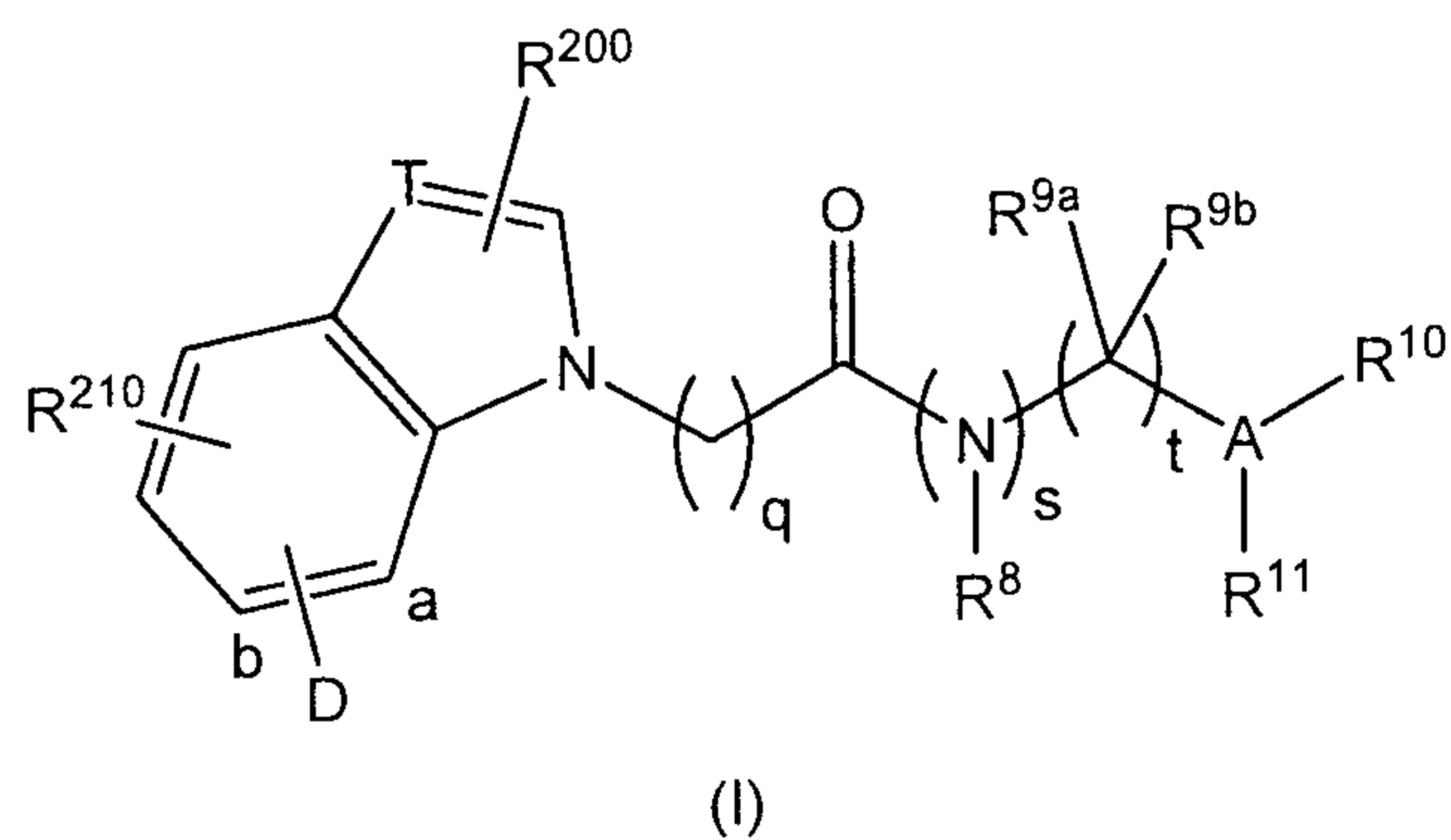
GRA3454-WO
22nd December 2009

G_CC-119	72	
G_CC-120	72	
G_CC-123	67	
G_CC-127	63	
G_CC-128	61	
G_CC-138	52	
G_CC-139	50	

GRA3454-WO
22nd December 2009

Claims

1. Substituted indole compound having the general formula (I),



wherein

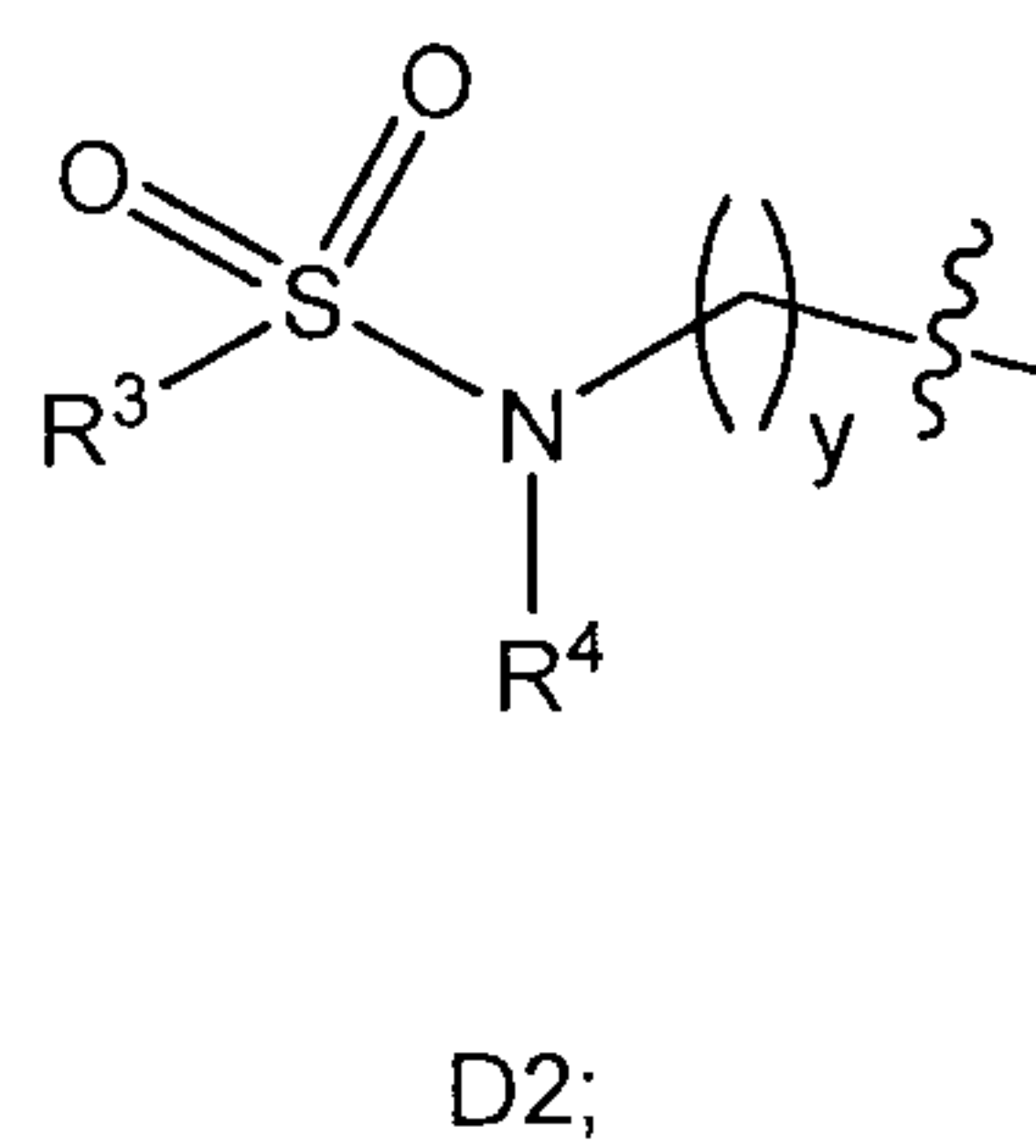
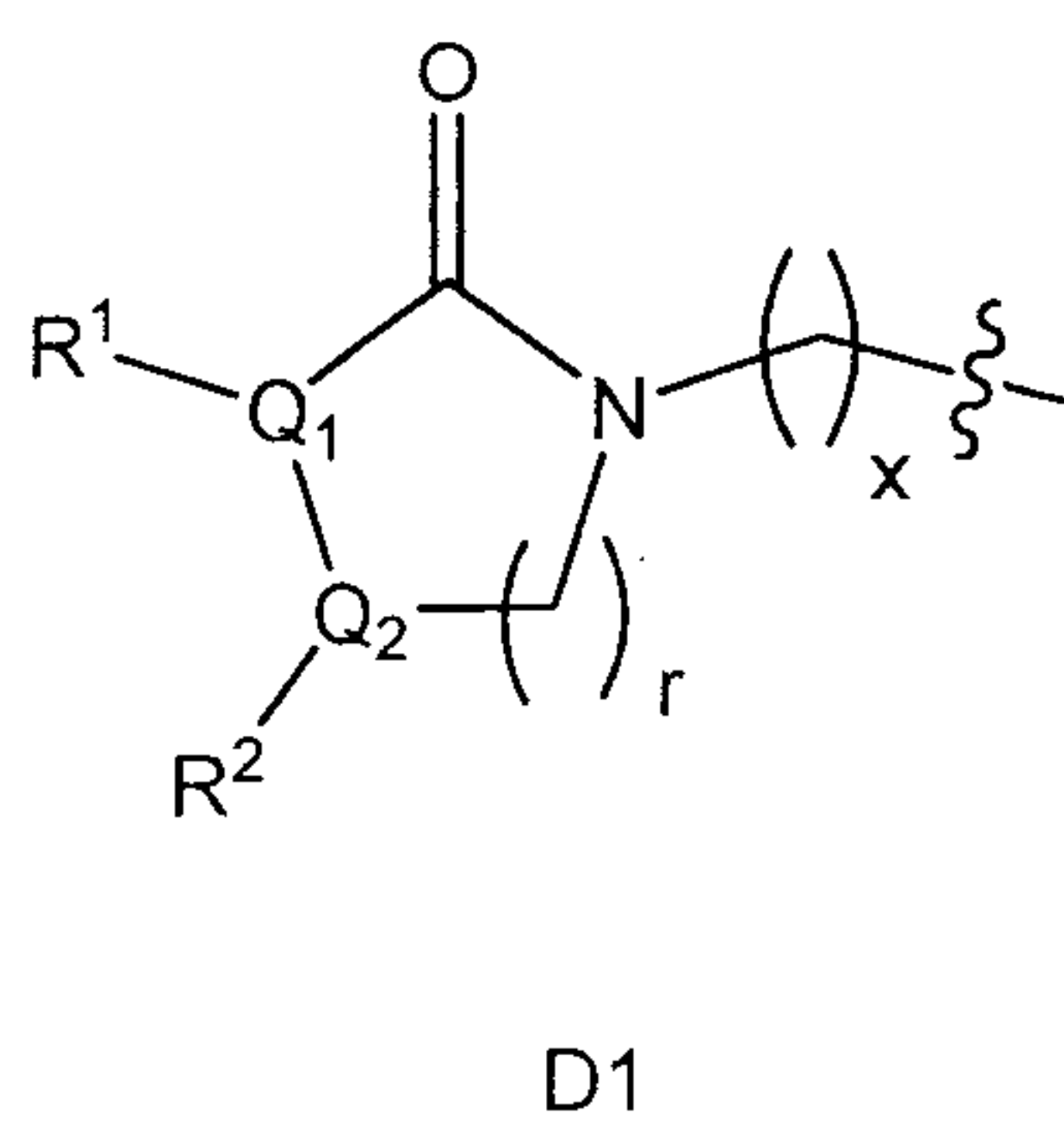
T stands for CH or N;

 $q = 1, 2 \text{ or } 3;$

$s = 0$ or 1 ;

 $t = 0, 1, 2 \text{ or } 3;$

D in position a or b is bound to the indole skeleton and stands for one of the following radicals D1 or D2



GRA3454-WO
22nd December 2009

x and y, mutually independently, stand for 0 or 1;

r stands for 1, 2 or 3;

Q₁ and Q₂ mutually independently stand for C, CH or N;

R¹ and R² together with the -Q₁-Q₂- group linking them form a cyclic compound which can be substituted at one or more of its carbon ring members with one or more radicals mutually independently selected from the group consisting of F, Cl, Br, I, CF₃, C₁₋₆ alkyl, O-C₁₋₆ alkyl, OH, OCF₃, SH, SCF₃, aryl and heteroaryl and/or anellated with at least one aryl or heteroaryl, wherein the cyclic compound is saturated, mono- or polyunsaturated or aromatic, is 4-, 5-, 6- or 7-membered and can optionally contain one or more heteroatoms or heteroatom groups mutually independently selected from the group consisting of N, NR⁵⁰, O, S, S=O and S(=O)₂; wherein the radical R⁵⁰ denotes H, C₁₋₆ alkyl, -C(=O)-R⁵¹, C₃₋₈ cycloalkyl, aryl or heteroaryl or a C₃₋₈ cycloalkyl, aryl or heteroaryl bound by a C₁₋₃ alkylene group, and R⁵¹ denotes C₁₋₆ alkyl, C₃₋₈ cycloalkyl, aryl, heteroaryl or a C₃₋₈ cycloalkyl, aryl or heteroaryl bound by a C₁₋₃ alkylene group;

R³ stands for aryl, heteroaryl or an aryl or heteroaryl bound by a C₁₋₃ alkylene group, wherein aryl and heteroaryl can each be anellated with a 4-, 5-, 6- or 7-membered cyclic compound, wherein the cyclic compound is in each case saturated or mono- or polyunsaturated but is not aromatic and can be substituted at one or more of its carbon ring members with one or more radicals mutually independently selected from the group consisting of F, Cl, Br, I, -CF₃, -O-CF₃, C₁₋₆ alkyl and O-C₁₋₆ alkyl and can optionally contain one or more heteroatoms or heteroatom groups mutually independently selected from the group consisting of N, NR^{50a}, O, S, S=O and S(=O)₂, wherein R^{50a} denotes H, C₁₋₆ alkyl, -C(=O)-R^{51a}, C₃₋₈ cycloalkyl, aryl, heteroaryl or a C₃₋₈ cycloalkyl, aryl or heteroaryl bound by a C₁₋₃ alkylene group and R^{51a} denotes C₁₋₆ alkyl, C₃₋₈ cycloalkyl, aryl, heteroaryl or a C₃₋₈ cycloalkyl, aryl or heteroaryl bound by a C₁₋₃ alkylene group;

R⁴ stands for H, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, aryl or heteroaryl or for a C₃₋₈ cycloalkyl, aryl or heteroaryl bound by a C₁₋₆ alkylene group;

GRA3454-WO
22nd December 2009

R^{200} stands for 0 to 2 substituents, which are mutually independently selected from the group consisting of F, Cl, Br, I, CF_3 , OCF_3 , OH, O- C_{1-6} alkyl, C_{1-6} alkyl, aryl and heteroaryl and/or two adjacent substituents R^{200} form an anellated aryl or heteroaryl;

R^{210} stands for 0 to 3 substituents which are mutually independently selected from the group consisting of F, Cl, Br, I, CF_3 , OCF_3 , OH, O- C_{1-6} alkyl, C_{1-6} alkyl, aryl and heteroaryl;

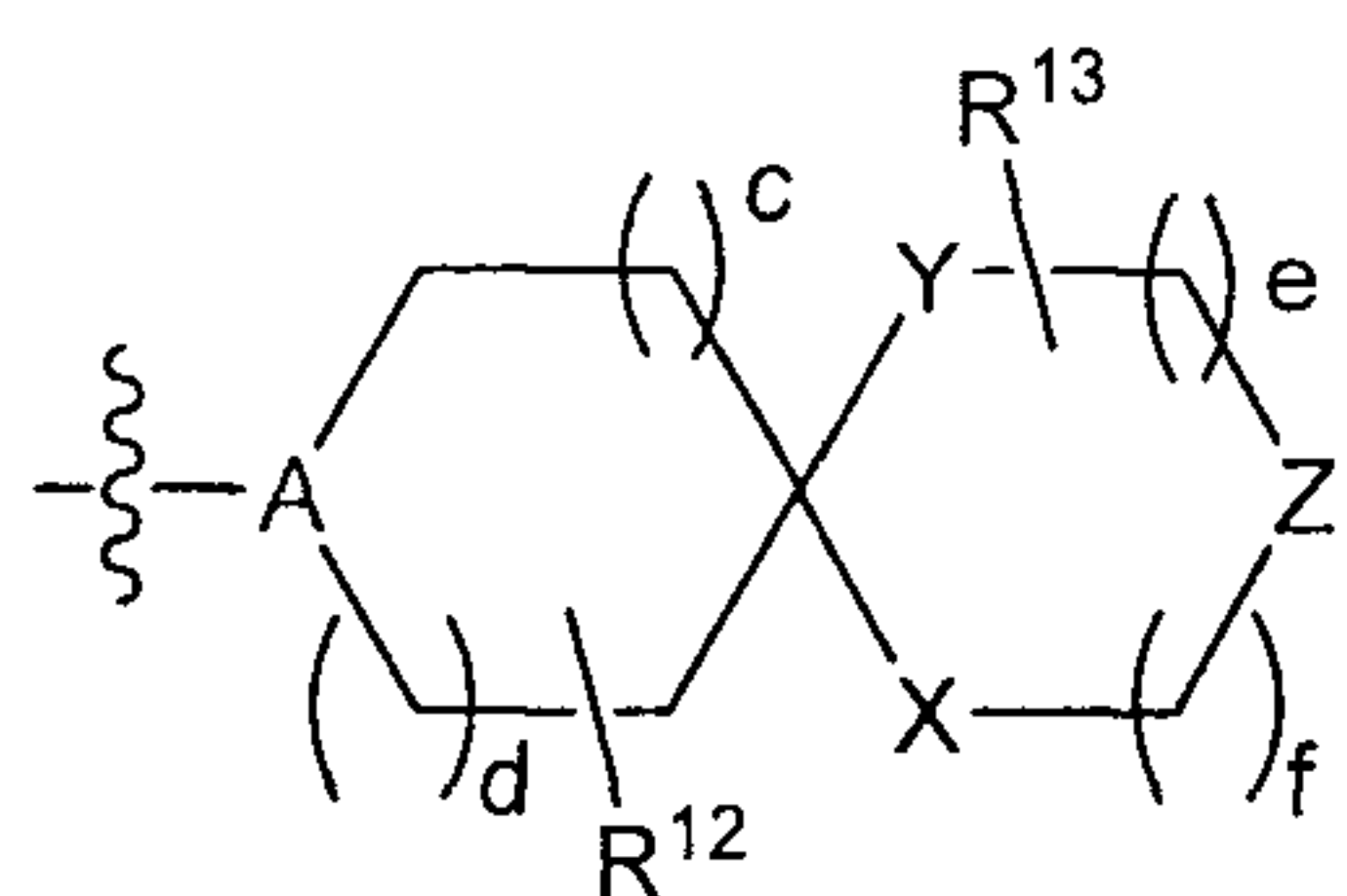
R^8 stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or for a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

R^{9a} and R^{9b} mutually independently denote H, F, Cl, OH, C_{1-6} alkyl, O- C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

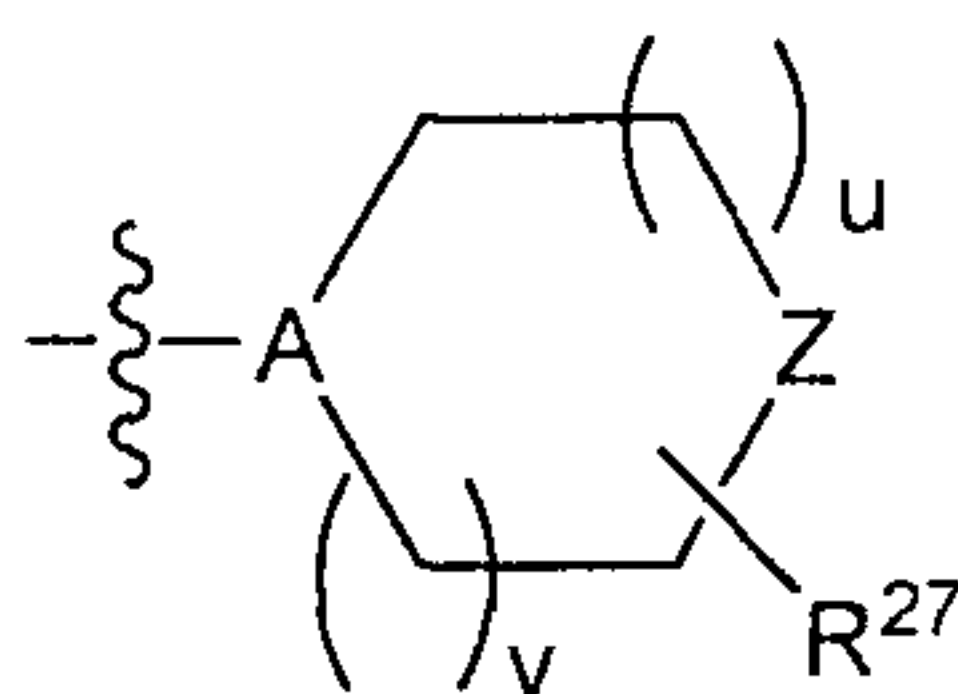
A stands for N or CH;

with the proviso that if s stands for 1 and t stands for 0 then A stands for CH; and
with the proviso that if s and t each stand for 0 then A stands for N;

the radicals R^{10} and R^{11} with inclusion of A represent a spirocyclic or cyclic group according to one of the general formulae (II) or (III),



(II)



(III)

wherein

c, d, e, f, u and v mutually independently denote 0, 1 or 2;

GRA3454-WO
22nd December 2009

R^{12} , R^{13} and R^{27} mutually independently stand for 0 to 4 substituents which are mutually independently selected from the group consisting of F, Cl, OH, =O, C_{1-6} alkyl, O- C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl and C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

and/or two of the 0 to 4 substituents R^{27} together represent a C_{1-3} alkylene bridge such that the cyclic compound represented in the general formula (III) assumes a bicyclically bridged form;

and/or two adjacent substituents out of the 0 to 4 substituents R^{13} form an anellated aryl or heteroaryl;

and/or two adjacent substituents out of the 0 to 4 substituents R^{27} form an anellated aryl or heteroaryl;

X stands for $CR^{14a}R^{14b}$, NR^{15} or O;

Y stands for $CR^{16a}R^{16b}$, NR^{17} or O;

with the proviso that X does not denote NR^{15} if Y denotes NR^{17} ; and

with the proviso that X and Y do not simultaneously denote O;

wherein

R^{14a} , R^{14b} , R^{16a} and R^{16b} mutually independently denote H, F, Cl, OH, C_{1-6} alkyl, O- C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or stand for a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group,

and/or R^{14a} and R^{14b} can together stand for =O and/or R^{16a} and R^{16b} can together stand for =O;

GRA3454-WO
22nd December 2009

R^{15} and R^{17} mutually independently stand for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denote a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

Z in the general formula (II) stands for $CR^{18a}R^{18b}$, NR^{19} or O;

or

Z in the general formula (II), if X stands for O and f stands for 0, denotes $-(C(R^{124})-C(R^{125}))-$, wherein

R^{124} and R^{125} together with the carbon atoms linking them form a fused aryl or heteroaryl; or

Z in the general formula (II), if X stands for O and f stands for 0, denotes $=(N(CR^{126}))-$, wherein the N atom is singly bound to the O atom, and

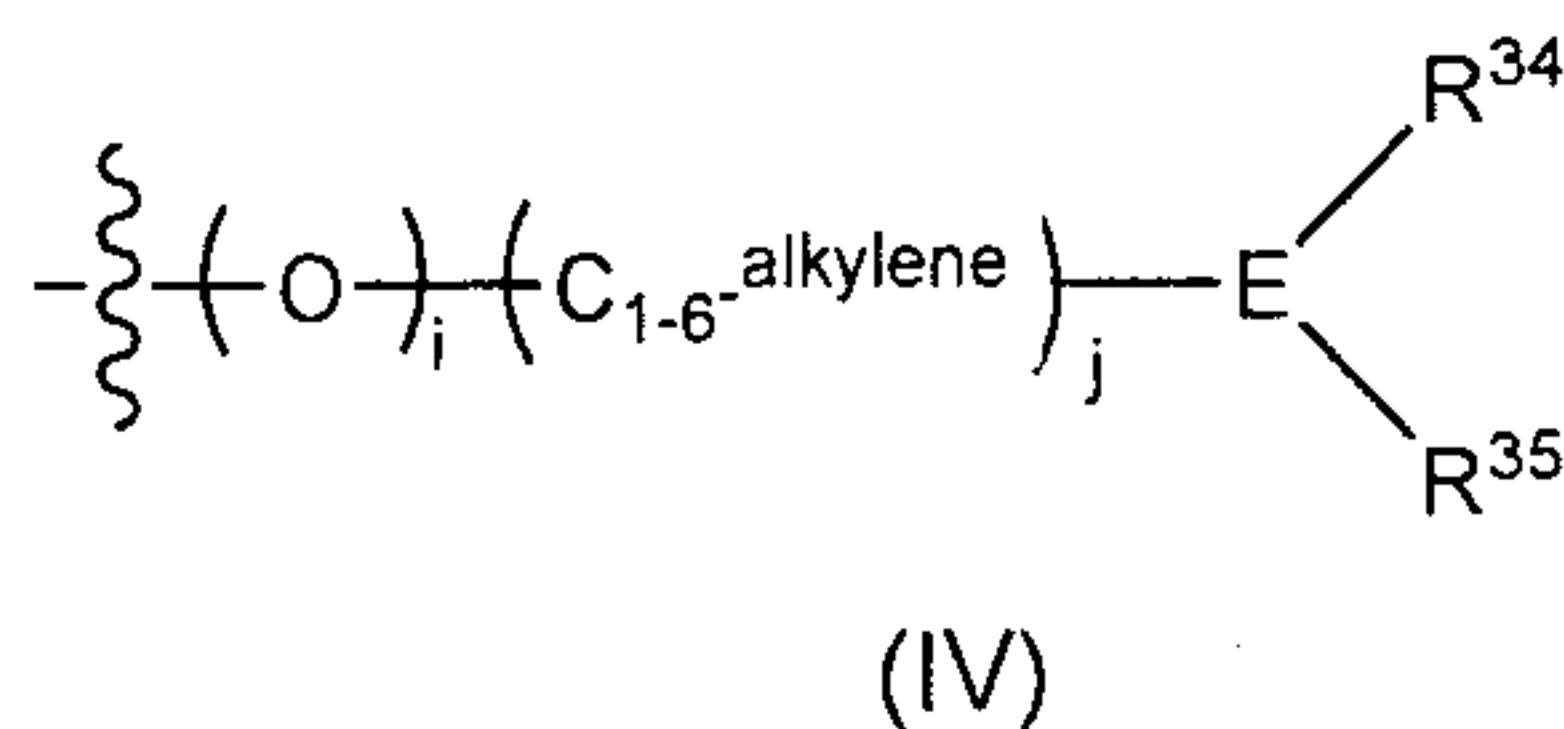
R^{126} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

Z in the general formula (III) stands for $CR^{18a}R^{18b}$, NR^{19} , O, S, $S(=O)$ or $S(=O)_2$;

wherein

R^{18a} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group,

or R^{18a} stands for a group according to the general formula (IV),



GRA3454-WO
22nd December 2009

wherein

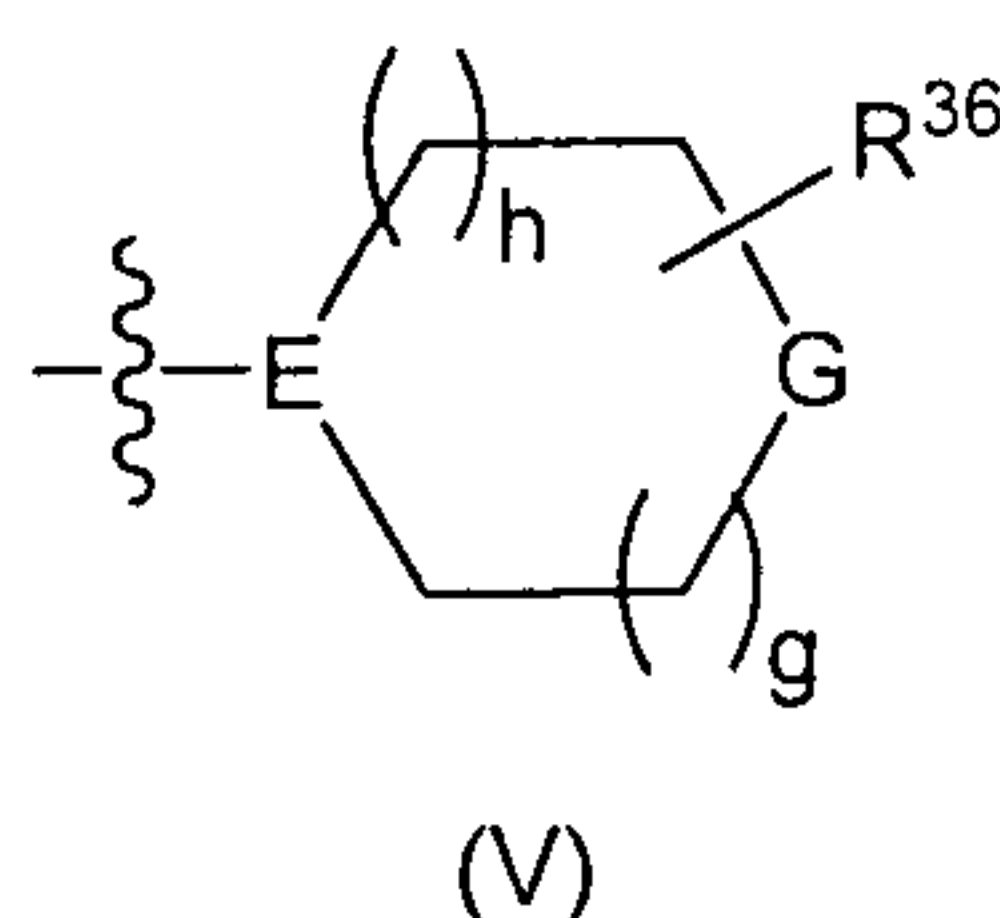
i and j mutually independently stand for 0 or 1;

E stands for N or CH, with the proviso that if i stands for 1 and j stands for 0 then E stands for CH,

R^{34} and R^{35} mutually independently denote H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or an aryl, heteroaryl or C_{3-8} cycloalkyl bound by a C_{1-3} alkylene group;

or R^{34} and R^{35} with inclusion of E form a 5- or 6-membered aryl or heteroaryl;

or R^{34} and R^{35} with inclusion of E form a saturated heterocyclic compound according to the general formula (V),



wherein

h and g mutually independently denote 0, 1 or 2;

G stands for $CR^{37a}R^{37b}$, NR^{38} , O, S, S=O or S(=O)₂, with the proviso that if E stands for CH then G does not stand for $CR^{37a}R^{37b}$;

R^{36} stands for 0 to 4 substituents which are mutually independently selected from the group consisting of F, Cl, Br, I, OH, SH, =O, O- C_{1-6} alkyl, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl and C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

and/or two adjacent substituents R^{36} together represent an anellated aryl or heteroaryl;

GRA3454-WO

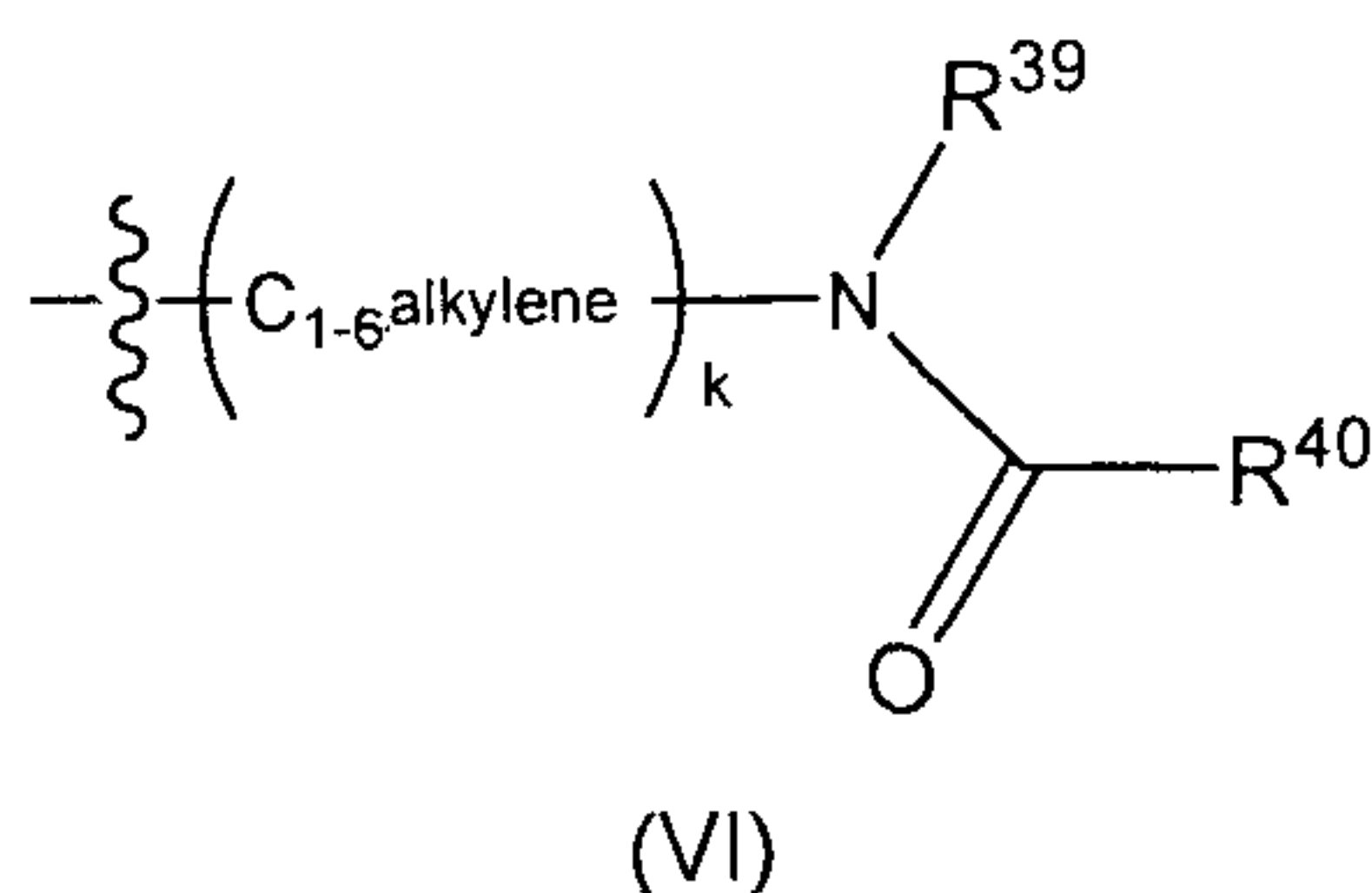
22nd December 2009

R^{37a} and R^{37b} mutually independently denote H, F, Cl, Br, I, OH, SH, =O, O- C_{1-6} alkyl, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or stand for a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

R^{38} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes an aryl, heteroaryl or C_{3-8} cycloalkyl bound by a C_{1-3} alkylene group;

R^{18b} stands for H, OH, C_{1-6} alkyl, C_{3-8} cycloalkyl, O- C_{1-6} alkyl, O-(C_{3-8} cycloalkyl), (C_{1-6} alkylene)-O- C_{1-6} alkyl, (C_{1-6} alkylene)-O-(C_{3-8} cycloalkyl), aryl, heteroaryl, O-aryl or O-heteroaryl or denotes an aryl, O-aryl, heteroaryl or O-heteroaryl bound by a C_{1-6} alkylene group;

or R^{18b} stands for a group according to the general formula (VI),



wherein

k stands for 0 or 1;

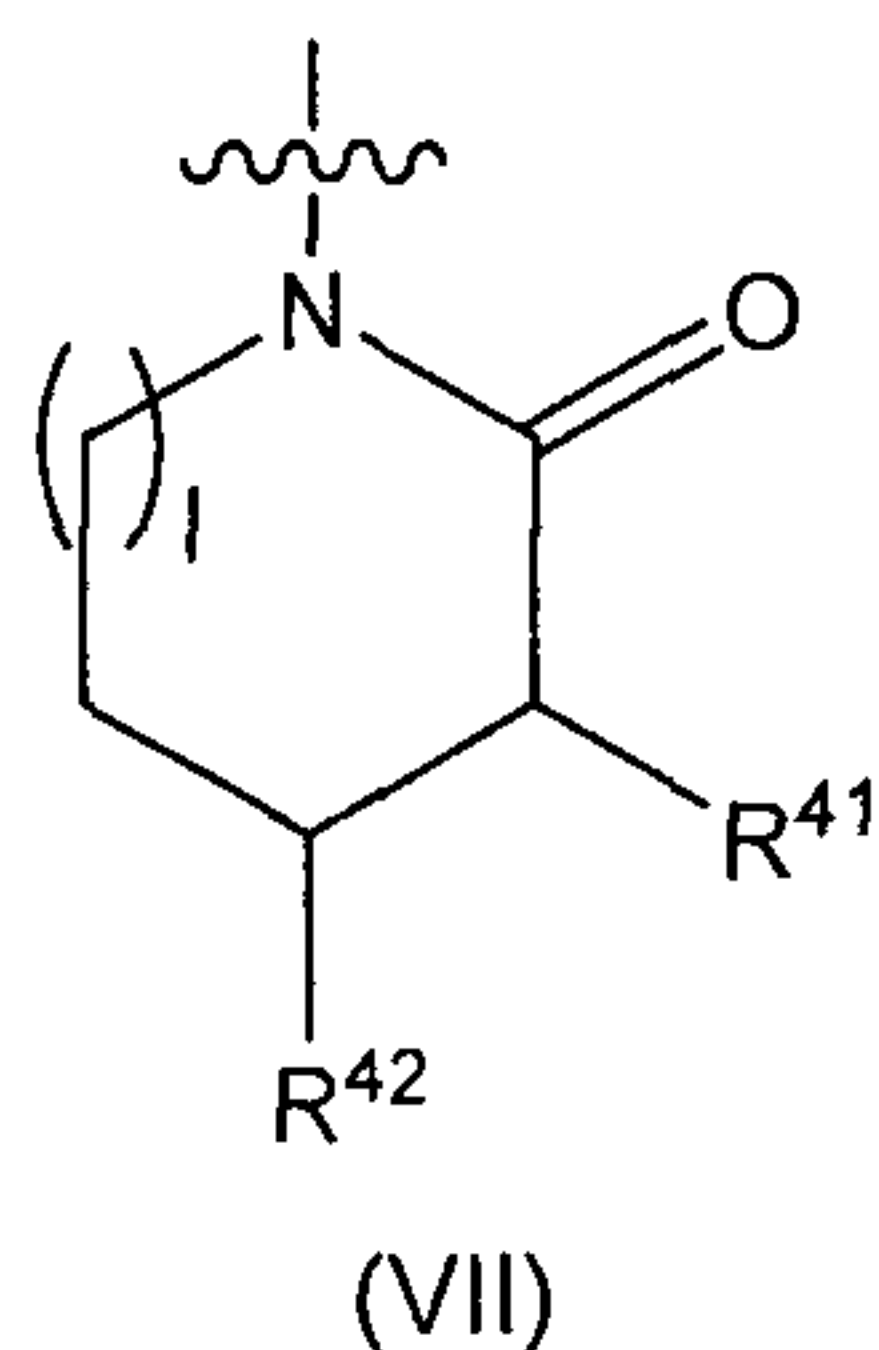
R^{39} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-3} alkylene group;

R^{40} stands for C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes a C_{3-8} cycloalkyl, aryl or heteroaryl bound by a C_{1-6} alkylene group;

or

R^{39} and R^{40} together with the N-C(=O) group linking them form a ring according to the general formula (VII),

GRA3454-WO
22nd December 2009



wherein

I stands for 0, 1 or 2;

and R^{41} and R^{42} together with the carbon atoms linking them form an anellated aryl or heteroaryl;

R^{19} stands for H; or $(P)_z-R^{22}$,

wherein

z stands for 0 or 1;

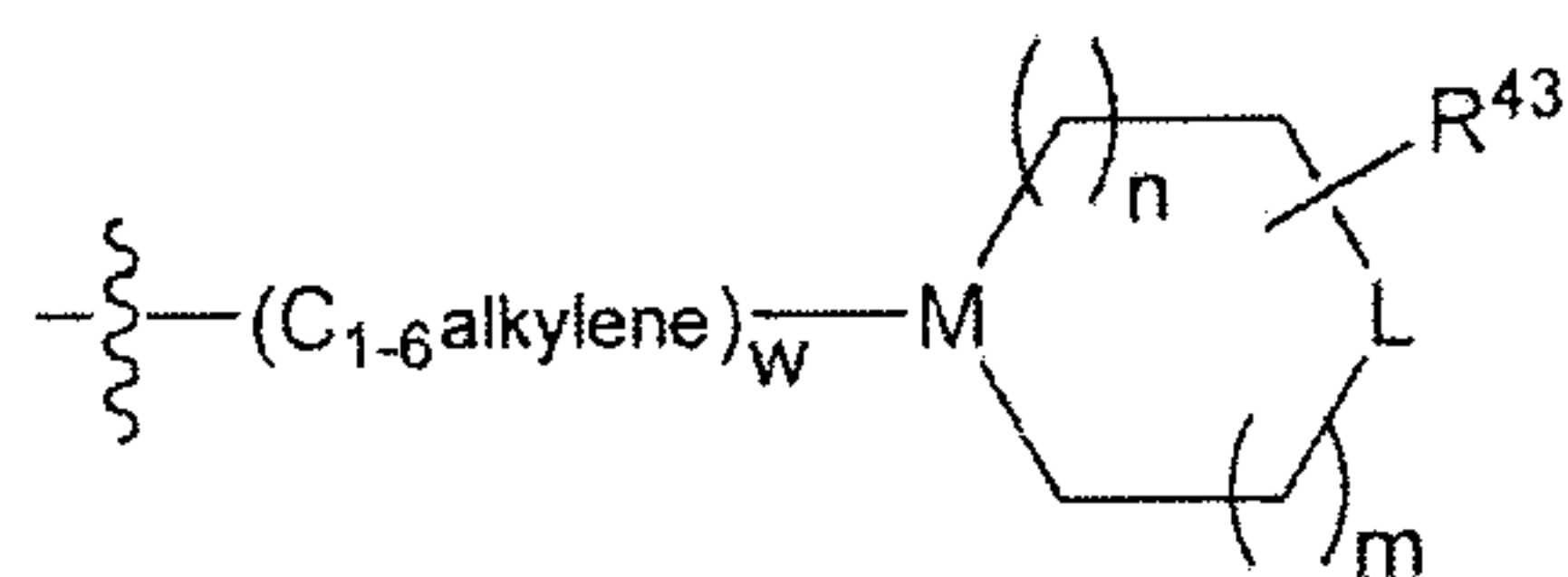
P stands for $(C=O)$, $S(=O)_2$ or $C(=O)-N(R^{24})$, wherein the N atom in the $C(=O)-N(R^{24})$ group is linked to R^{22} , wherein

R^{24} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl or for an aryl, heteroaryl or C_{3-8} cycloalkyl bound by a C_{1-3} alkylene group;

R^{22} stands for C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes an aryl or heteroaryl bound by a C_{1-6} alkylene group; or

R^{22} stands for a group according to the general formula (VIII), wherein

GRA3454-WO
22nd December 2009



(VIII)

n stands for 0, 1 or 2;

m stands for 0, 1 or 2;

w stands for 0 or 1,

M stands for CH or N;

with the proviso that if P stands for C(=O)-NR²⁴ and w stands for 0 then M stands for CH; and

with the proviso that if z and w simultaneously stand for 0 then M stands for CH;

L stands for CR^{44a}R^{44b}, NR⁴⁵, O, S, S=O or S(=O)₂;

R⁴³ stands for 0 to 4 substituents which are mutually independently selected from the group consisting of F, Cl, OH, =O, C₁₋₆ alkyl, O-C₁₋₆ alkyl, C₃₋₈ cycloalkyl, aryl, heteroaryl and C₃₋₈ cycloalkyl, aryl or heteroaryl bound by a C₁₋₆ alkylene group;

and/or two adjacent radicals out of the 0 to 4 radicals R⁴³ together represent an annellated aryl or heteroaryl;

R^{44a} and R^{44b} mutually independently stand for H, F, Cl, Br, I, OH, C₁₋₆ alkyl, O-C₁₋₆ alkyl, C₃₋₈ cycloalkyl, aryl or heteroaryl or denote a C₃₋₈ cycloalkyl, aryl or heteroaryl bound by a C₁₋₆ alkylene group;

or R^{44a} and R^{44b} can together stand for =O;

GRA3454-WO
22nd December 2009

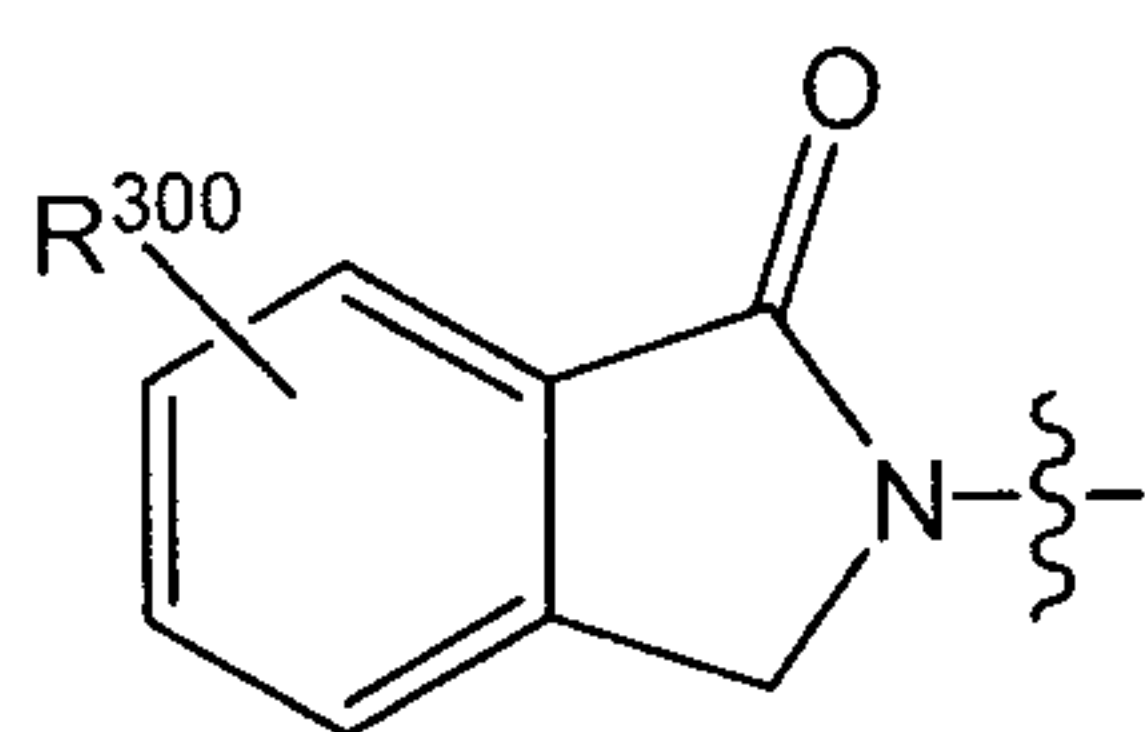
R^{45} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or heteroaryl or denotes an aryl, heteroaryl or C_{3-8} cycloalkyl bound by a C_{1-3} alkylene group;

wherein the aforementioned radicals C_{1-6} alkyl, C_{1-3} alkylene, C_{1-6} alkylene, C_{3-8} cycloalkyl, aryl and heteroaryl can each be unsubstituted or mono- or polysubstituted with identical or different radicals and the aforementioned radicals C_{1-6} alkyl, C_{1-3} alkylene and C_{1-6} alkylene can each be branched or unbranched;

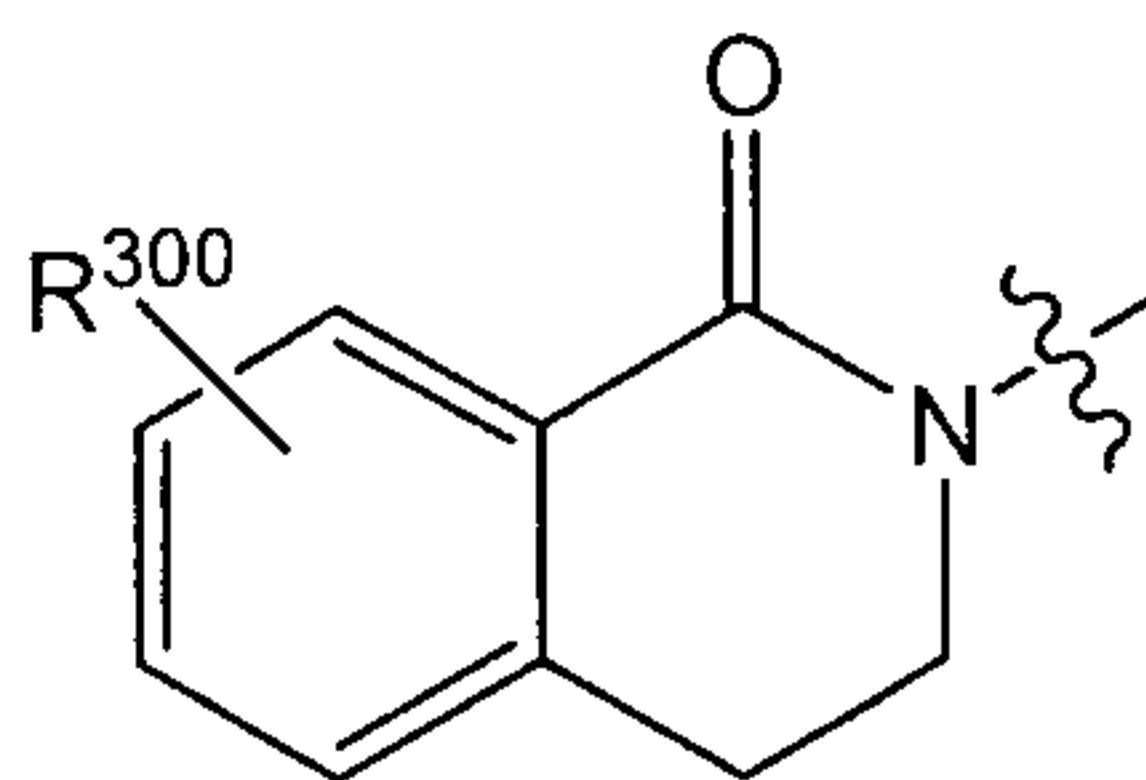
optionally in the form of a single enantiomer or a single diastereomer, the racemate, the enantiomers, the diastereomers, mixtures of enantiomers and/or diastereomers, and each in the form of their bases and/or physiologically compatible salts.

GRA3454-WO
22nd December 2009

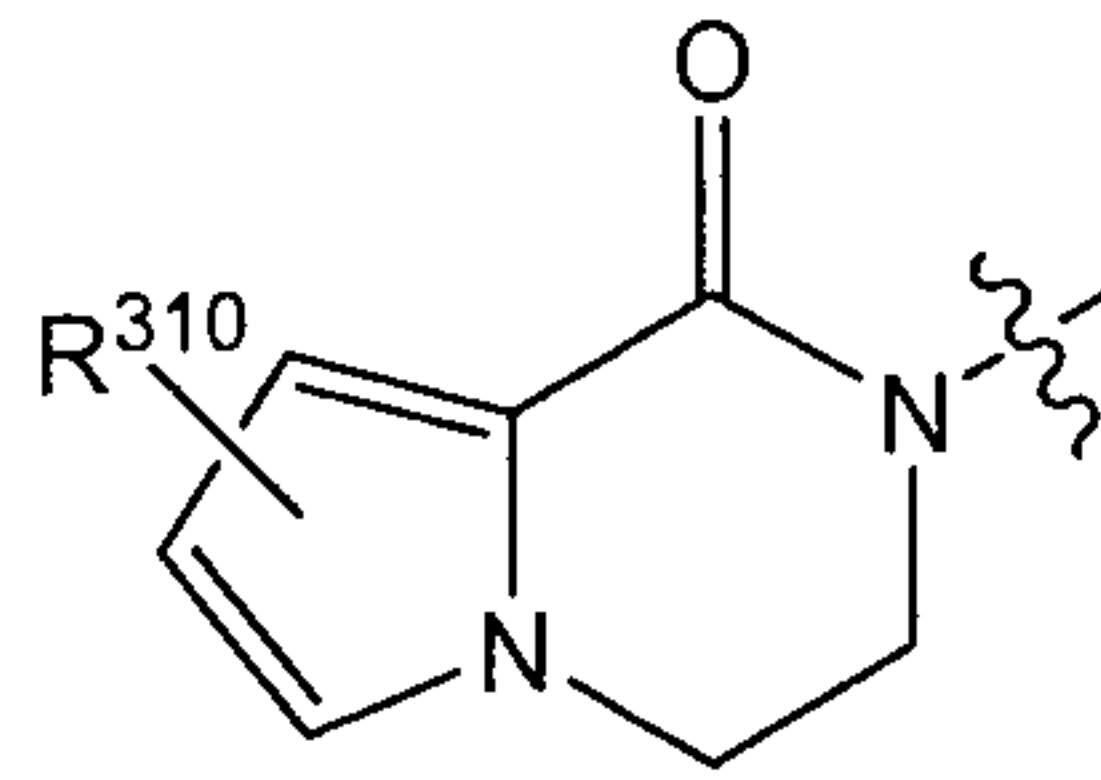
2. Substituted compound according to claim 1, wherein D1 stands for a radical which is selected from the group consisting of



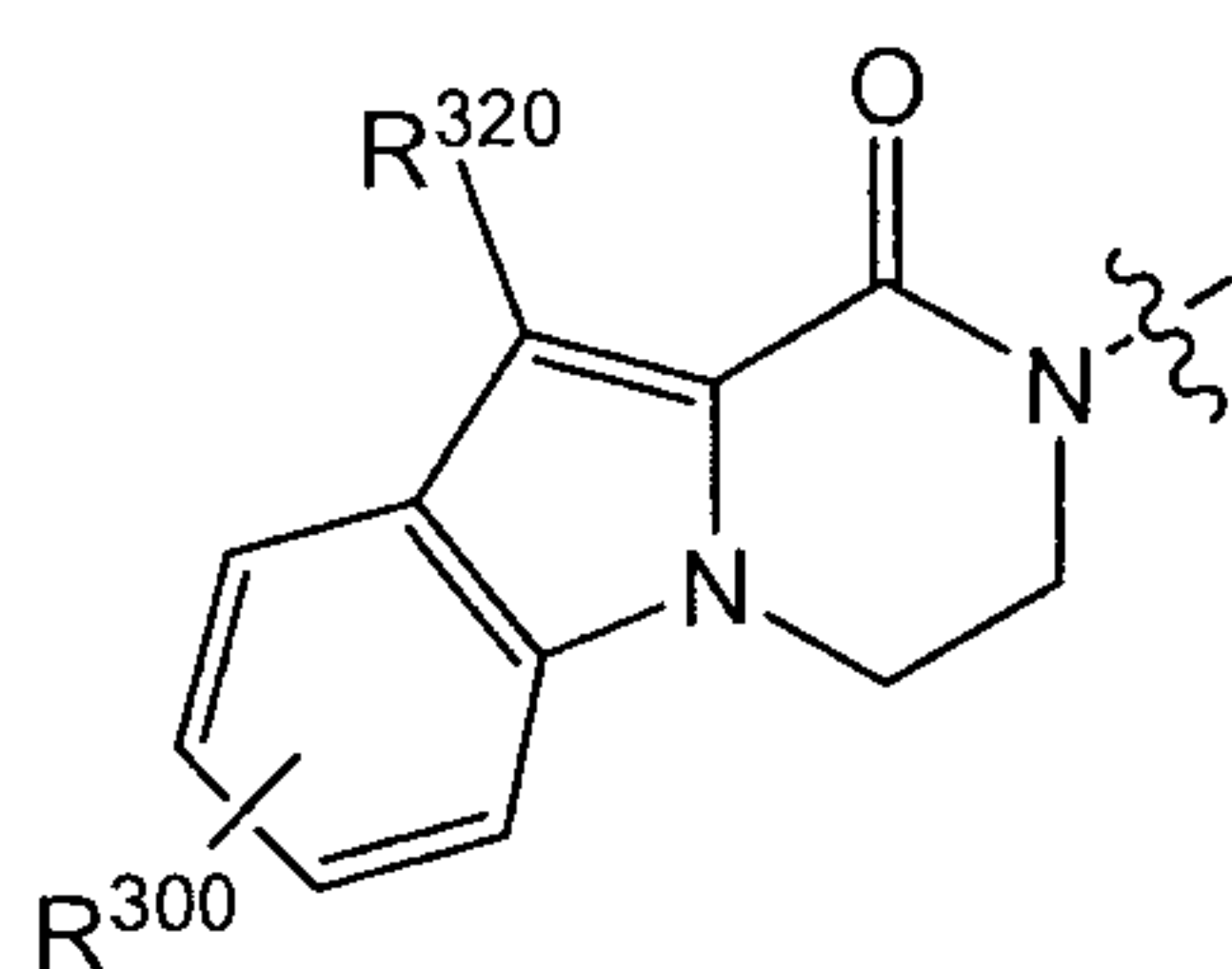
D1a



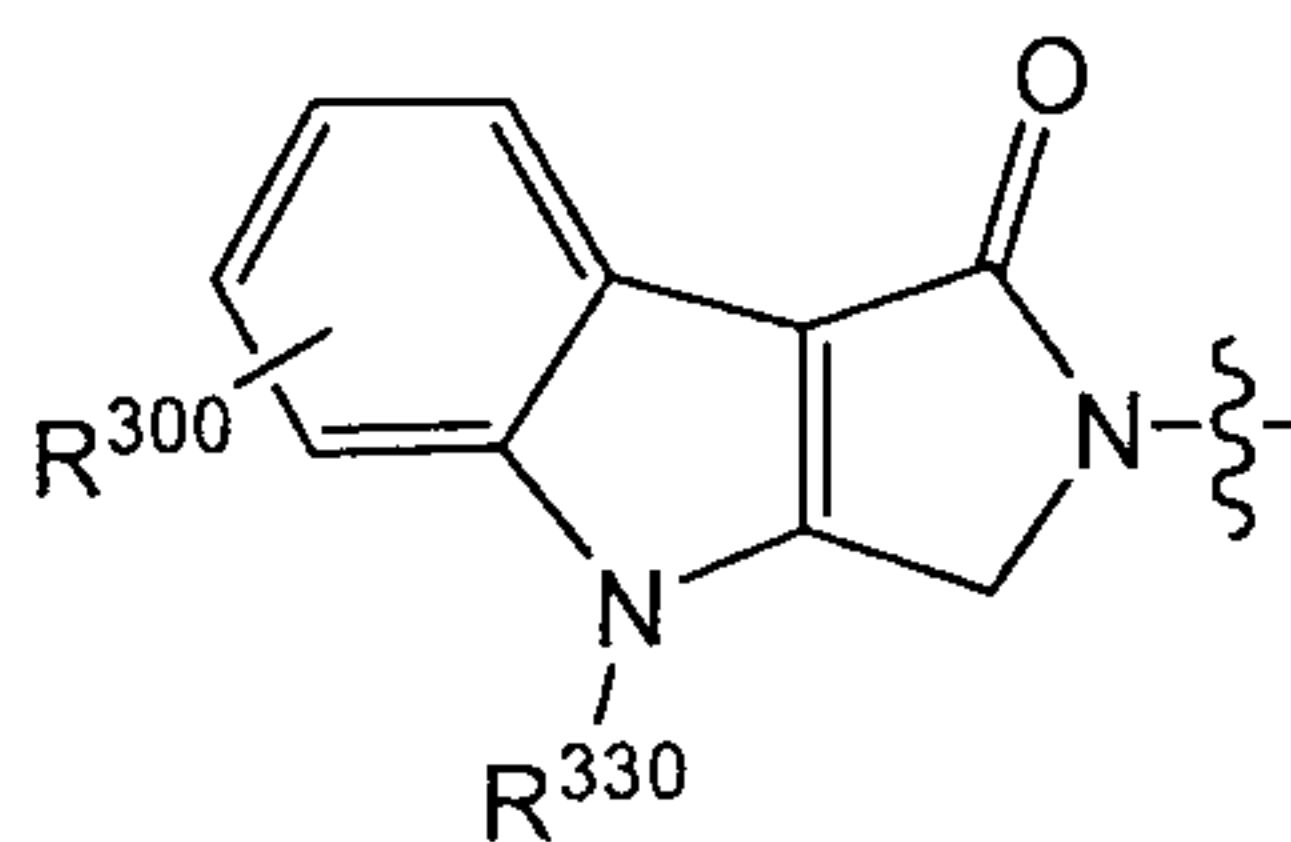
D1b



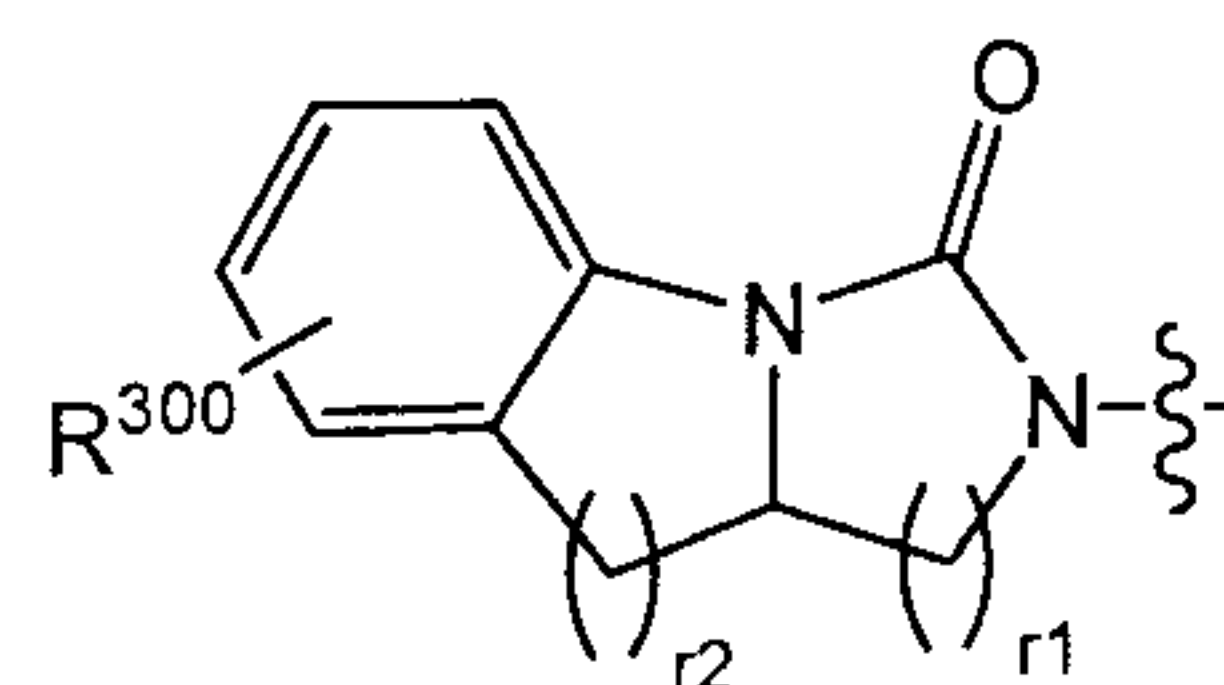
D1c



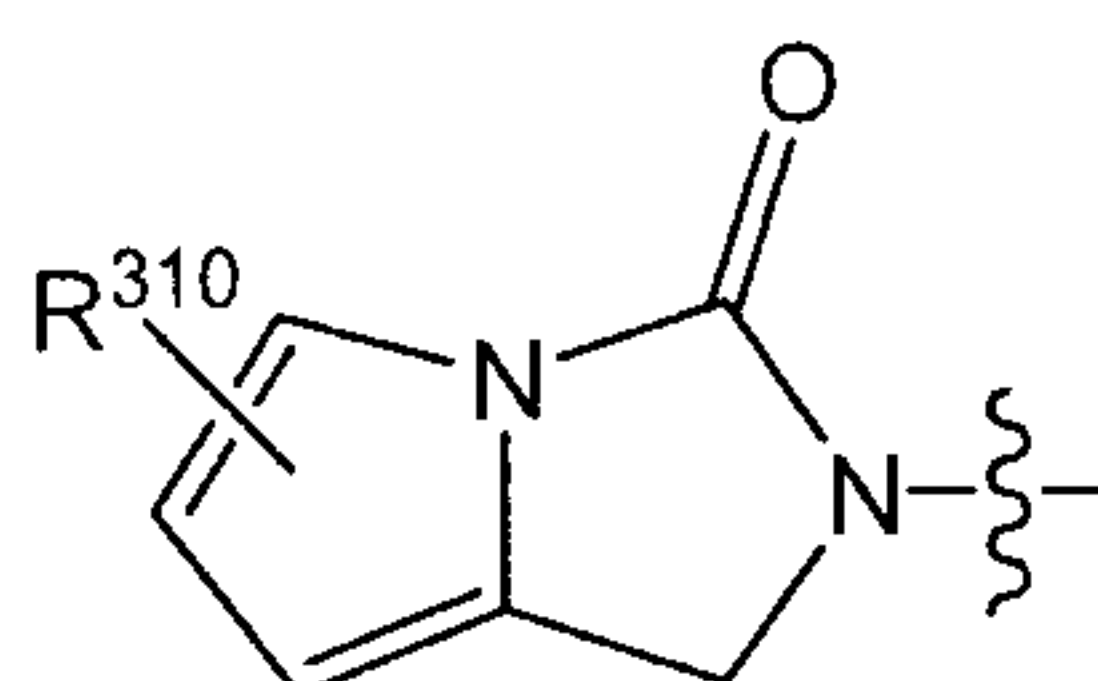
D1d



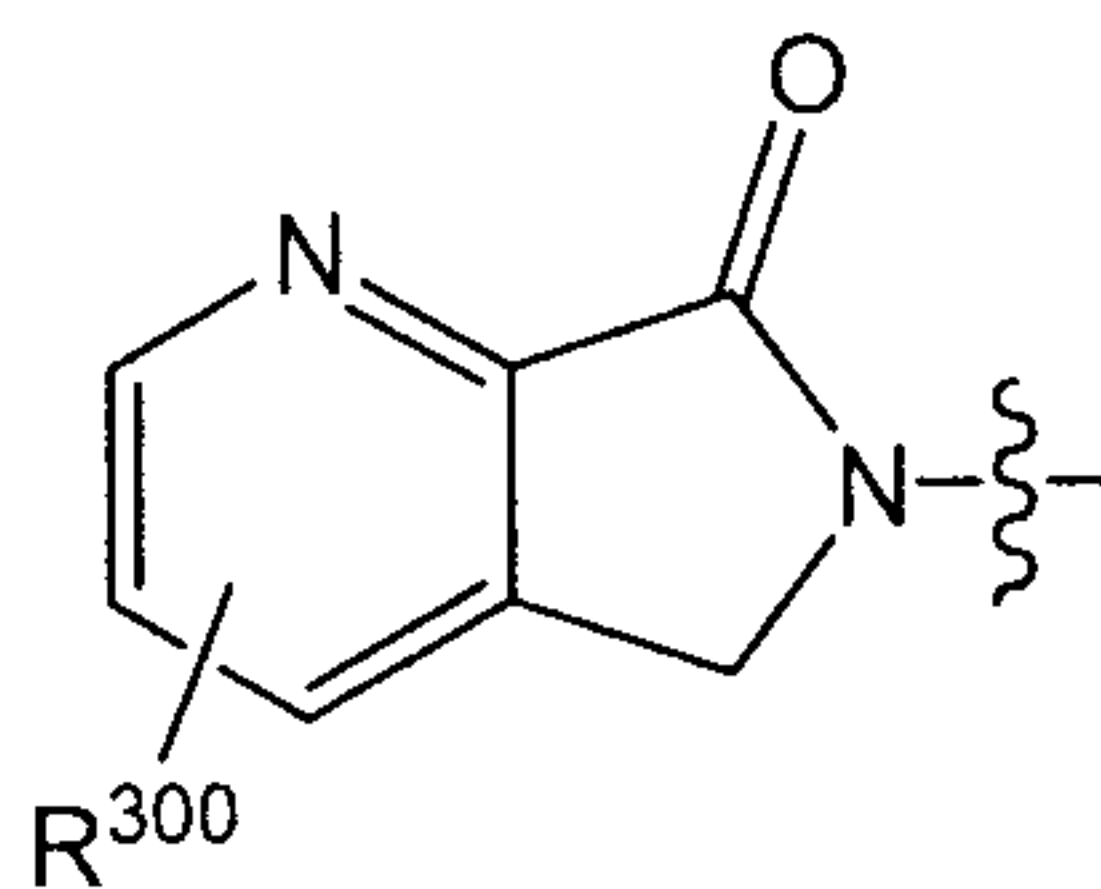
D1e



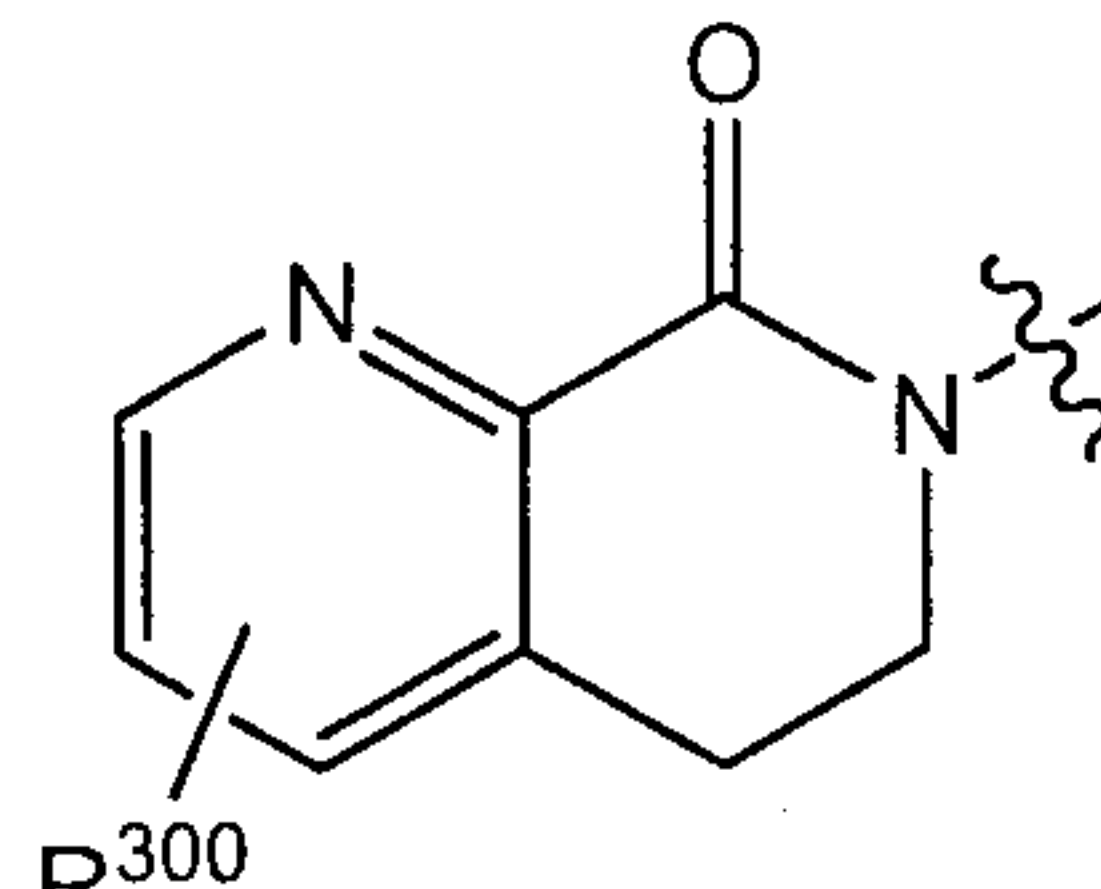
D1f



D1g

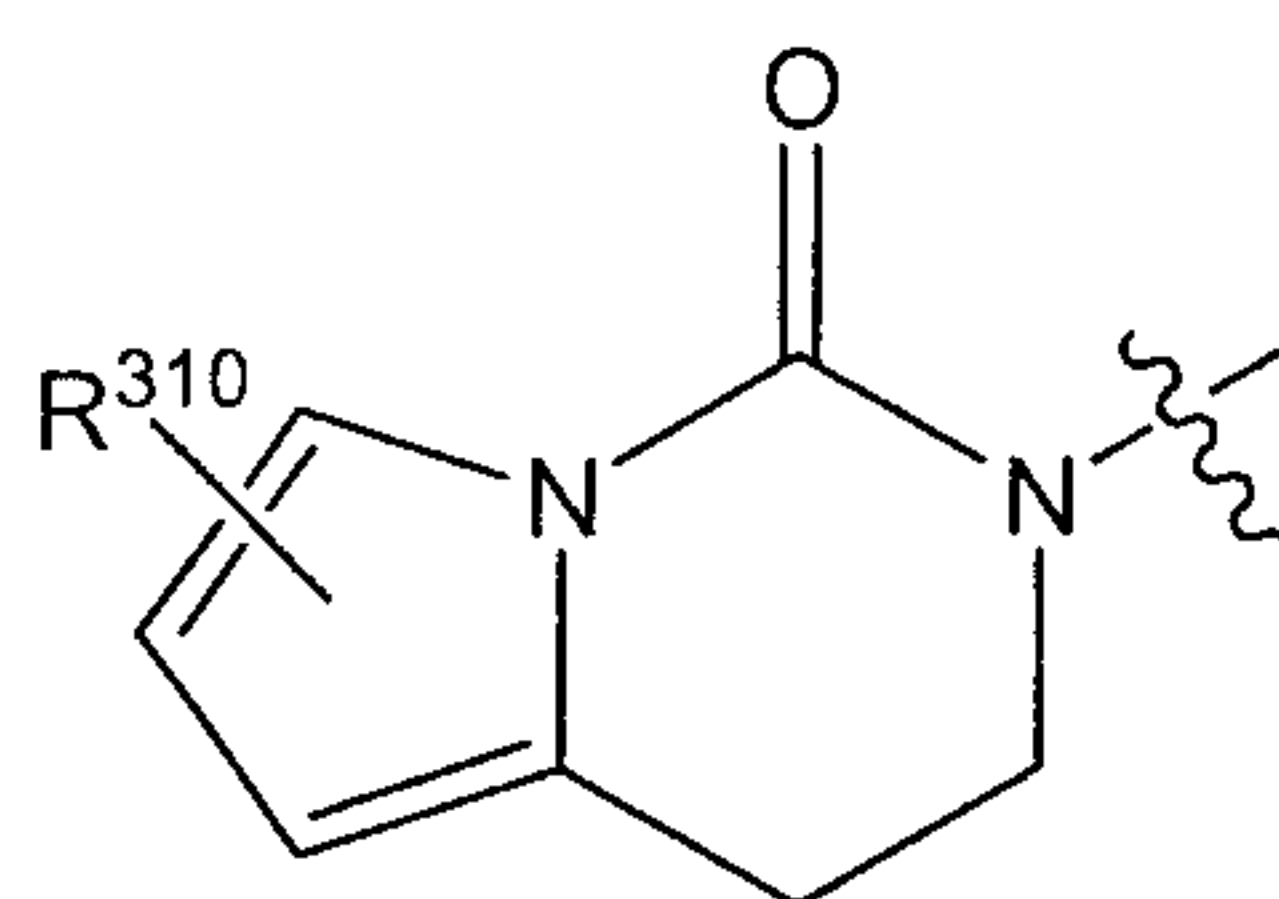


D1h



D1i

and



D1j

GRA3454-WO
22nd December 2009

wherein

R^{300} stands for 0, 1, 2, 3 or 4 substituents, which are mutually independently selected from the group consisting of F, Cl, Br, I, $-CF_3$, $-O-CF_3$, C_{1-4} alkyl and $O-C_{1-4}$ alkyl;

R^{310} stands for 0, 1, 2 or 3 substituents, which are mutually independently selected from the group consisting of F, Cl, Br, I, $-CF_3$, $-O-CF_3$, C_{1-4} alkyl and $O-C_{1-4}$ alkyl;

R^{320} stands for a substituent selected from the group consisting of H, F, Cl, Br, I, $-CF_3$, $-O-CF_3$ and C_{1-4} alkyl;

R^{330} stands for a substituent selected from the group consisting of H, C_{1-4} alkyl, aryl, $-CH_2$ aryl and heteroaryl;

r1 stands for 1 or 2 and

r2 stands for 1 or 2.

3. Substituted compound according to claim 1 or 2, wherein

R^3 stands for phenyl, naphthyl, chromanyl, indolyl, benzofuranyl, benzothiophenyl (benzothienyl); benzooxazolyl, benzooxadiazolyl, pyrrolyl, furanyl, thienyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazothiazolyl, carbazolyl, dibenzofuranyl, dibenzothiophenyl (dibenzothienyl) or for a phenyl or naphthyl bound by a C_{1-3} alkylene group, preferably for phenyl, naphthyl, chromanyl, benzothiophenyl (benzothienyl), benzooxadiazolyl, thienyl, pyridinyl, imidazothiazolyl, dibenzofuranyl or for a phenyl bound by a C_{1-3} alkylene group, particularly preferably for phenyl, naphthyl, chromanyl, benzothiophenyl (benzothienyl) or for a phenyl bound by a $C_{1 \text{ or } 2}$ alkylene group, wherein the aforementioned aryl or heteroaryl radicals are each unsubstituted or mono- or polysubstituted, identically or differently, wherein the substituents are mutually independently selected in particular from the group consisting of $-O-C_{1-3}$ alkyl, C_{1-6} alkyl, F, Cl, Br, I, CF_3 , OCF_3 , OH, SH, phenyl, phenoxy, naphthyl, furyl, thienyl and pyridinyl and wherein the aforementioned alkylene groups are each unsubstituted or mono- or polysubstituted, identically or

GRA3454-WO
22nd December 2009

differently, wherein the substituents are mutually independently selected in particular from the group consisting of $-O-C_{1-3}$ alkyl, F, Cl, Br, I, CF_3 , OCF_3 , OH, SH, phenyl, phenoxy, naphthyl, furyl, thienyl and pyridinyl.

4. Substituted compound according to one or more of claims 1 to 3, wherein R^4 stands for a substituent which is selected from the group consisting of H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl and cyclopropyl, in particular for H.

5. Substituted compound according to one or more of claims 1 to 4, wherein R^8 stands for H; C_{1-6} alkyl, in particular methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl; cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2CF_3$, phenyl, benzyl, phenylethyl, phenylpropyl, or cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl bound by a C_{1-3} alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents.

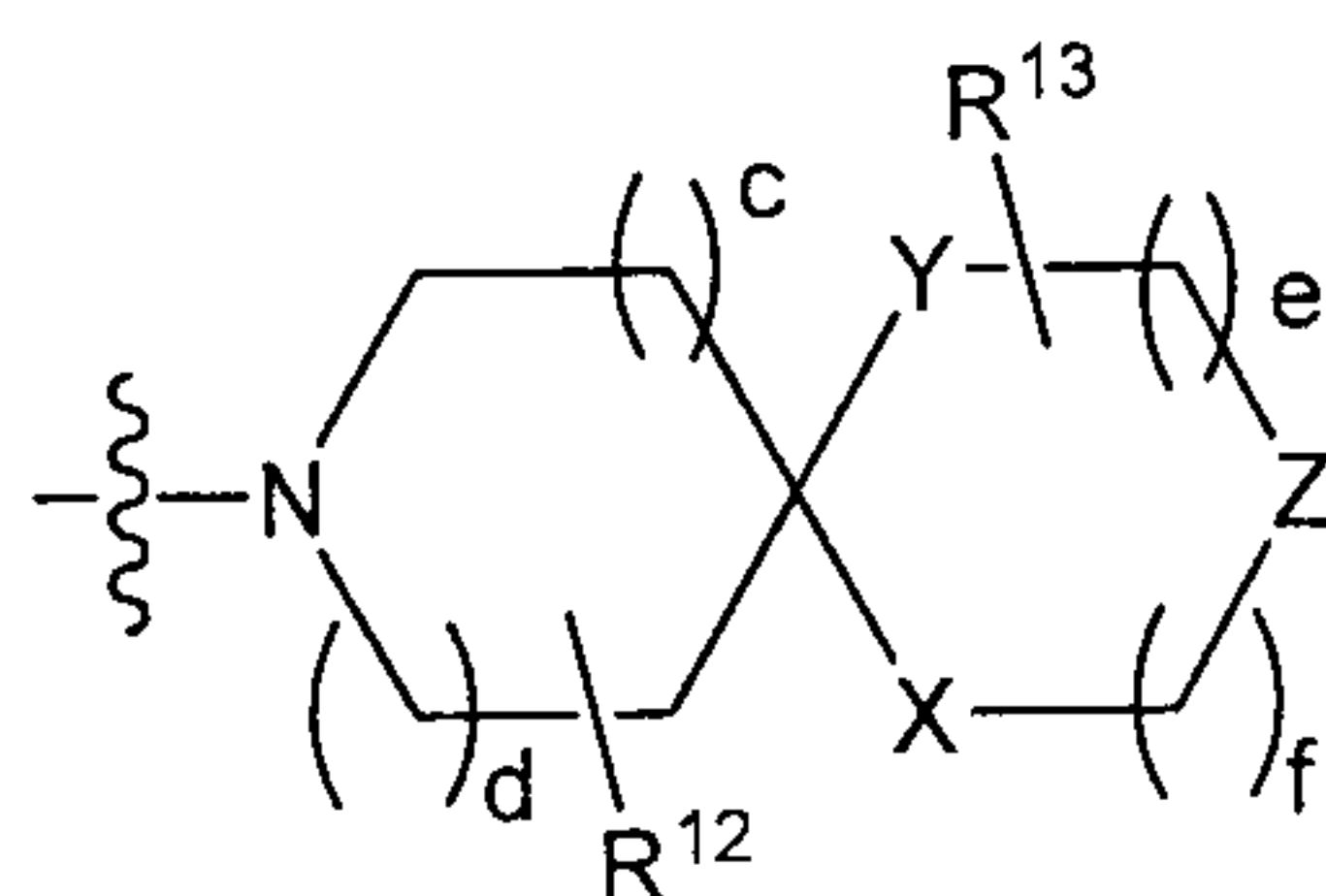
6. Substituted compound according to one or more of claims 1 to 5, wherein R^{9a} and R^{9b} each mutually independently stand for H; F; methyl; ethyl, isopropyl, CF_3 , methoxy; cyclopropyl; phenyl; benzyl, phenylethyl, C_{1-3} alkylene-cyclopropyl, C_{1-3} alkylene-cyclobutyl, C_{1-3} alkylene-cyclopentyl, C_{1-3} alkylene-cyclohexyl or C_{1-3} alkylene- CF_3 , each unsubstituted or mono- or polysubstituted with identical or different substituents, R^{9a} and R^{9b} preferably both standing simultaneously for H.

GRA3454-WO

22nd December 2009

7. Substituted compound according to one or more of claims 1 to 6, wherein

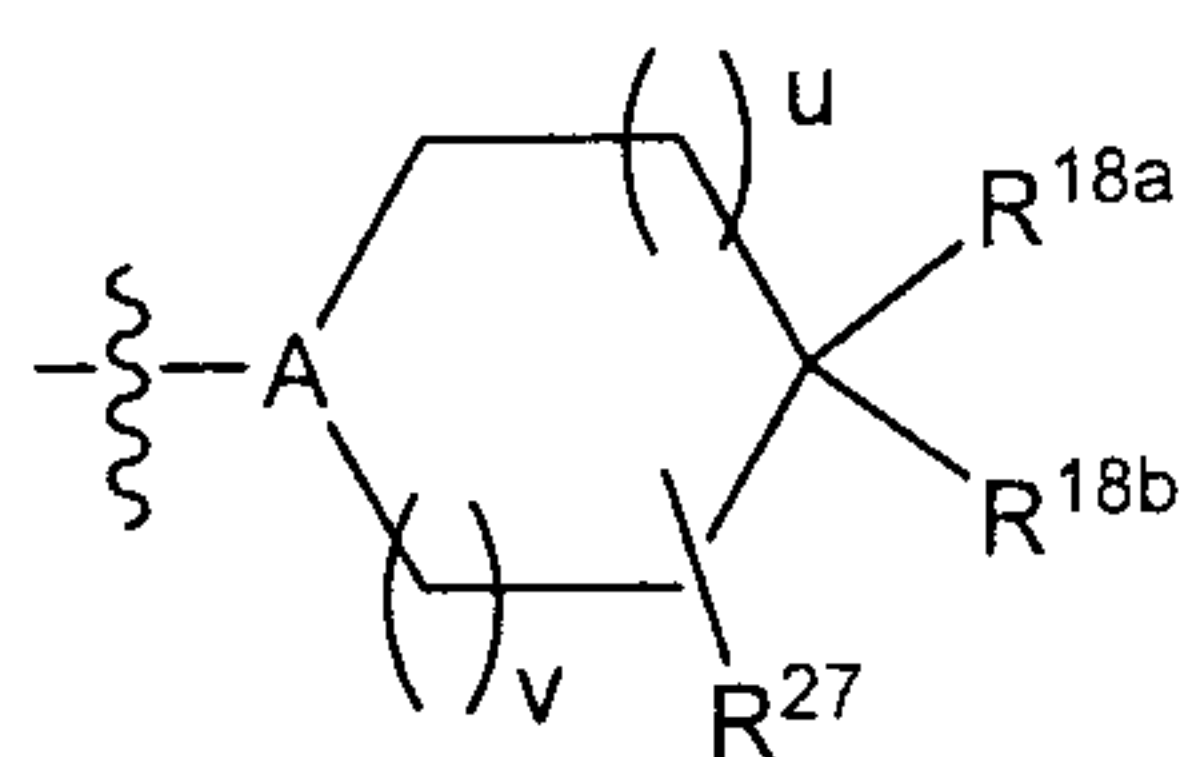
(a1) the general formula (II) assumes the following substructure (IIa):



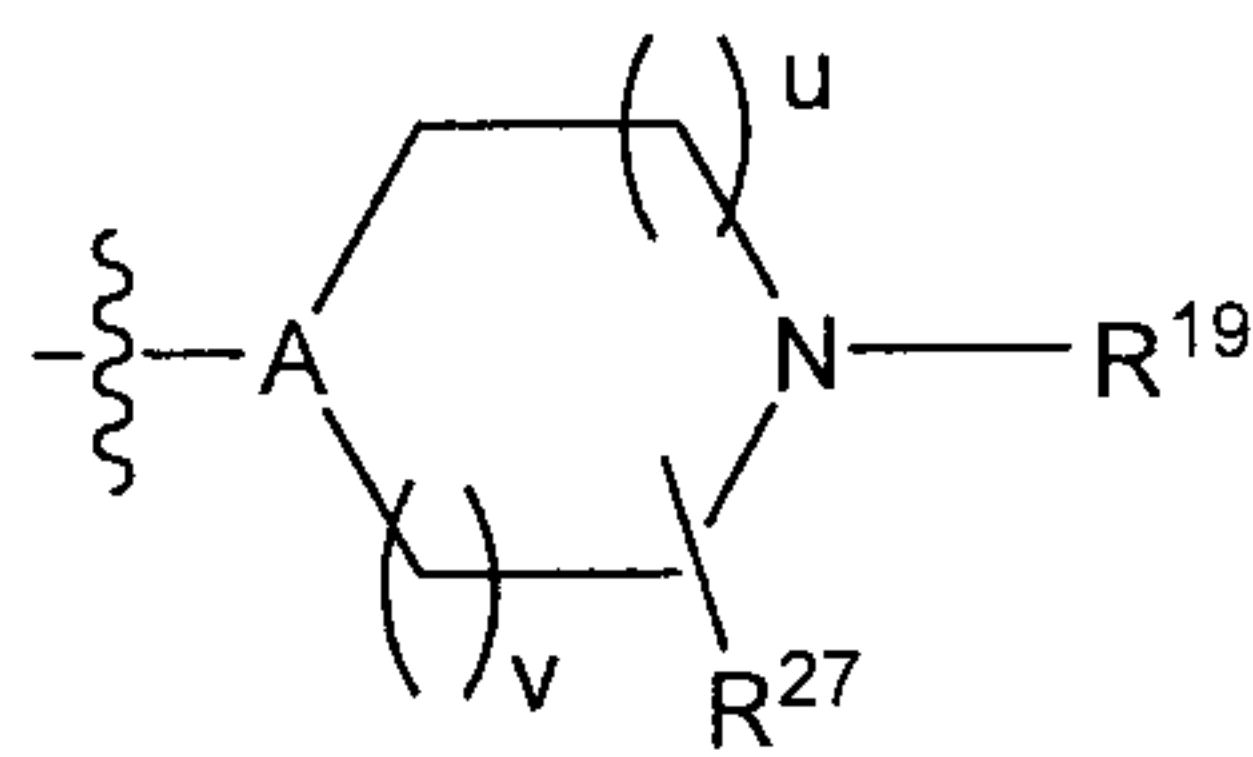
(IIa)

or

(a2) the general formula (III) assumes one of the following substructures (IIIa) or (IIIb):



(IIIa)

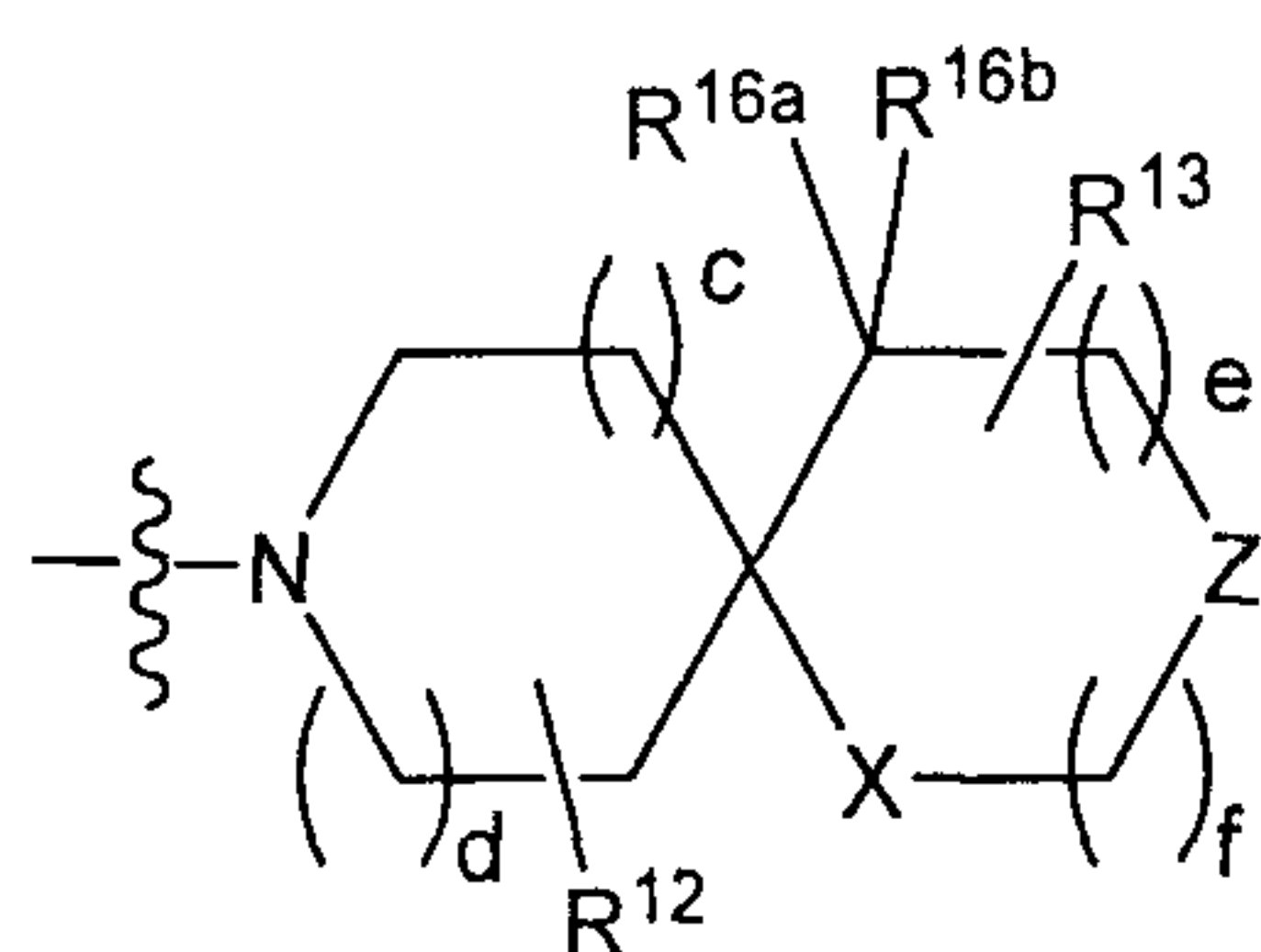


(IIIb)

GRA3454-WO
22nd December 2009

8. Substituted compound according to claim 7, wherein

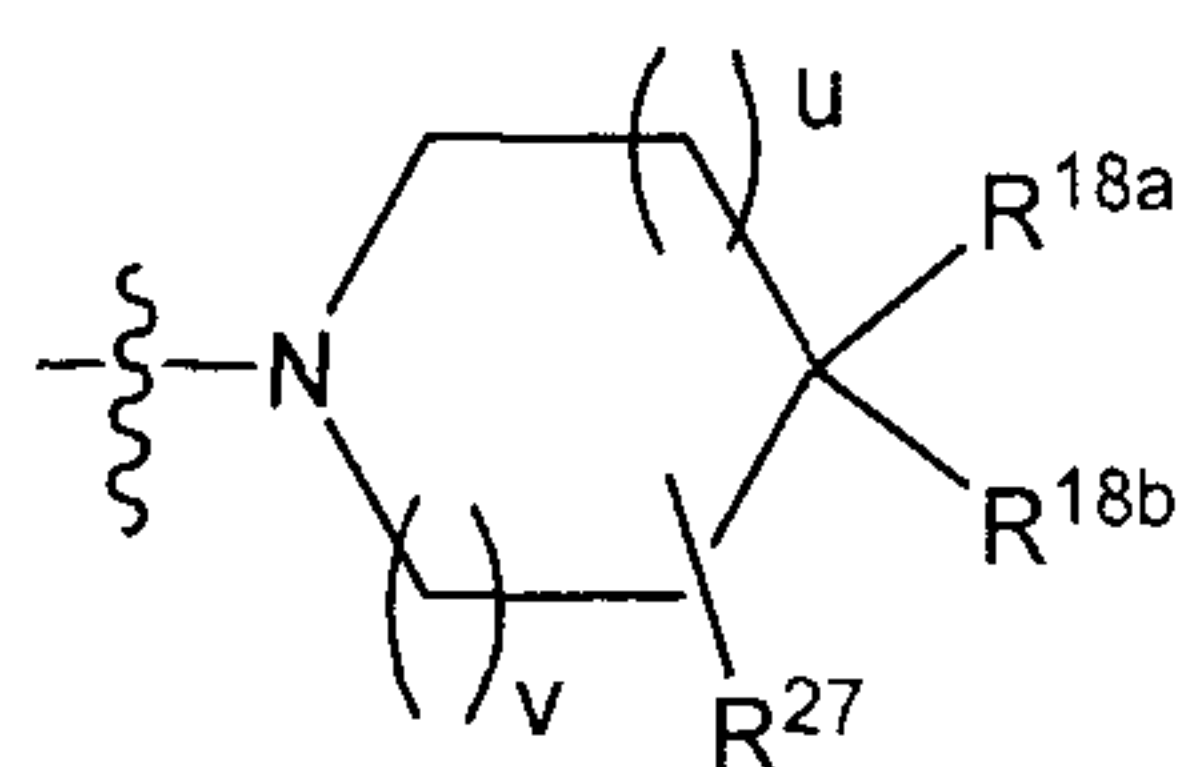
(a1) the substructure having formula (IIa) assumes the following substructure (IIb):



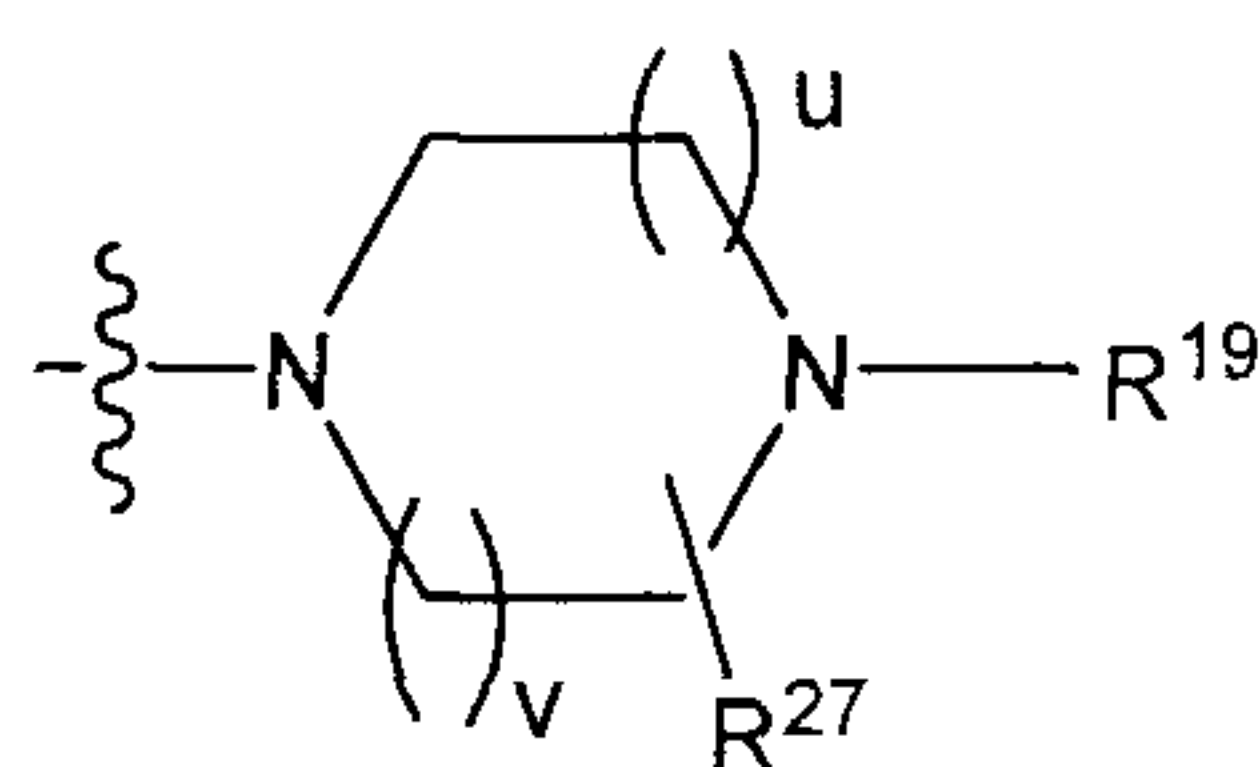
(IIb)

or

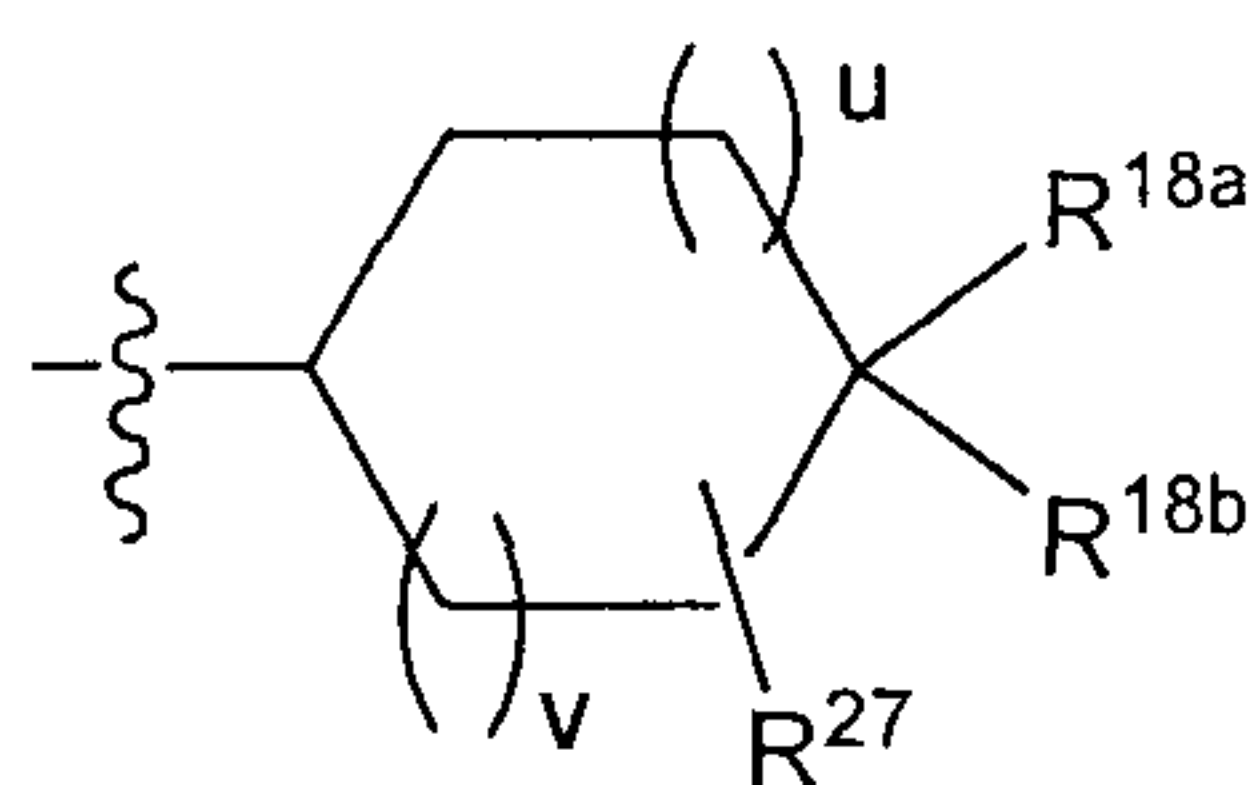
(a2) the substructures having formulae (IIIa) and (IIIb) assume one of the following substructures (IIIc), (IIId), (IIIe) or (IIIf):



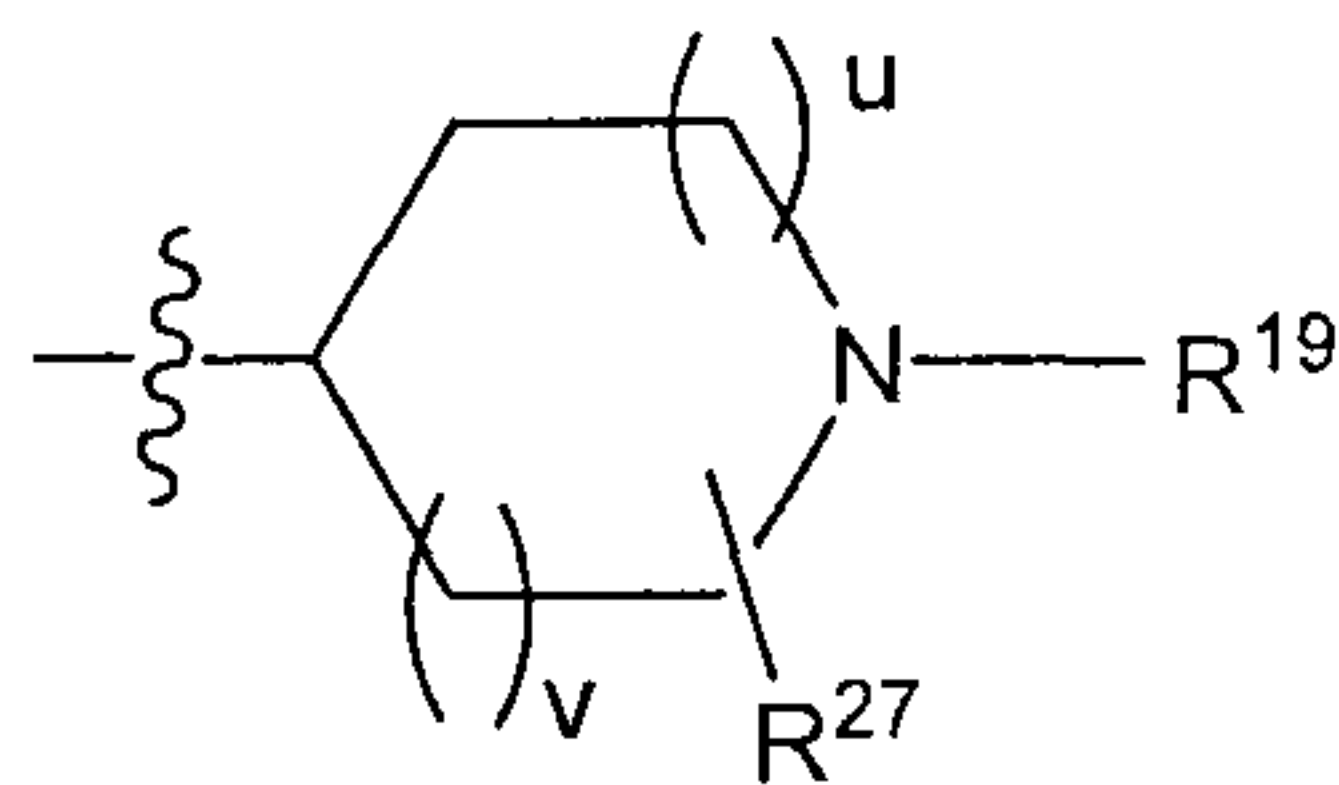
(IIIc)



(IIId)



(IIIe)



(IIIf).

GRA3454-WO
22nd December 2009

9. Substituted compound according to claim 8, wherein

(a1) the substructure having formula (IIa) assumes the substructure (IIb) and s and t each stand for 0;

or

(a2) the substructures having formulae (IIIa) and (IIIb) assume one of the substructures (IIIc) or (IIId) and s and t each stand for 0;

or

(a3) the substructures having formulae (IIIa) and (IIIb) assume one of the substructures (IIIc) or (IIId) and two of the substituents R^{27} together form a C_{1-3} alkylene bridge such that the cyclic compound represented in substructure (IIIc) or (IIId) assumes a bicyclically bridged form and s and t each stand for 0;

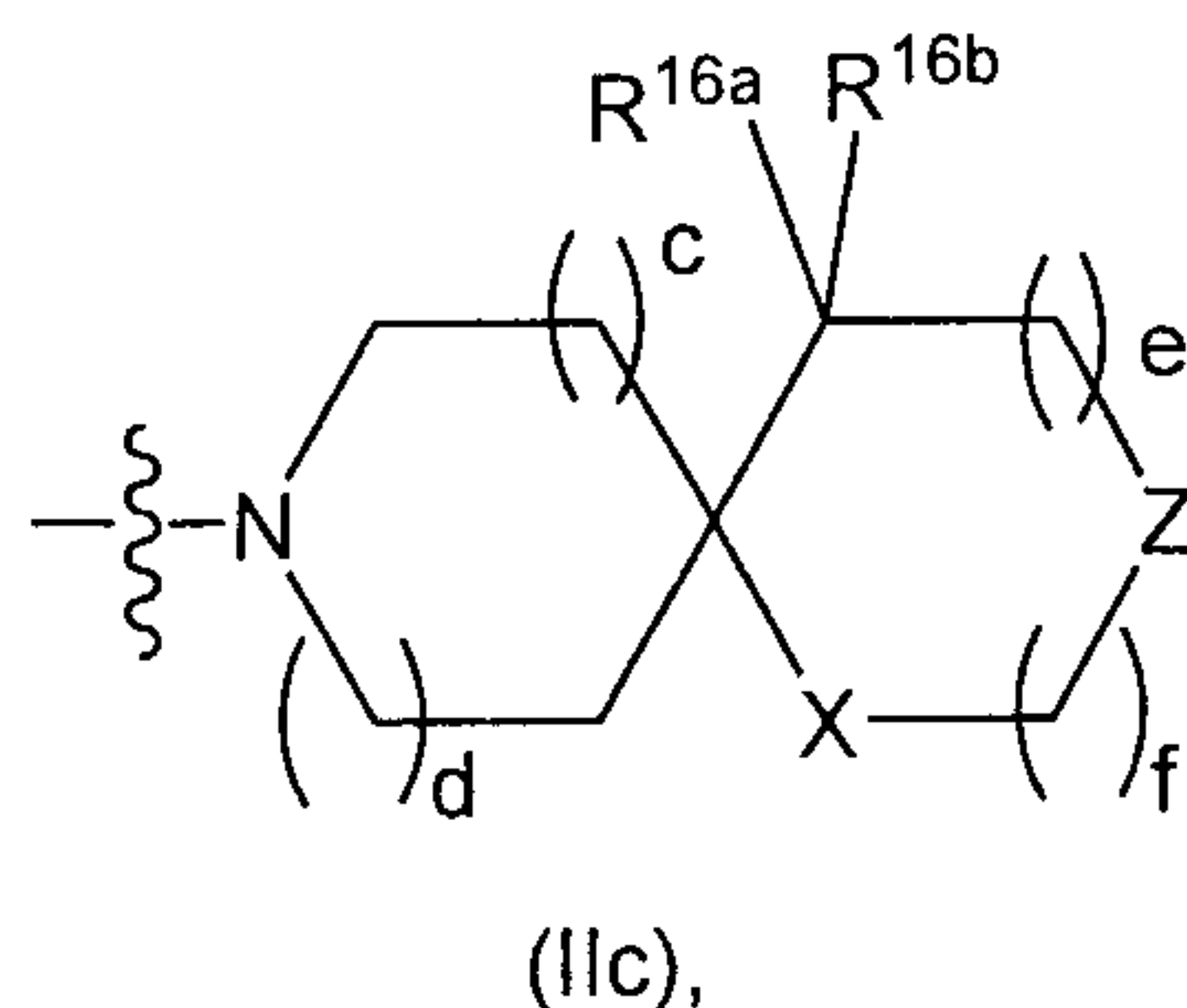
or

(a4) the substructures having formulae (IIIa) and (IIIb) assume one of the substructures (IIIc), (IIId), (IIIe) or (IIIf), s stands for 1 and t stands for 0, 1, 2 or 3 and R^8 stands for H, C_{1-6} alkyl or C_{3-6} cycloalkyl, in each case unsubstituted or mono- or polysubstituted with identical or different substituents, and R^{9a} and R^{9b} mutually independently stand for H, C_{1-6} alkyl or C_{3-6} cycloalkyl.

GRA3454-WO
22nd December 2009

10. Substituted compound according to one or more of claims 1 to 9, wherein

(a1) s and t each stand for 0 and the general formula (II) assumes the following substructure (IIc)



wherein

c, d, e and f each mutually independently denote 0, 1 or 2;

X stands for $\text{CR}^{14a}\text{R}^{14b}$, NR^{15} or O,

Z stands for $\text{CR}^{18a}\text{R}^{18b}$ or NR^{19} ,

or

if X stands for O and f stands for 0, Z denotes $=\text{N}(\text{CR}^{126})-$, wherein the N atom is singly bound to the O atom,

R^{126} stands for H, C_{1-4} alkyl or for an unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl optionally bound by a C_{1-3} alkylene group, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O-C_{1-4} alkyl,

GRA3454-WO
22nd December 2009

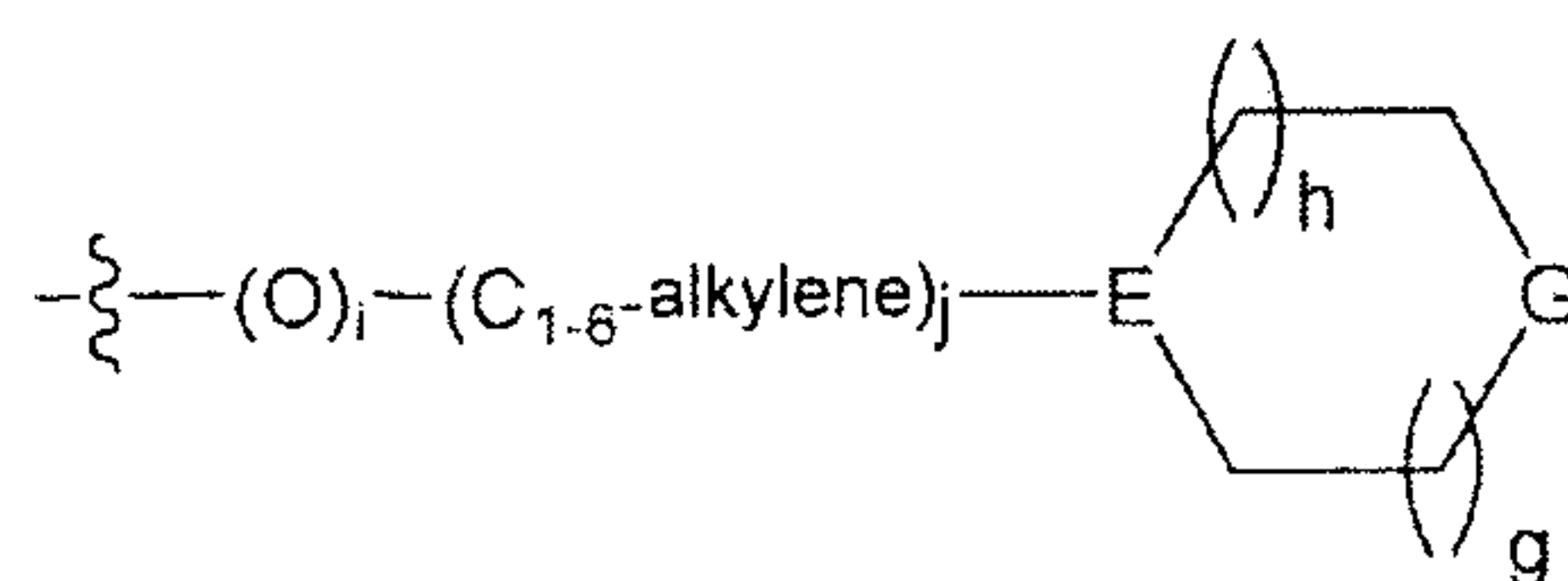
R^{14a} , R^{14b} , R^{16a} and R^{16b} mutually independently stand for H or for an unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl optionally bound by a C_{1-3} alkylene group, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl, and/or R^{16a} and R^{16b} together stand for =O;

R^{15} stands for H, C_{1-4} alkyl or for an unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl optionally bound by a C_{1-3} alkylene group, wherein the substituents are preferably selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

R^{18a} stands for H, C_{1-4} alkyl, C_{3-6} cycloalkyl, $-NH(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})_2$, unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, or for unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by an $-(O)_{0-1}-C_{1-6}$ alkylene group; wherein the substituents are preferably each mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

or

R^{18a} stands for the radical according to the general formula (IVa)



(IVa)

wherein

i stands for 0 or 1;

j stands for 0 or 1;

h and g, mutually independently, stand for 0 or 1;

GRA3454-WO
22nd December 2009

E stands for N or CH; with the proviso that if i stands for 1 and j stands for 0 then E stands for CH,

G stands for $\text{CR}^{37a}\text{R}^{37b}$ or NR^{38} ;

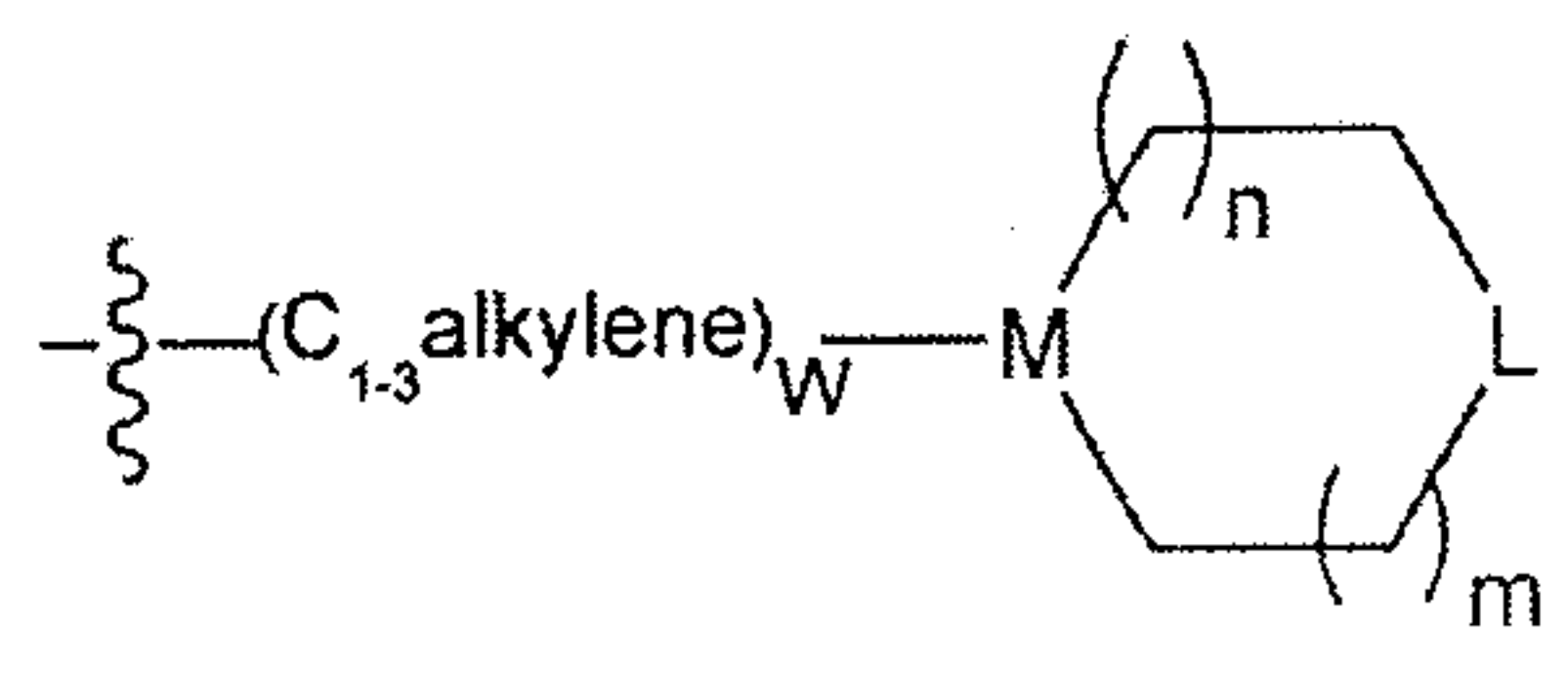
wherein R^{37a} and R^{37b} mutually independently stand for H; F or C_{1-4} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents,

R^{38} stands for H; C_{1-6} alkyl, C_{3-6} cycloalkyl or pyridyl;

R^{18b} stands for H, OH, C_{1-6} alkyl, phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by a C_{1-6} alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents; O-phenyl or O-pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, phenyl, pyridyl or thienyl bridged by C_{1-6} alkylene-NH(C=O), each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

R^{19} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-(\text{C}=\text{O})-\text{C}_{1-6}$ alkyl; C_{1-6} alkylene-NH(C_{1-6} alkyl), C_{1-6} alkylene-N(C_{1-6} alkyl)₂ or for phenyl, pyridyl, thienyl, thiazolyl, triazolyl, pyrimidinyl or imidazolyl; each unsubstituted or mono- or polysubstituted with identical or different substituents; or for phenyl, pyridyl, thienyl, thiazolyl, pyrimidinyl, triazolyl or imidazolyl bound by a C_{1-6} alkylene group; each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl, or for the radical according to the general formula (VIIIa)

GRA3454-WO
22nd December 2009



(VIIIa)

wherein

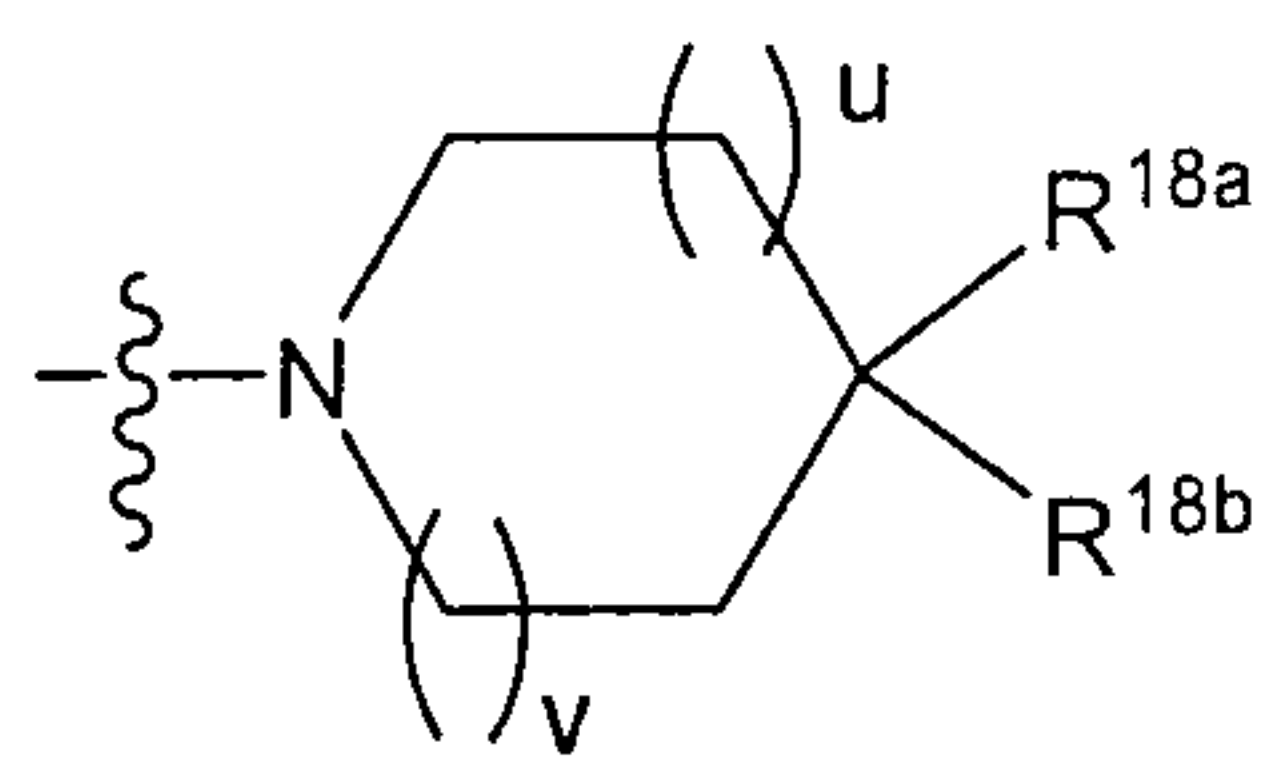
- | | |
|---|---|
| w | stands for 0 or 1; |
| n | stands for 0 or 1; |
| m | stands for 0 or 1; |
| M | stands for CH or N, with the proviso that if w stands for 0 then M stands for CH; |
| L | stands for CR ^{44a} R ^{44b} or NR ⁴⁵ ; |

wherein R^{44a} and R^{44b} mutually independently stand for H; F or C₁₋₆ alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents;

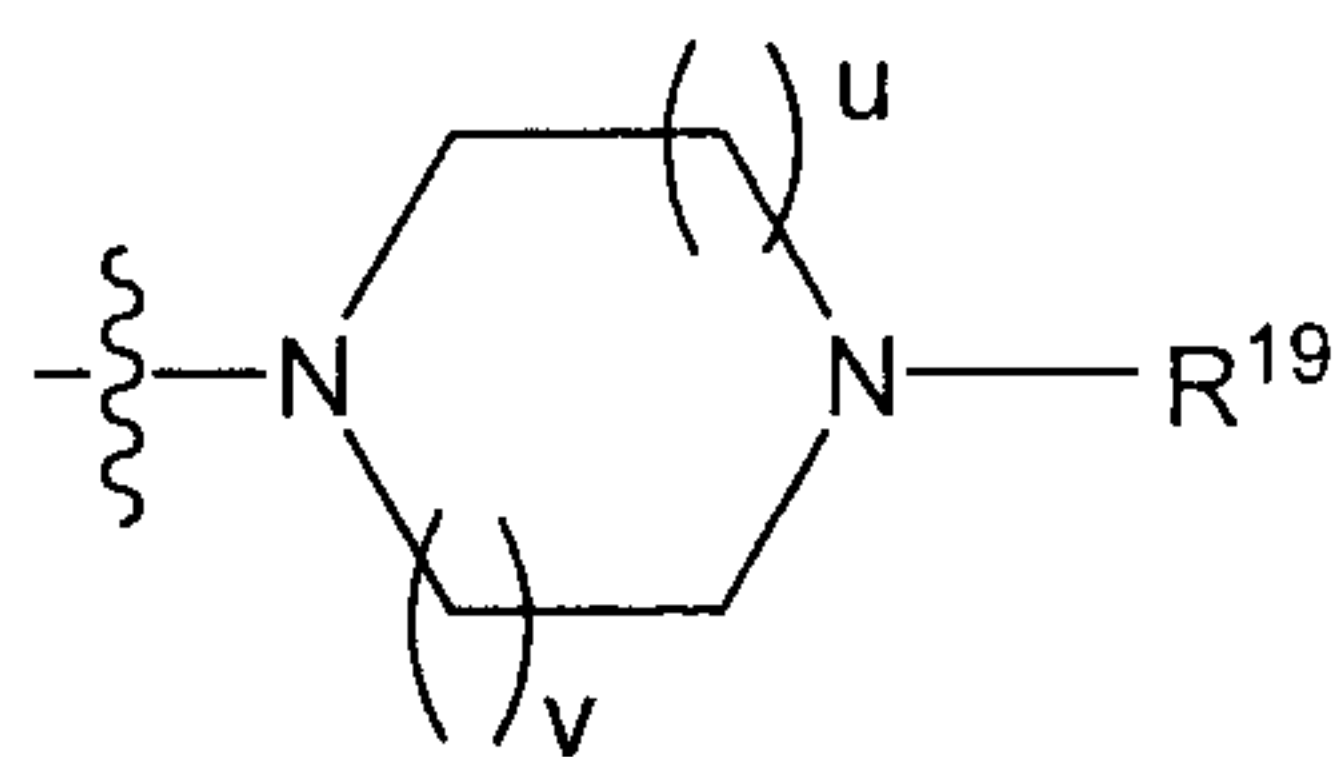
R⁴⁵ stands for H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or pyridyl;

or

(a2) s and t each stand for 0 and the general formula (III) assumes one of the substructures (IIIc') or (IIId')



(IIIc')



(IIId')

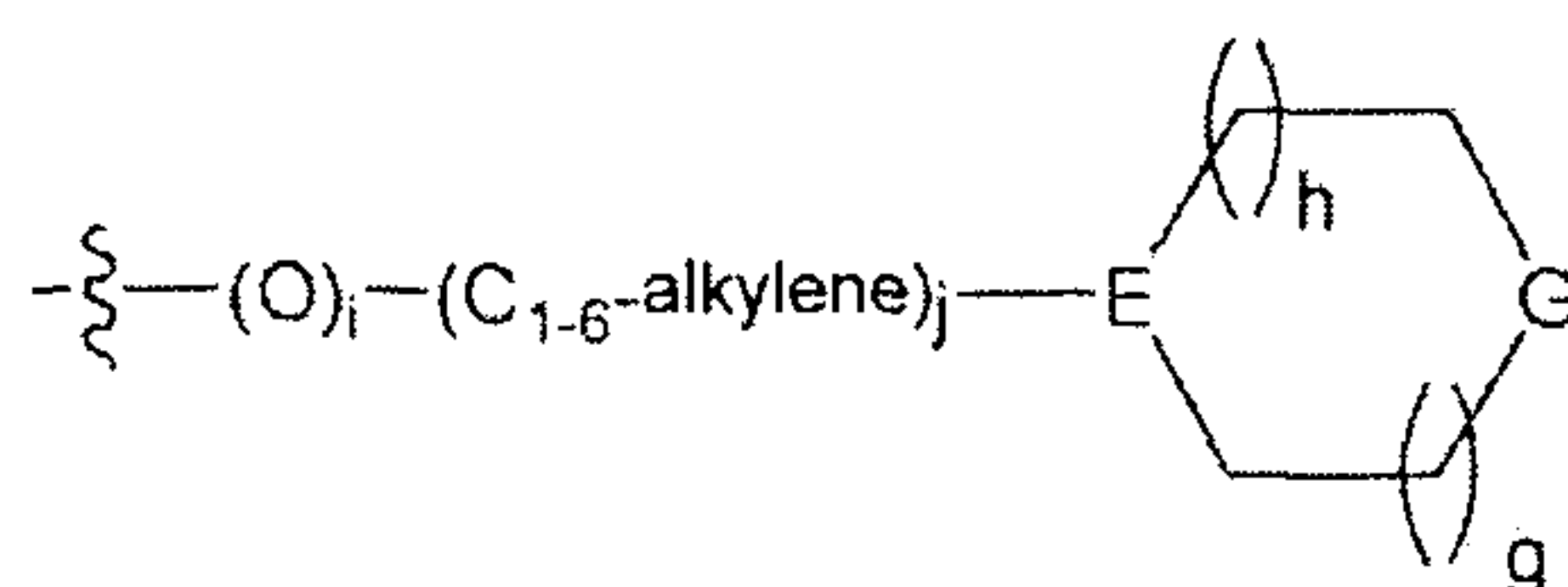
wherein u and v mutually independently stand for 0, 1 or 2,

GRA3454-WO
22nd December 2009

R^{18a} stands for H, C_{1-4} alkyl, C_{3-6} cycloalkyl, $-NH(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})_2$, unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, or for unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by an $-(O)_{0-1}-C_{1-6}$ alkylene group; wherein the substituents are preferably each mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and $O-C_{1-4}$ alkyl,

or

R^{18a} stands for the radical according to the general formula (IVa)



(IVa)

wherein

i stands for 0 or 1;

j stands for 0 or 1;

h and g, mutually independently, stand for 0 or 1,

E stands for N or CH; with the proviso that if i stands for 1 and j stands for 0 then E stands for CH,

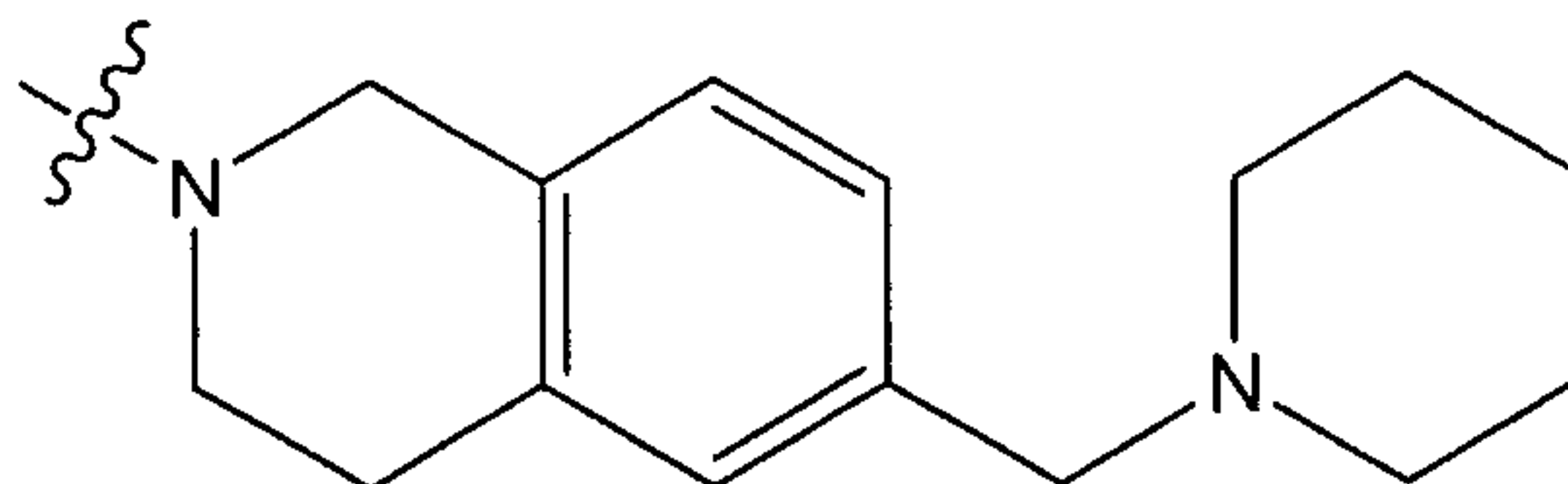
G stands for $CR^{37a}R^{37b}$ or NR^{38} ,

wherein R^{37a} and R^{37b} mutually independently stand for H; F or C_{1-4} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents,

R^{38} stands for H; C_{1-6} alkyl, C_{3-6} cycloalkyl or pyridyl; or

GRA3454-WO
22nd December 2009

R^{18a} stands for the following radical:

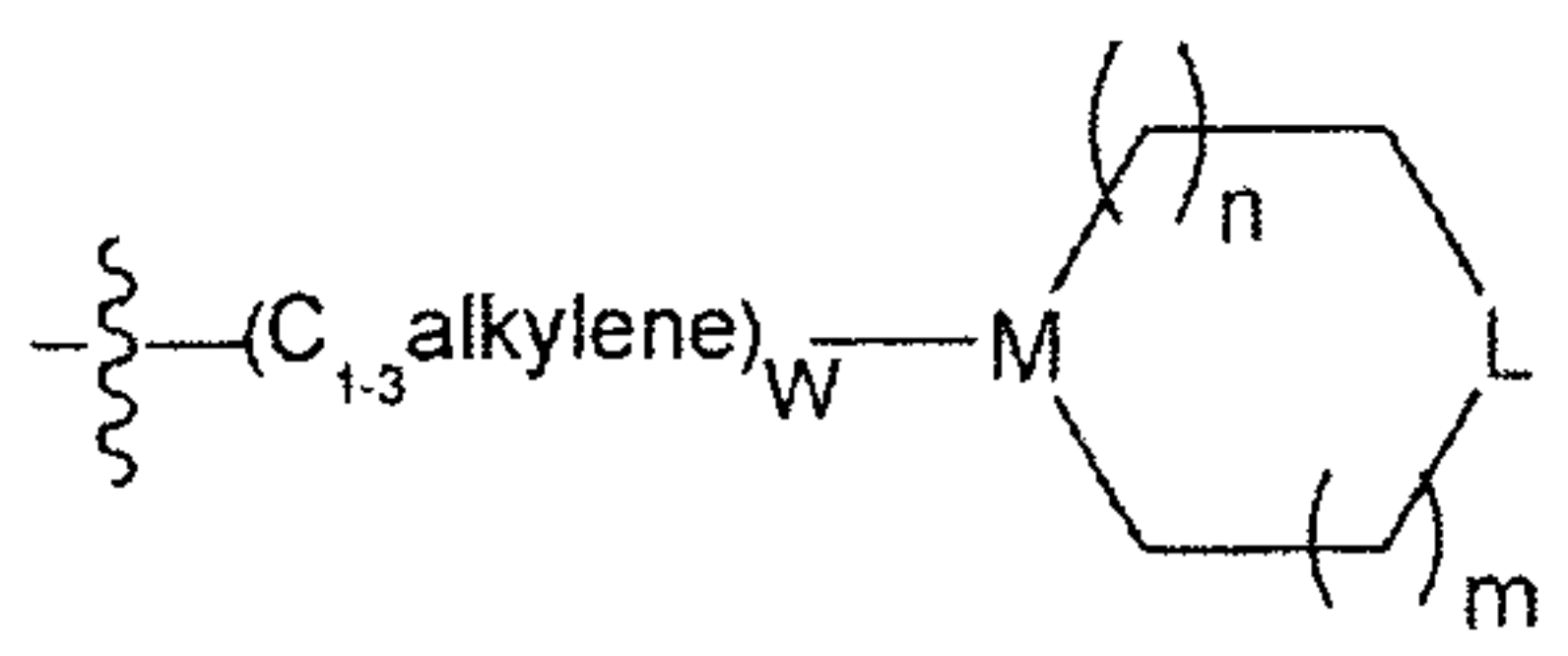


R^{18b} stands for H, OH, C₁₋₆ alkyl, phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by a C₁₋₆ alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents; O-phenyl or O-pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, phenyl, pyridyl or thienyl bridged by C₁₋₆ alkylene-NH(C=O), each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl,

R¹⁹ stands for H, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, -(C=O)-C₁₋₆ alkyl; C₁₋₆ alkylene-NH(C₁₋₆ alkyl), C₁₋₆ alkylene-N(C₁₋₆ alkyl)₂ or for phenyl, pyridyl, thienyl, thiazolyl, triazolyl, pyrimidinyl or imidazolyl; each unsubstituted or mono- or polysubstituted with identical or different substituents; or for phenyl, pyridyl, thienyl, thiazolyl, pyrimidinyl, triazolyl or imidazolyl bound by a C₁₋₆ alkylene group; each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl,

GRA3454-WO
22nd December 2009

or for the radical according to the general formula (VIIIa)



(VIIIa)

wherein

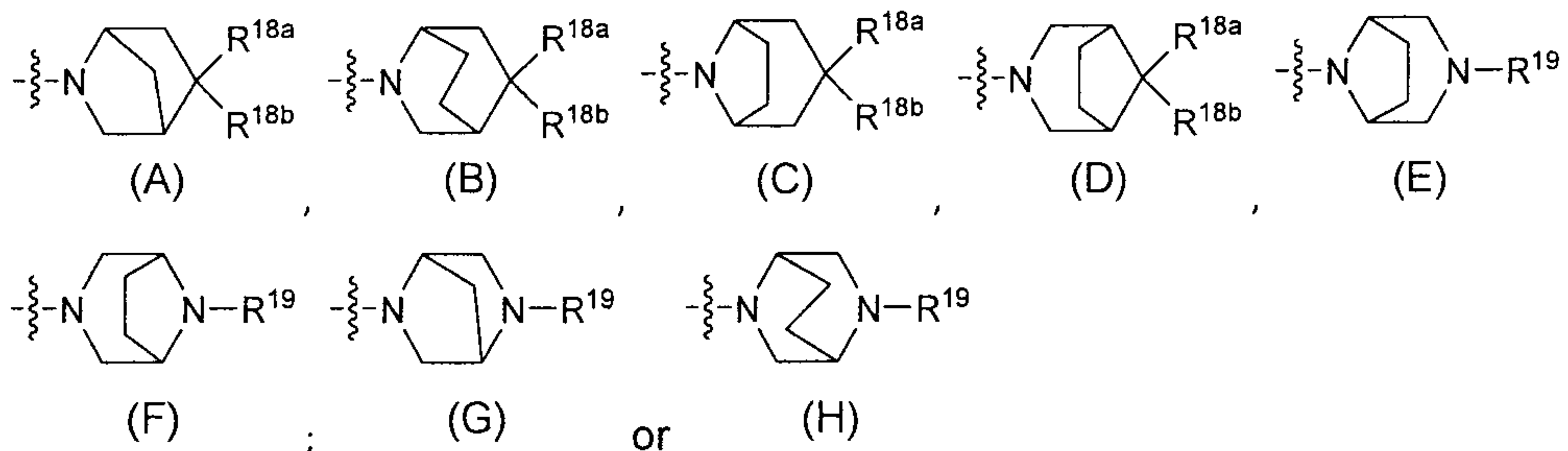
- w stands for 0 or 1;
- n stands for 0 or 1;
- m stands for 0 or 1;
- M stands for CH or N, with the proviso that if w stands for 0 then M stands for CH;
- L stands for $\text{CR}^{44a}\text{R}^{44b}$ or NR^{45} ;

wherein R^{44a} and R^{44b} mutually independently stand for H; F or C_{1-6} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents;

R^{45} stands for H, C_{1-6} alkyl, C_{3-6} cycloalkyl or pyridyl;

or

(a3) s and t each stand for 0 and the general formula (III) assumes one of the following substructures (A) to (H)



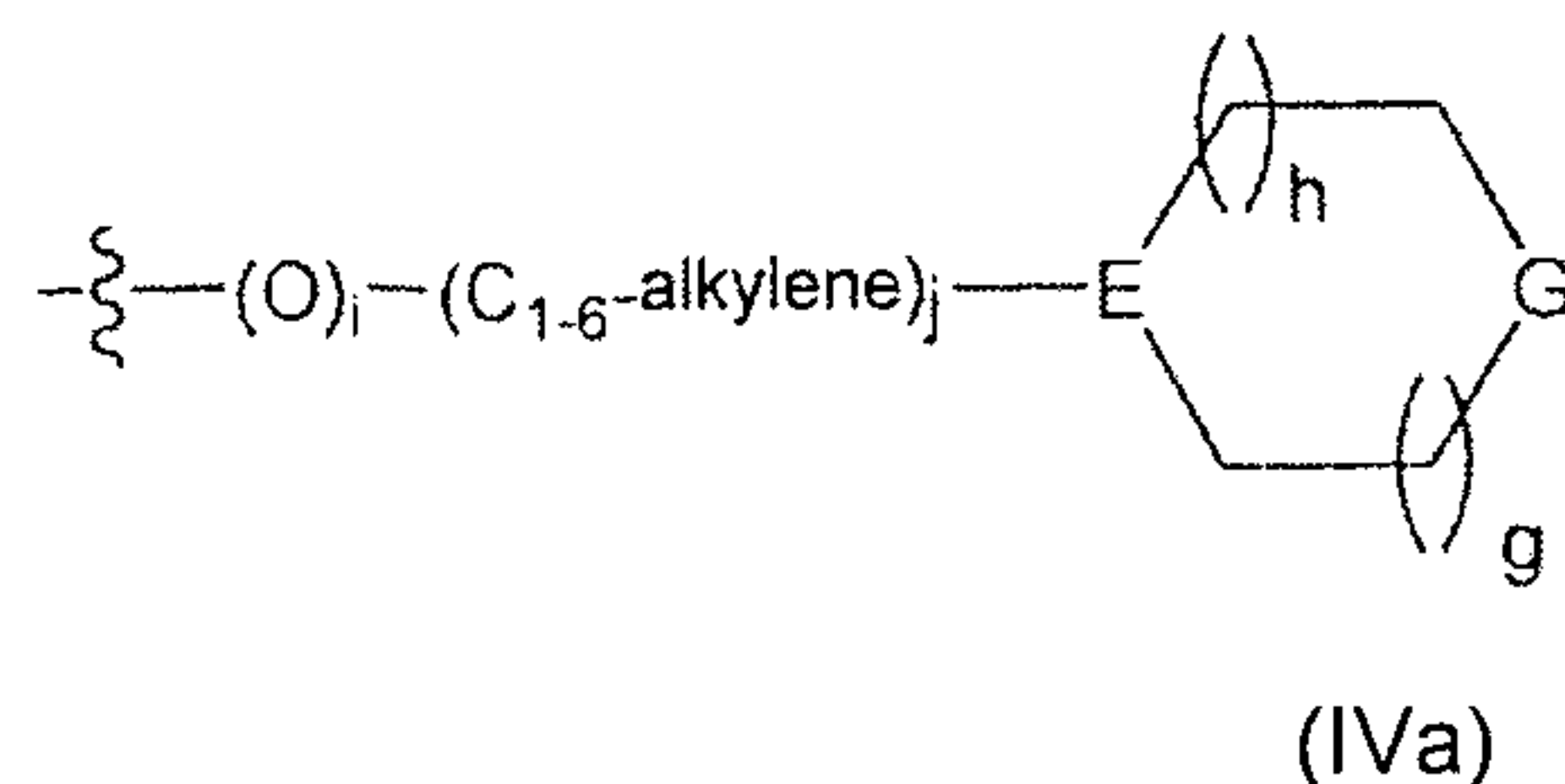
GRA3454-WO
22nd December 2009

and wherein

R^{18a} stands for H, C_{1-4} alkyl, C_{3-6} cycloalkyl, $-NH(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})_2$, unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, or for unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by an $-(O)_{0-1}-C_{1-6}$ alkylene group; wherein the substituents are preferably each mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and $O-C_{1-4}$ alkyl,

or

R^{18a} stands for the radical according to the general formula (IVa)



wherein

i stands for 0 or 1;

j stands for 0 or 1;

h and g, mutually independently, stand for 0 or 1,

E stands for N or CH; with the proviso that if i stands for 1 and j stands for 0 then E stands for CH,

G stands for $CR^{37a}R^{37b}$ or NR^{38} ;

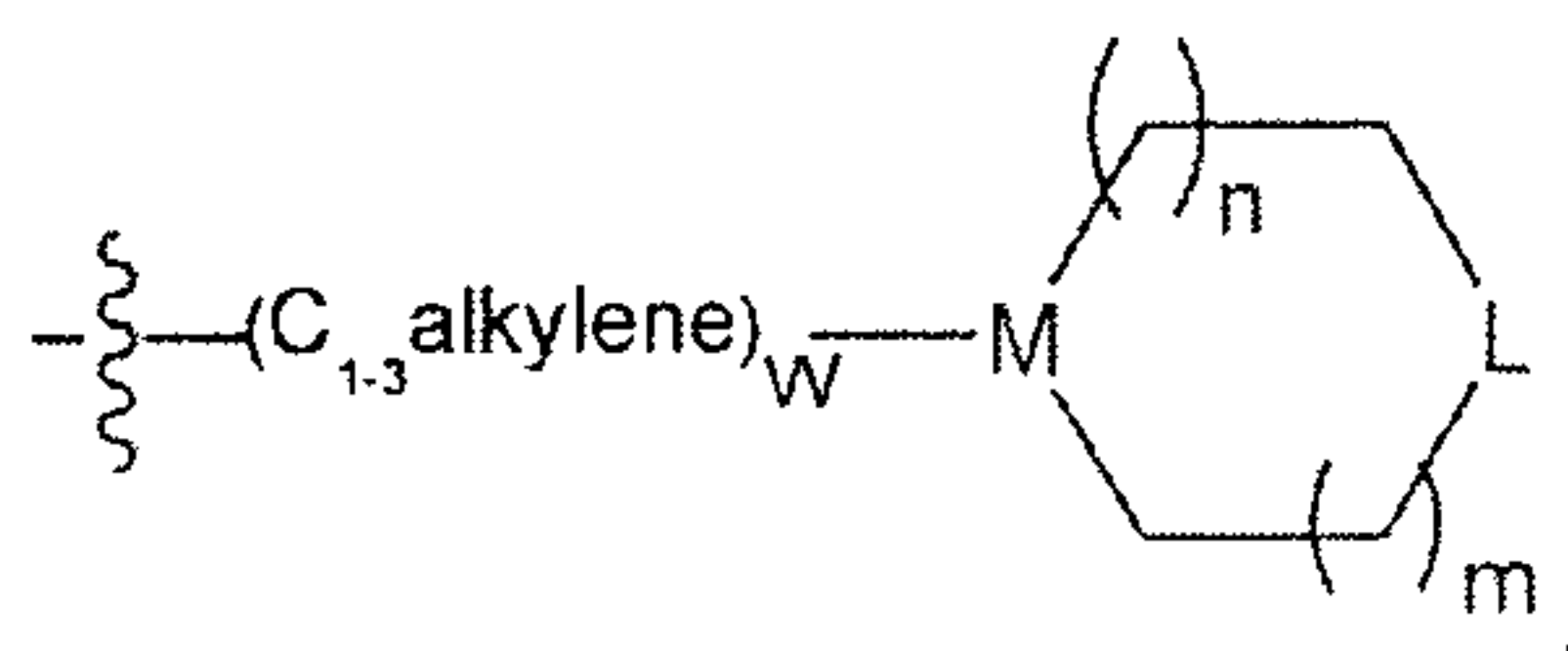
wherein R^{37a} and R^{37b} mutually independently stand for H; F or C_{1-4} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents,

GRA3454-WO
22nd December 2009

R^{38} stands for H; C_{1-6} alkyl, C_{3-6} cycloalkyl or pyridyl;

R^{18b} stands for H, OH, C_{1-6} alkyl, phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by a C_{1-6} alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents; O-phenyl or O-pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, phenyl, pyridyl or thienyl bridged by C_{1-6} alkylene-NH(C=O), each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,

R^{19} stands for H, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-(C=O)-C_{1-6}$ alkyl; C_{1-6} alkylene-NH(C_{1-6} alkyl), C_{1-6} alkylene-N(C_{1-6} alkyl) $_2$ or for phenyl, pyridyl, thienyl, thiazolyl, triazolyl, pyrimidinyl or imidazolyl; each unsubstituted or mono- or polysubstituted with identical or different substituents; or for phenyl, pyridyl, thienyl, thiazolyl, pyrimidinyl, triazolyl or imidazolyl bound by a C_{1-6} alkylene group; each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and O- C_{1-4} alkyl,
or for the radical according to the general formula (VIIIa)



(VIIIa)

wherein

w	stands for 0 or 1;
n	stands for 0 or 1;
m	stands for 0 or 1;
M	stands for CH or N, with the proviso that if w stands for 0 then M stands for CH;
L	stands for $CR^{44a}R^{44b}$ or NR^{45} ;

GRA3454-WO
22nd December 2009

wherein R^{44a} and R^{44b} mutually independently stand for H; F or C_{1-6} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents;

R^{45} stands for H, C_{1-6} alkyl, C_{3-6} cycloalkyl or pyridyl;

or

(a4)

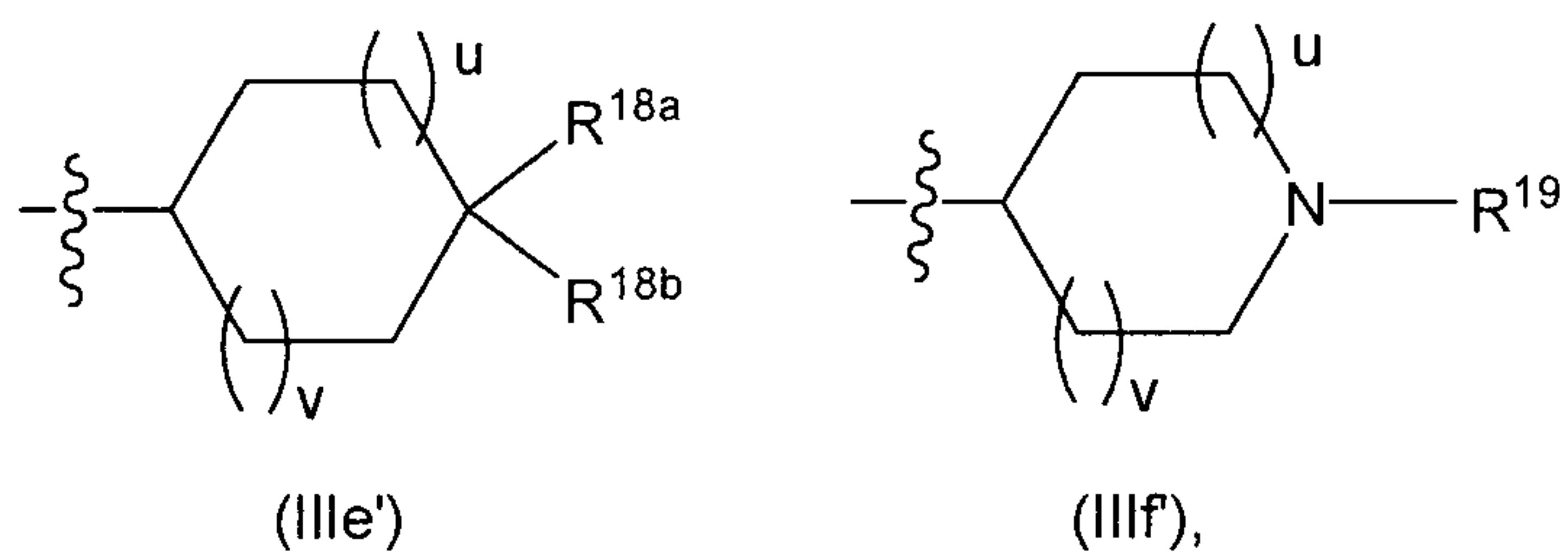
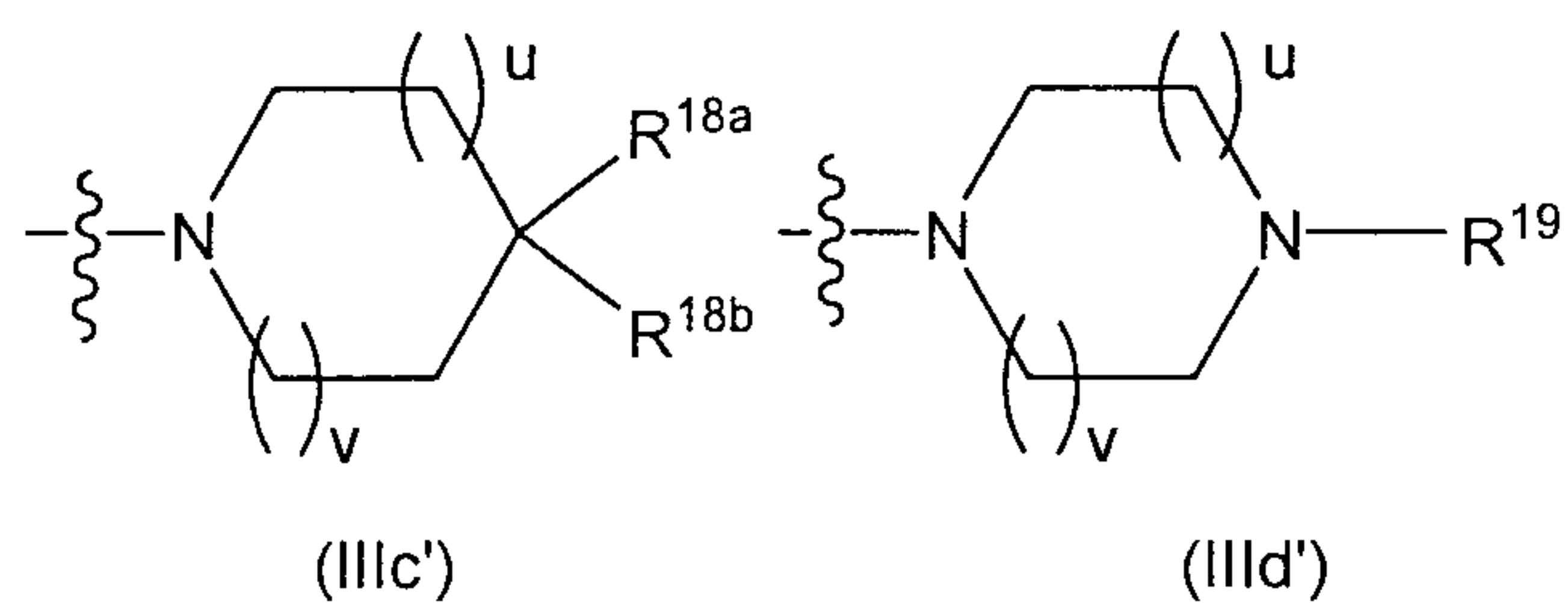
s stands for 1,

t stands for 0, 1, 2 or 3,

R^8 stands for H, C_{1-4} alkyl or C_{3-6} cycloalkyl

R^{9a} and R^{9b} mutually independently stand for H, C_{1-4} alkyl or C_{3-6} cycloalkyl, preferably both stand for H;

the general formula (III) assumes one of the following substructures (IIIc'), (IIId'), (IIIe') or (IIIf')



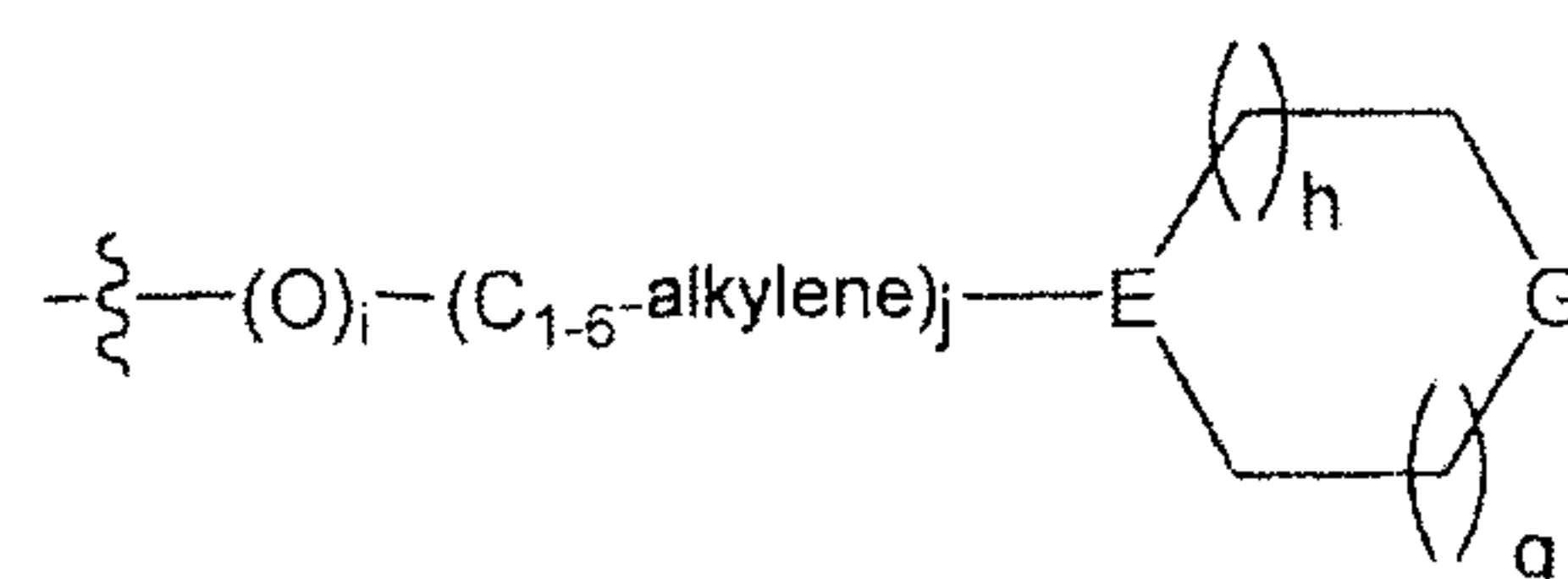
GRA3454-WO
22nd December 2009

wherein u and v mutually independently stand for 0, 1 or 2,

R^{18a} stands for H, C_{1-4} alkyl, C_{3-6} cycloalkyl, $-NH(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})_2$, unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl, or for unsubstituted or mono- or polysubstituted phenyl, pyridyl, imidazolyl, triazolyl, pyrimidyl, thiazolyl or thienyl bound by an $-(O)_{0-1}-C_{1-6}$ alkylene group; wherein the substituents are preferably each mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and $O-C_{1-4}$ alkyl,

or

R^{18a} stands for the radical according to the general formula (IVa)



(IVa)

wherein

i stands for 0 or 1;

j stands for 0 or 1;

h and g, mutually independently, stand for 0 or 1,

E stands for N or CH; with the proviso that if i stands for 1 and j stands for 0 then E stands for CH,

G stands for $CR^{37a}R^{37b}$ or NR^{38} ;

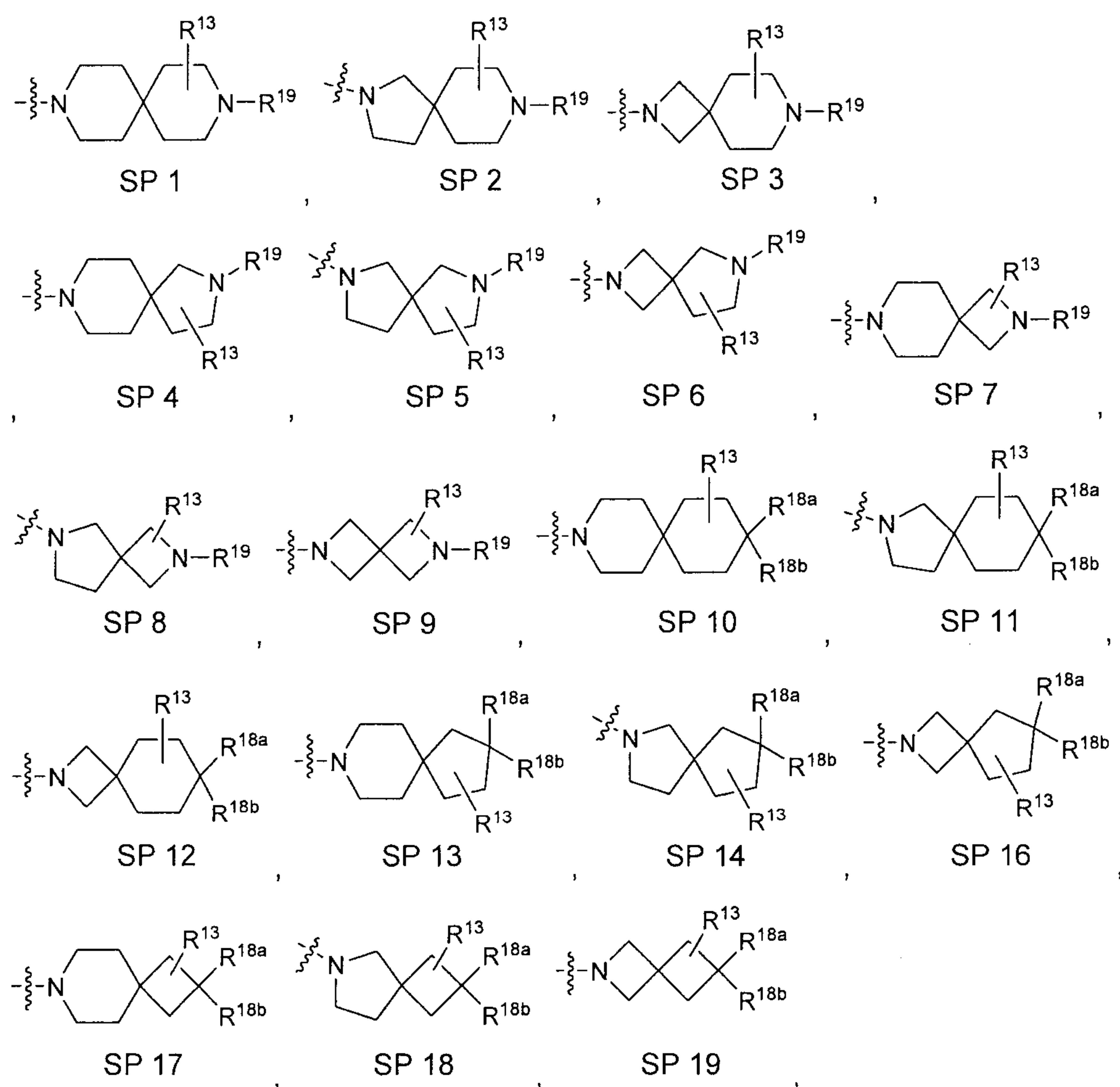
wherein R^{37a} and R^{37b} mutually independently stand for H; F or C_{1-4} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents,

GRA3454-WO
22nd December 2009

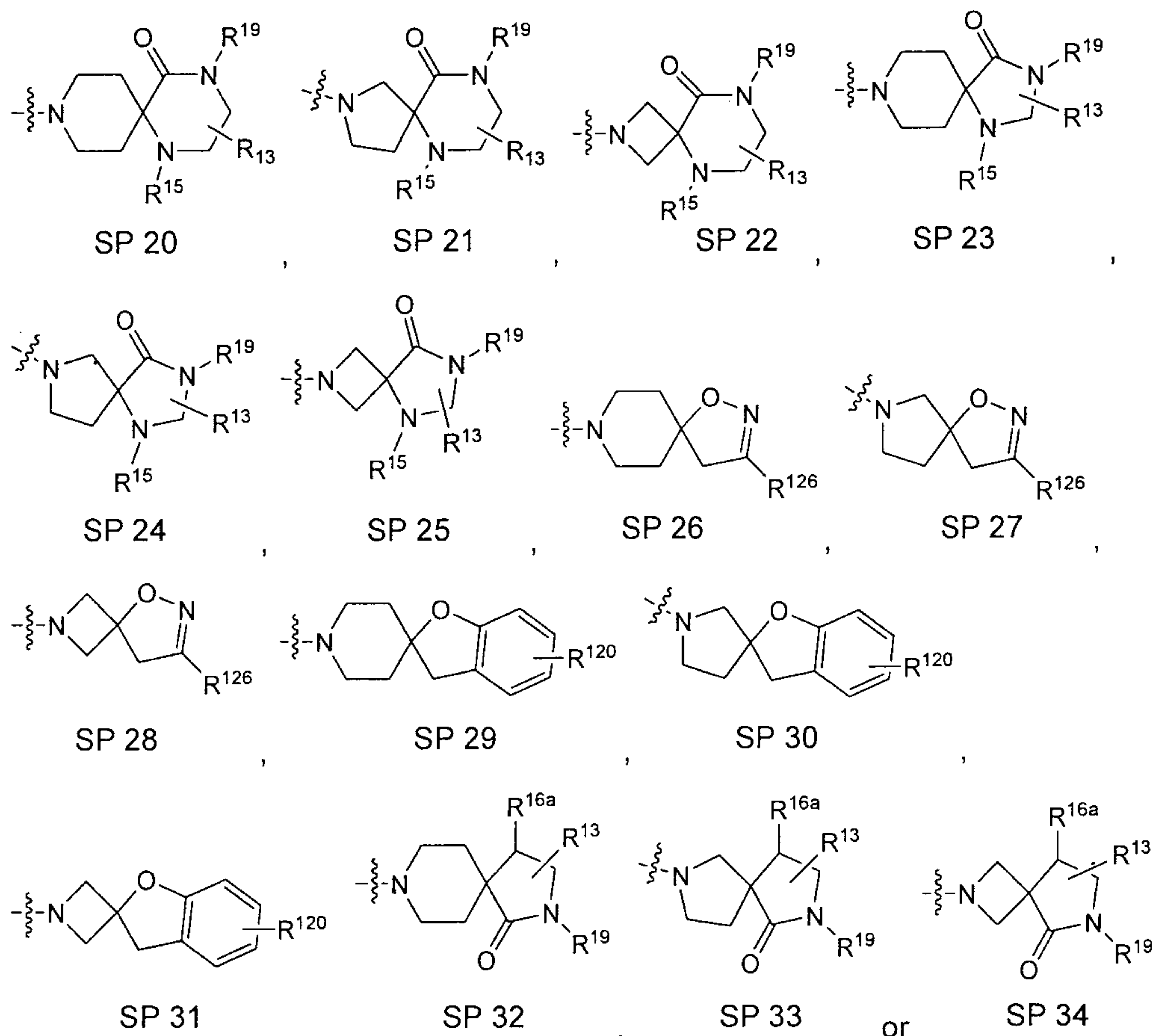
wherein R^{44a} and R^{44b} mutually independently stand for H; F or C_{1-6} alkyl, each unsubstituted or mono- or polysubstituted with identical or different substituents;

R^{45} stands for H, C_{1-6} alkyl, C_{3-6} cycloalkyl or pyridyl.

11. Substituted compound according to one or more of claims 1 to 10, wherein the substructure (II) assumes one of the following substructures:



GRA3454-WO
22nd December 2009



wherein

R^{13} stands for 1 or 2 radicals selected from H and phenyl, unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and $O-C_{1-4}$ alkyl;

and/or two of the substituents R^{13} together form $=O$;

and/or two adjacent substituents R^{13} together form an anellated aryl or heteroaryl, in particular a benzo group, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF_3 , C_{1-4} alkyl, OCF_3 , OH and $O-C_{1-4}$ alkyl;

GRA3454-WO
22nd December 2009

R¹⁵ stands for H; C₁₋₆ alkyl; C₃₋₈ cycloalkyl or for unsubstituted or identically or differently mono- or polysubstituted phenyl or pyridyl or for a phenyl or pyridyl bound by a C₁₋₆ alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

R^{16a} stands for H, C₁₋₆ alkyl or for phenyl or pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

R^{18a} stands for H; C₁₋₆ alkyl; C₃₋₈ cycloalkyl, N(C₁₋₆ alkyl)₂; NH(C₁₋₆ alkyl), azetidiny; pyrrolidiny, piperidiny, 4-(C₁₋₆ alkyl)-piperaziny; phenyl or pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; or for N(C₁₋₆ alkyl)₂; NH(C₁₋₆ alkyl), azetidiny; pyrrolidiny, piperidiny, 4-(C₁₋₆ alkyl)-piperaziny; phenyl, imidazolyl, triazolyl or pyridyl bound by an -(O)_{0/1}-C₁₋₆ alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents of C₁₋₆ alkyl; C₃₋₈ cycloalkyl, azetidiny; pyrrolidiny, piperidiny and 4-(C₁₋₆ alkyl)-piperaziny are preferably mutually independently selected from the group consisting of F, Cl, CF₃, =O, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl and wherein the substituents of phenyl, imidazolyl, triazolyl or pyridyl are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

R^{18b} stands for H; OH; C₁₋₆ alkyl; phenyl or pyridyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, or for phenyl or pyridyl bound by a C₁₋₆ alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents; wherein the substituents of phenyl and pyridyl are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

GRA3454-WO
22nd December 2009

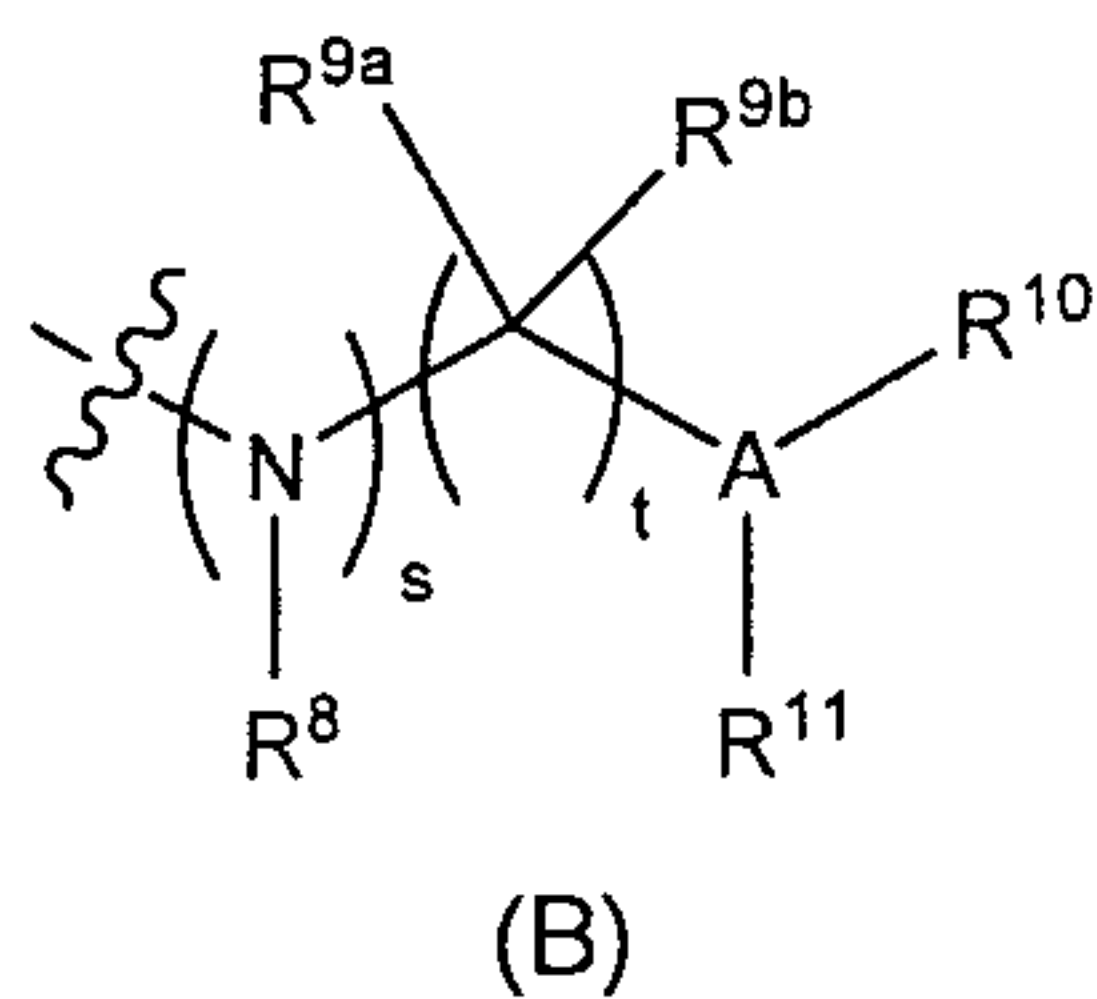
R¹⁹ stands for H; C₁₋₆ alkyl; C₃₋₈ cycloalkyl, phenyl, pyridyl, thienyl, imidazolyl, thiazolyl or triazolyl, each unsubstituted or mono- or polysubstituted with identical or different substituents, or for phenyl or pyridyl bound by a C₁₋₆ alkylene group or (C=O) group, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents of phenyl, pyridyl, thienyl, imidazolyl, thiazolyl and triazolyl are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

R¹²⁰ stands for H; F; Cl; OH; OCH₃, O-CF₃, C₁₋₆ alkyl; CF₃, phenyl, unsubstituted or mono- or polysubstituted, wherein the substituents of phenyl are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl;

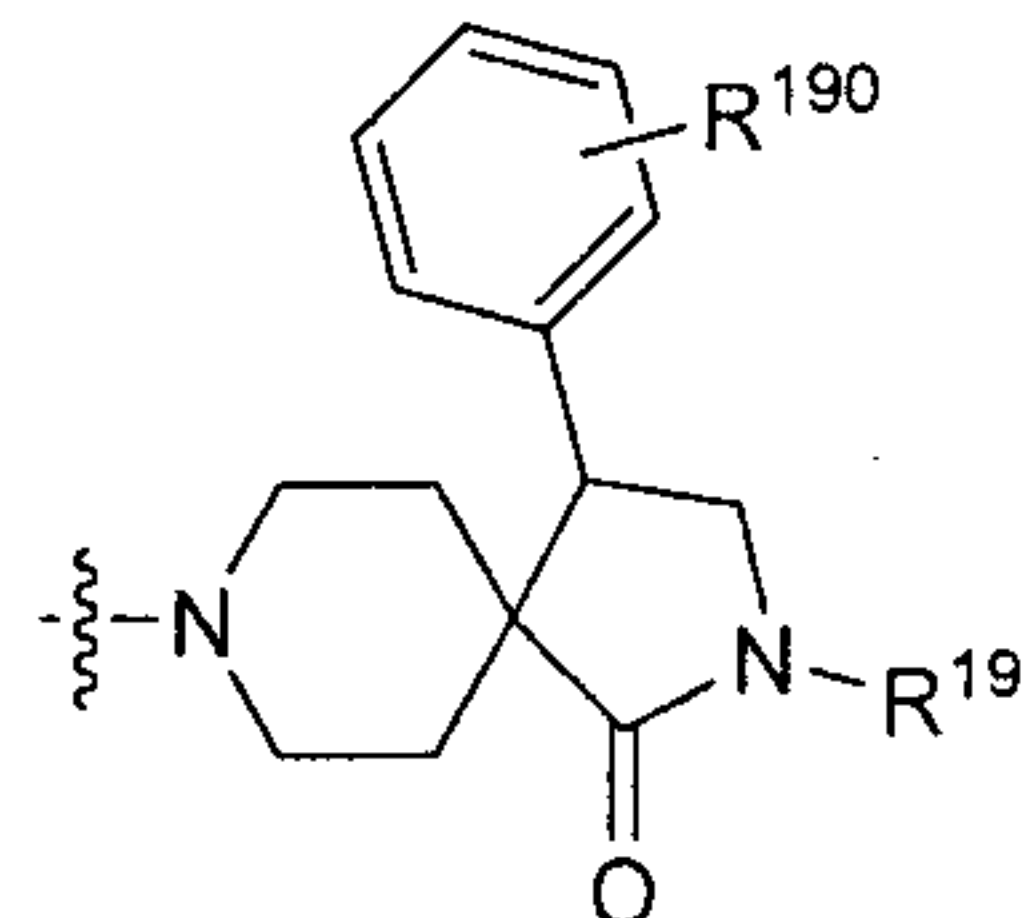
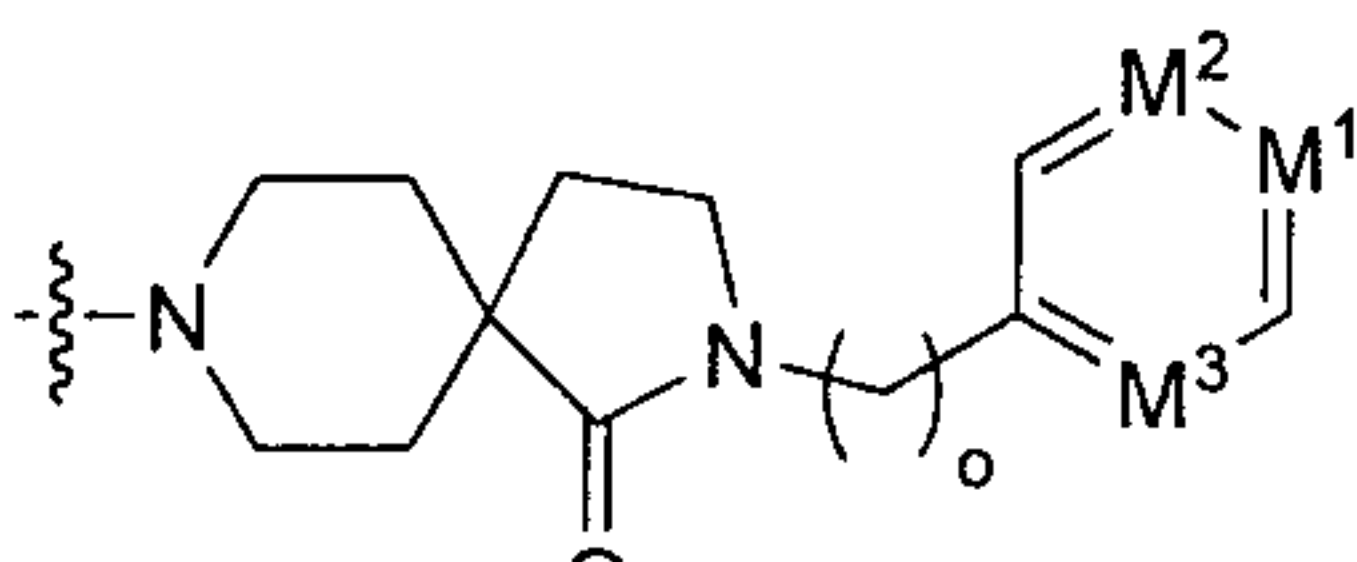
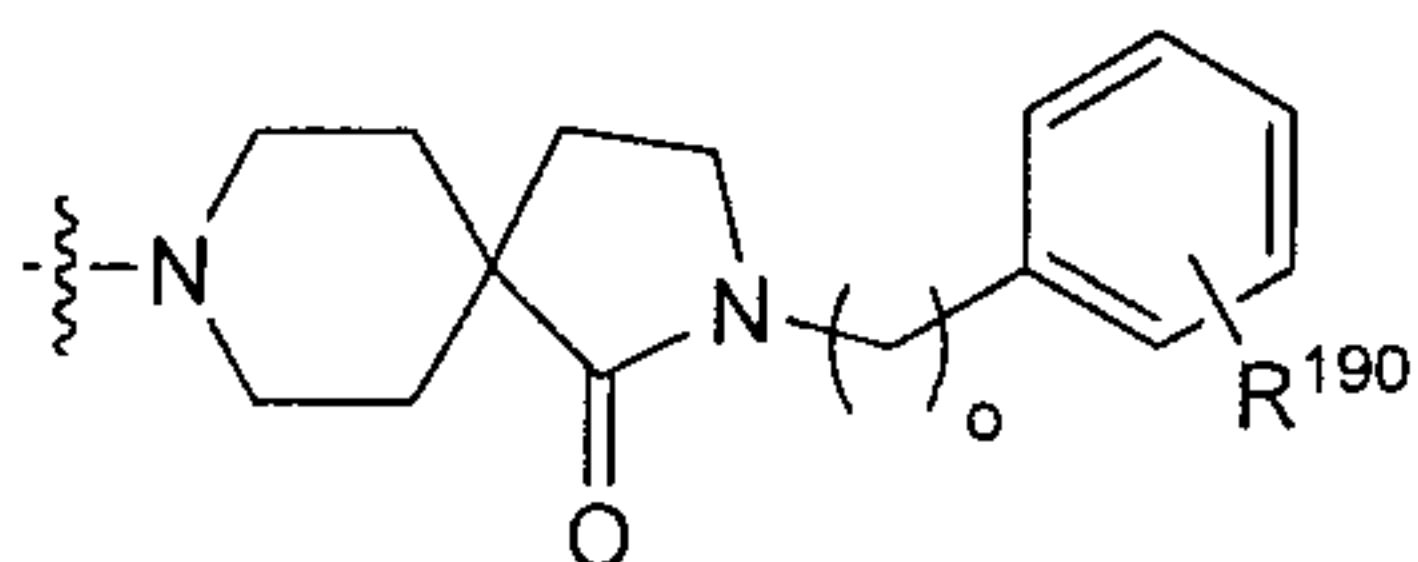
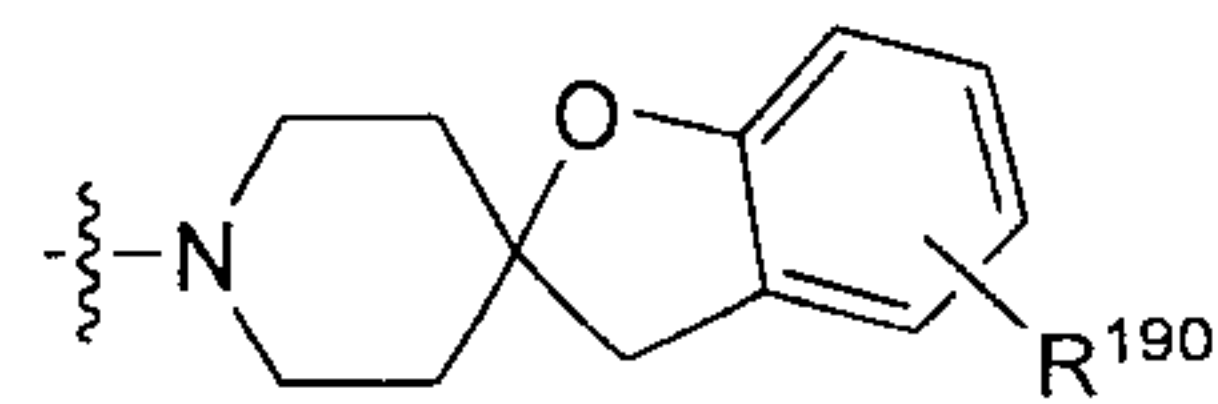
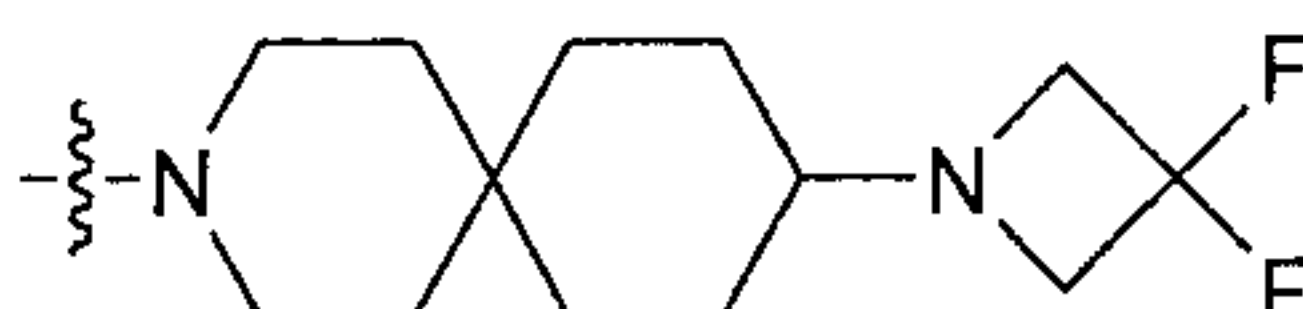
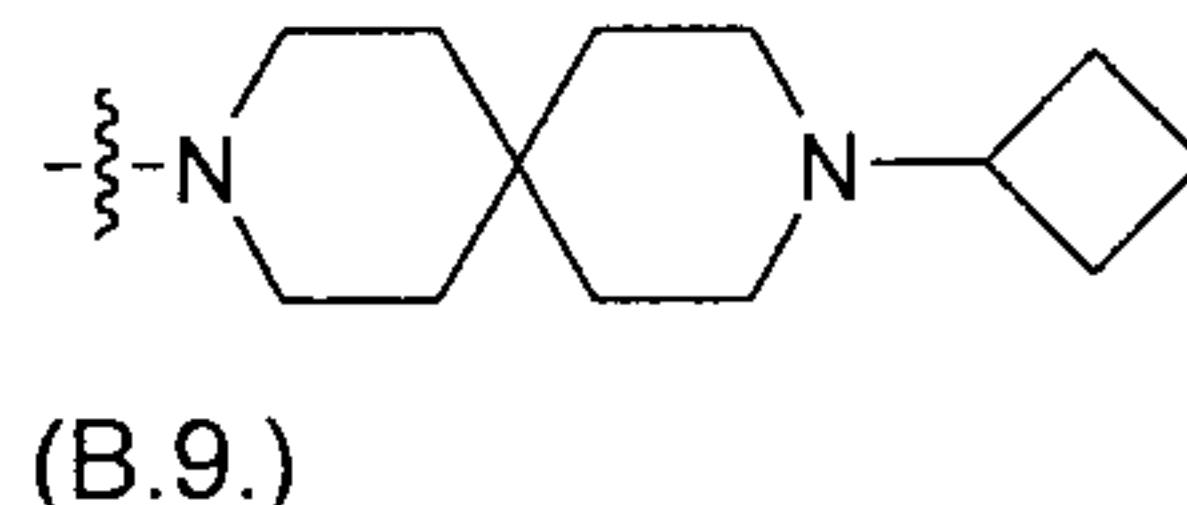
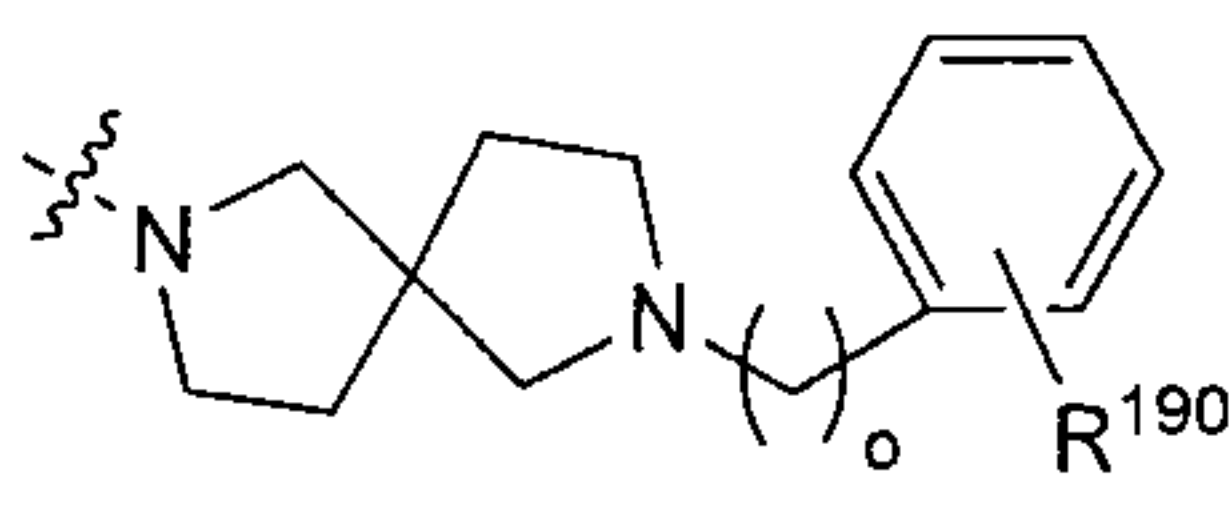
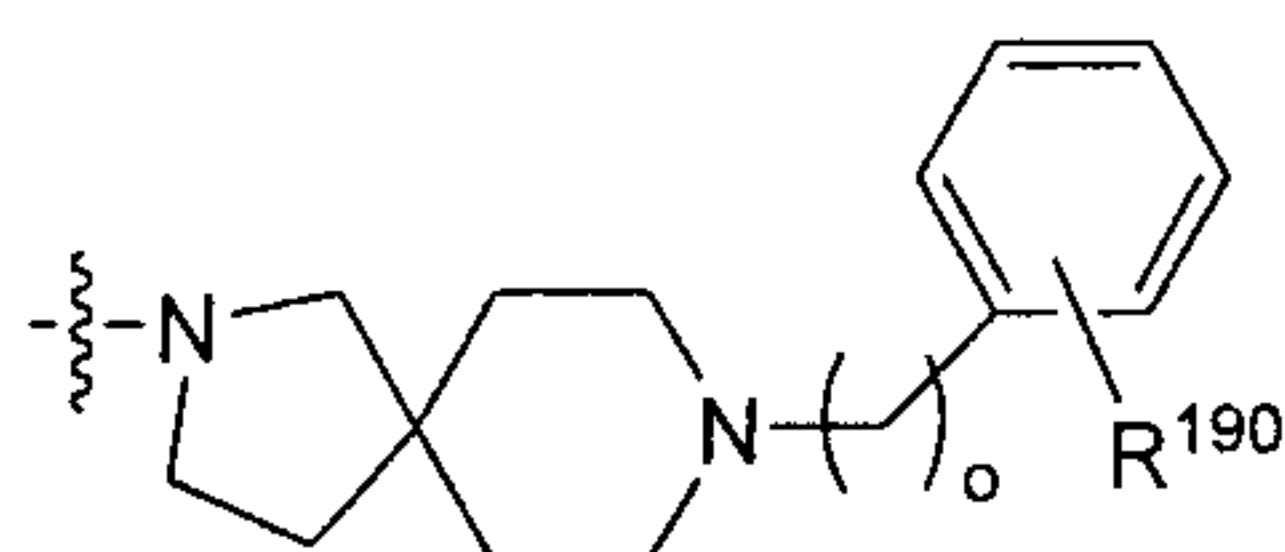
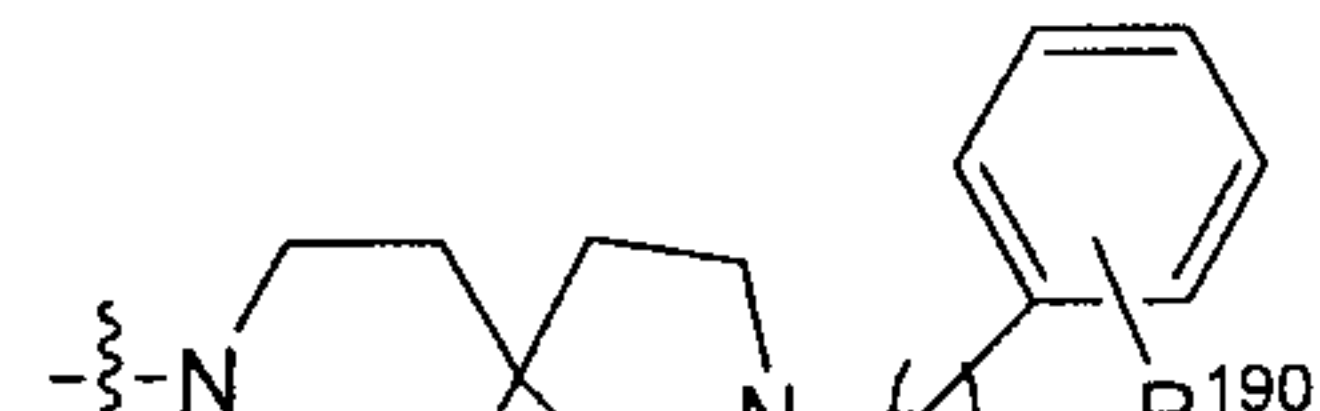
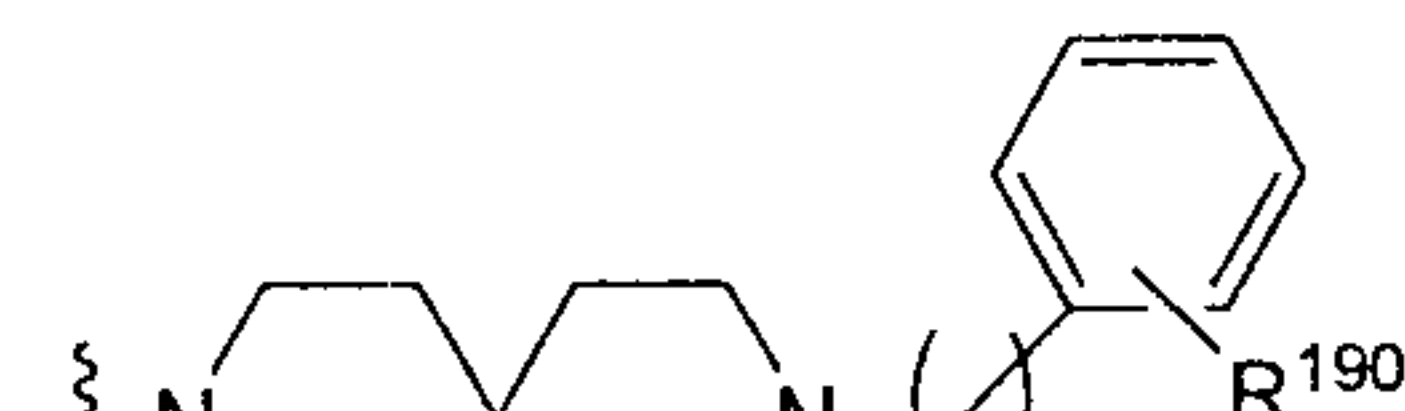
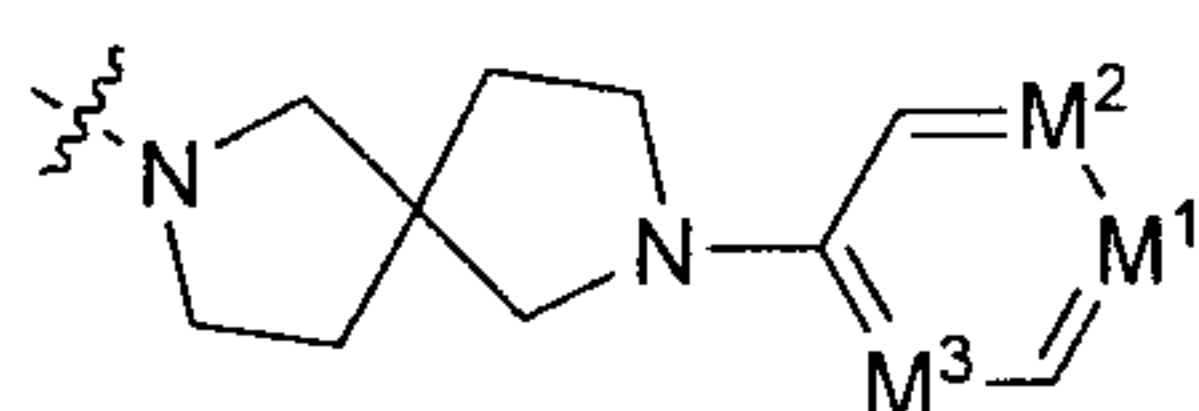
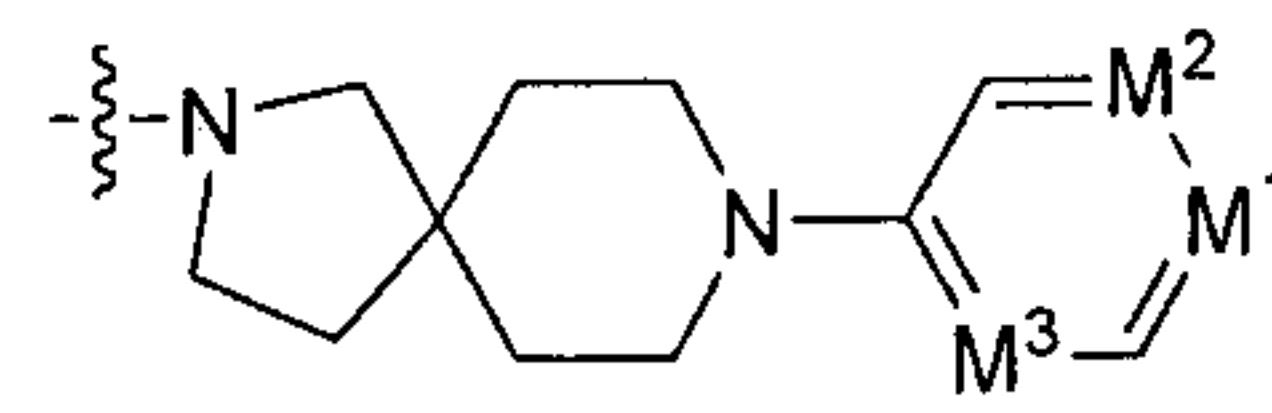
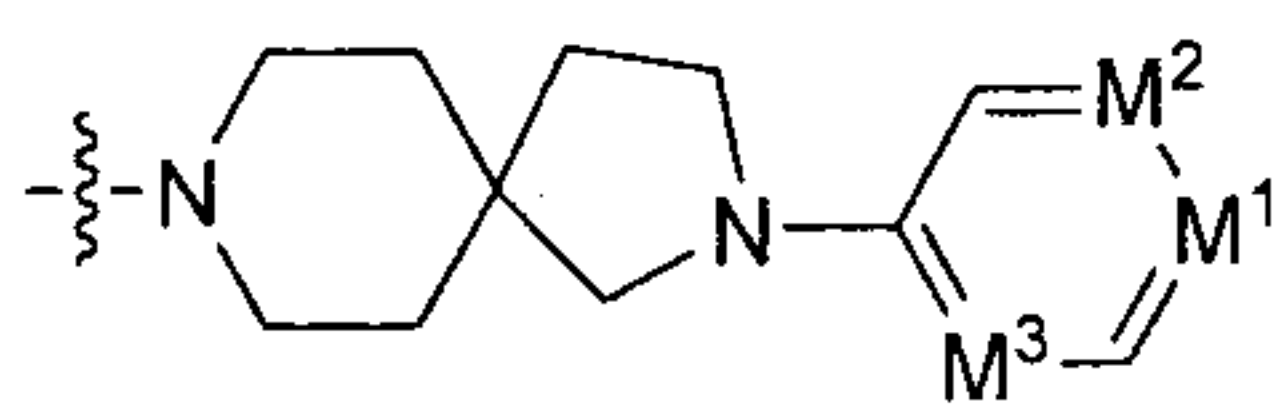
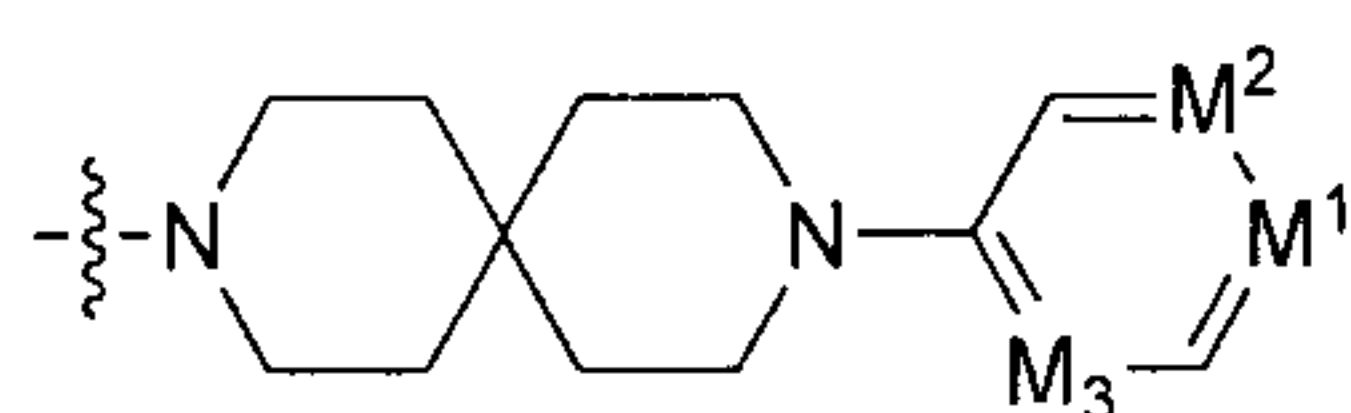
R¹²⁶ stands for H; C₁₋₆ alkyl; C₃₋₆ cycloalkyl; phenyl or pyridyl; or for C₃₋₆ cycloalkyl, phenyl or pyridyl bound by a C₁₋₃ alkylene group, each unsubstituted or mono- or polysubstituted with identical or different substituents, wherein the substituents of phenyl and pyridyl are preferably mutually independently selected from the group consisting of F, Cl, CF₃, C₁₋₄ alkyl, OCF₃, OH and O-C₁₋₄ alkyl.

GRA3454-WO
22nd December 2009

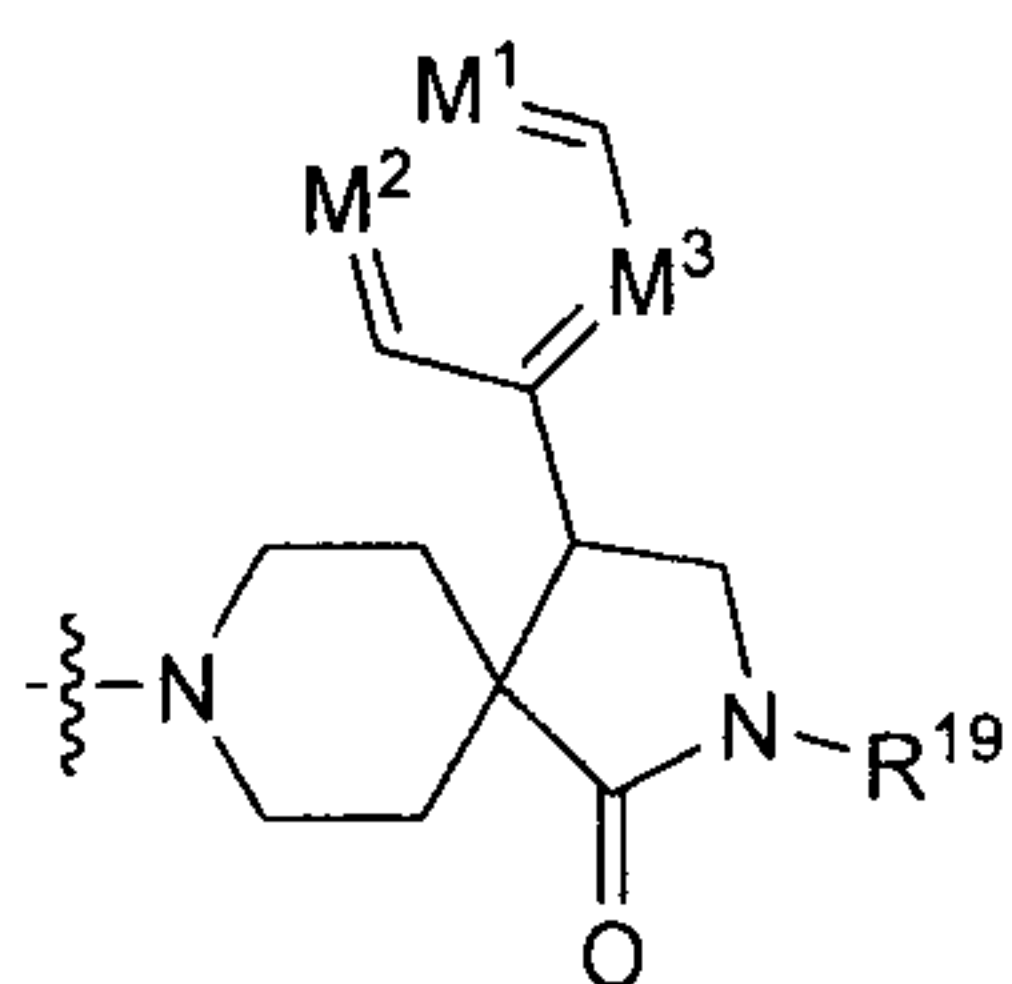
12. Compound according to one or more of claims 1 to 11, wherein
in the general formula (I) the following substructure (B)



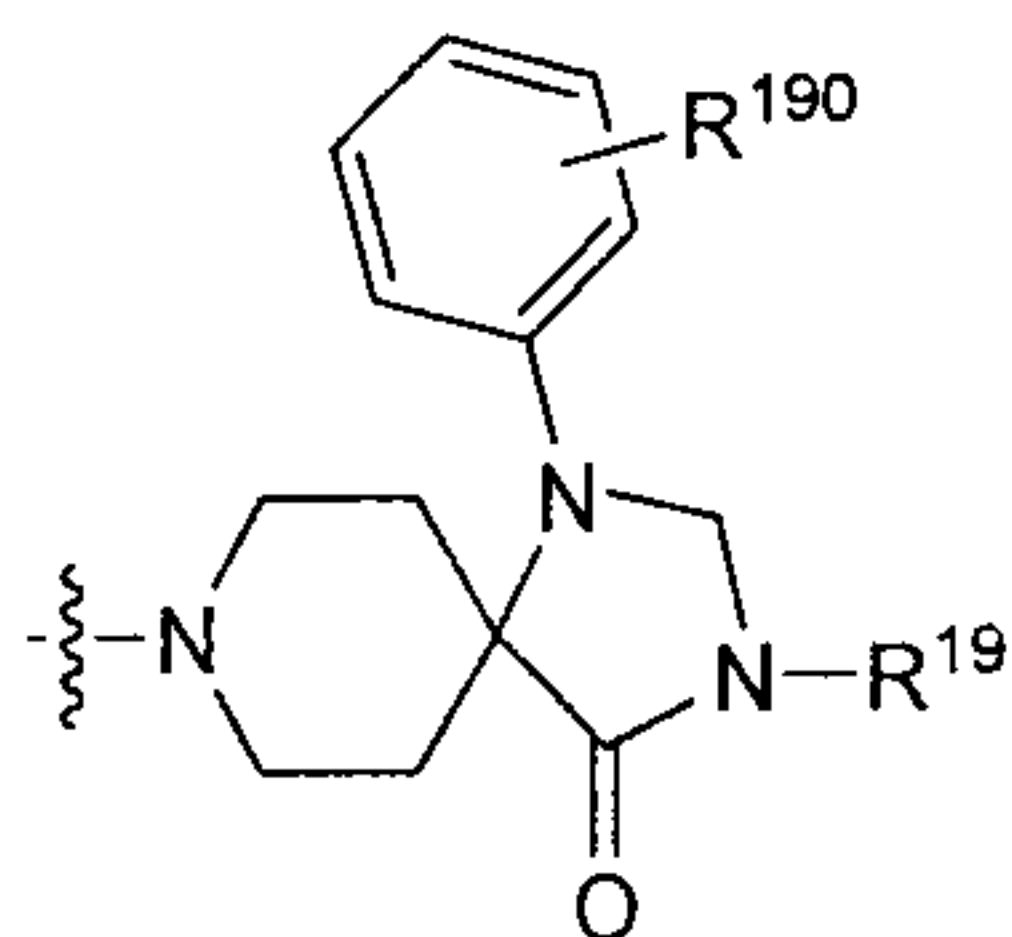
is selected from



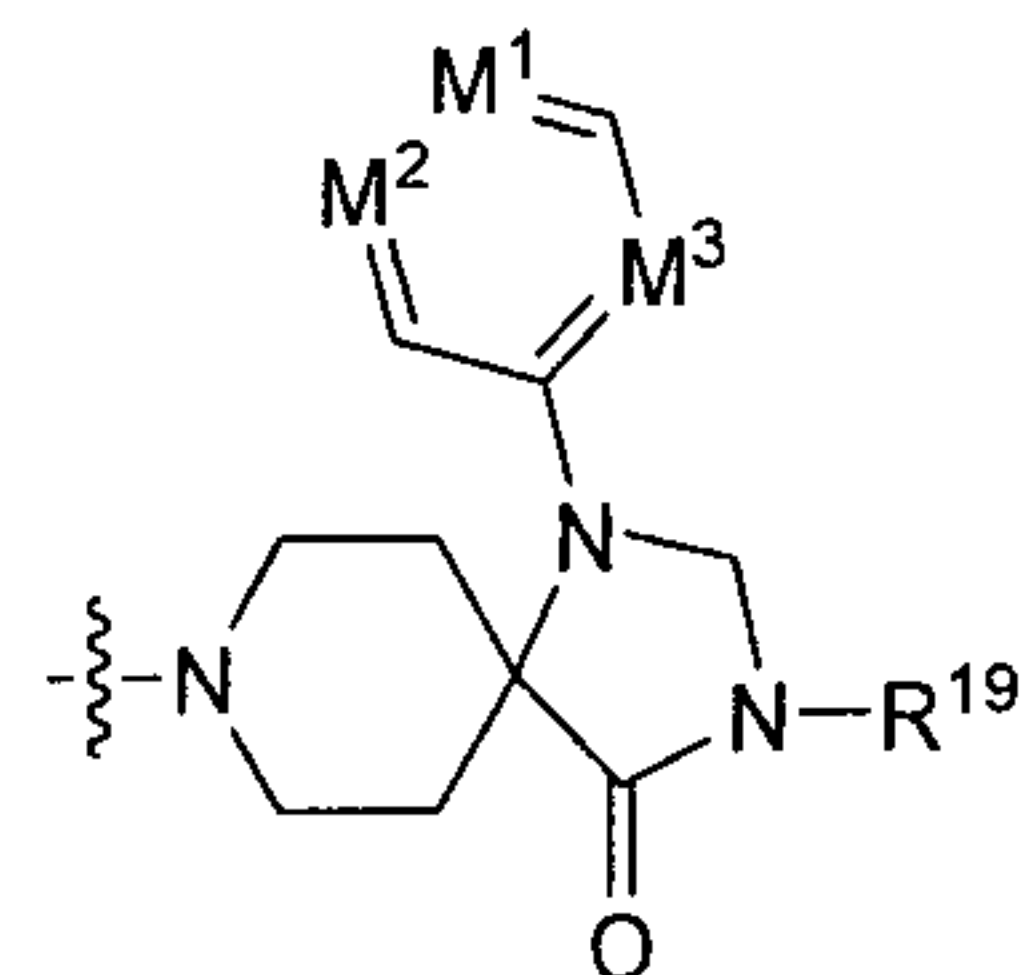
GRA3454-WO
22nd December 2009



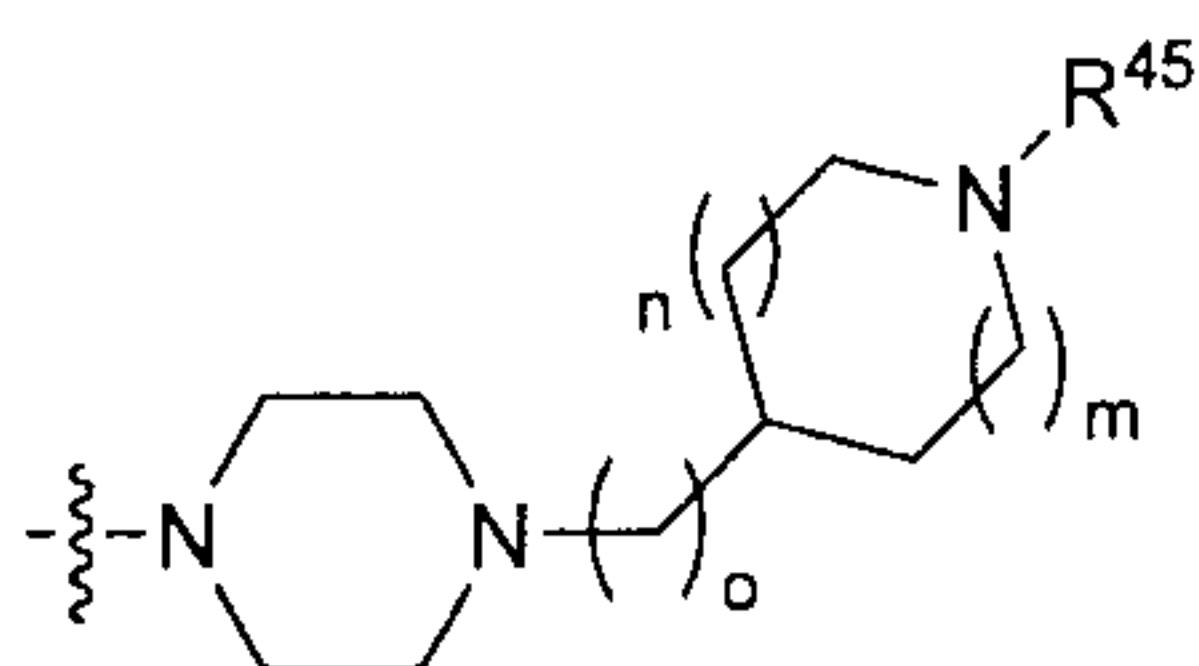
(B.16.)



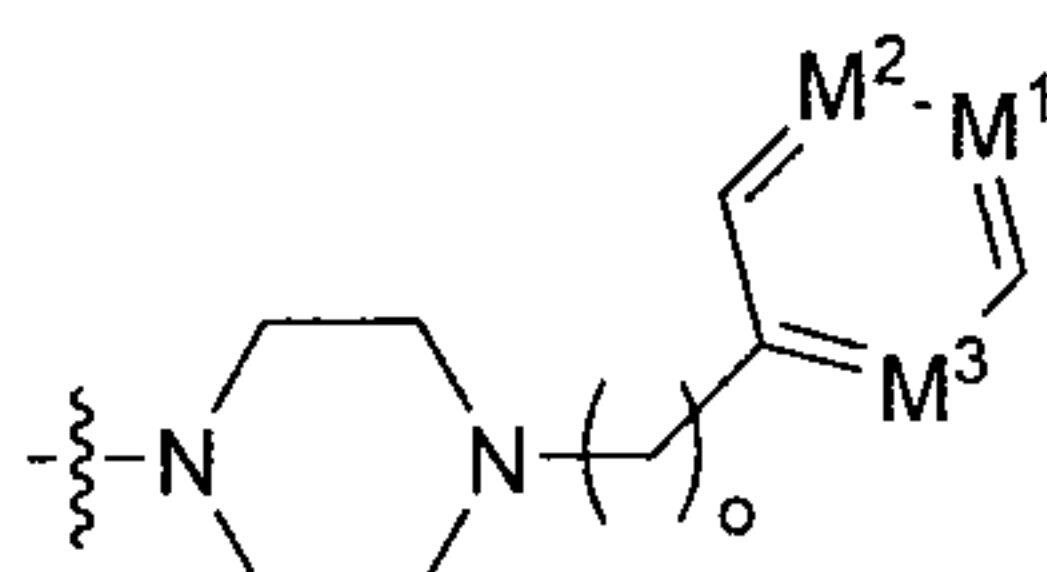
(B.17.)



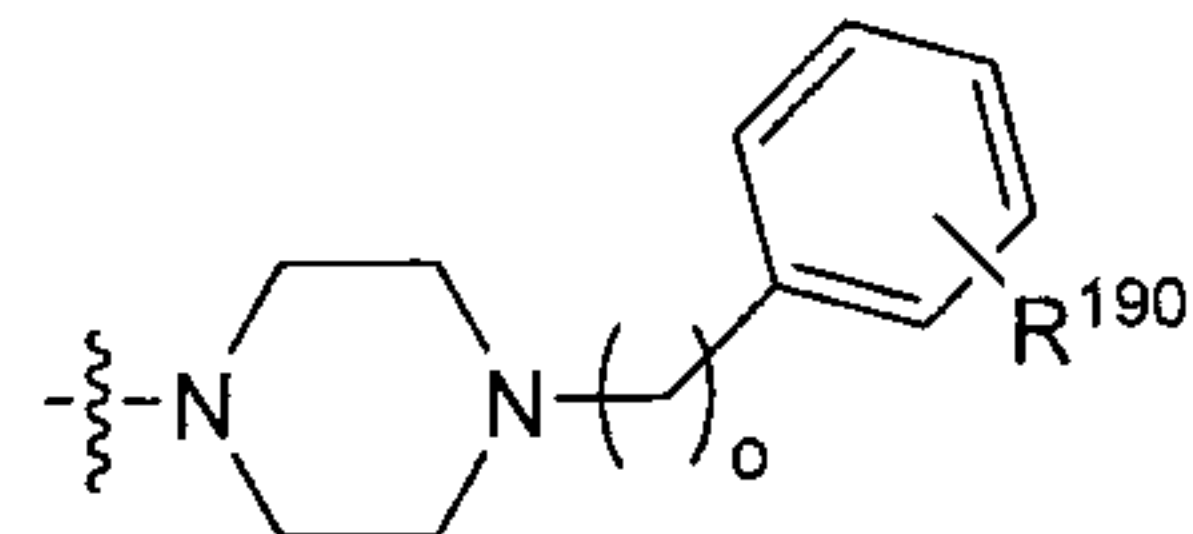
(B.18.)



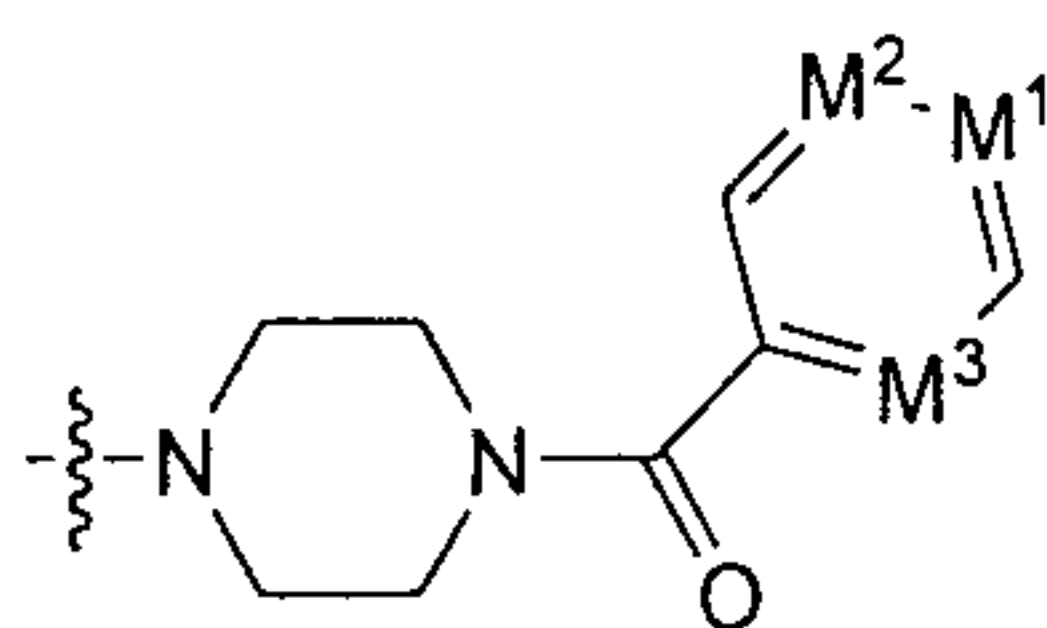
(B.19.)



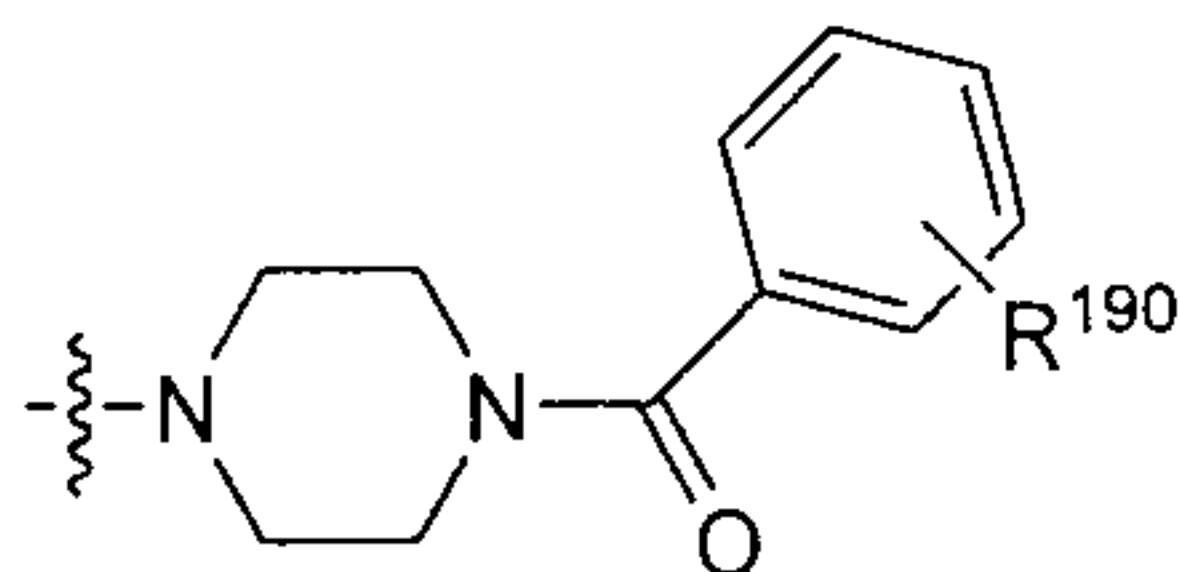
(B.20.)



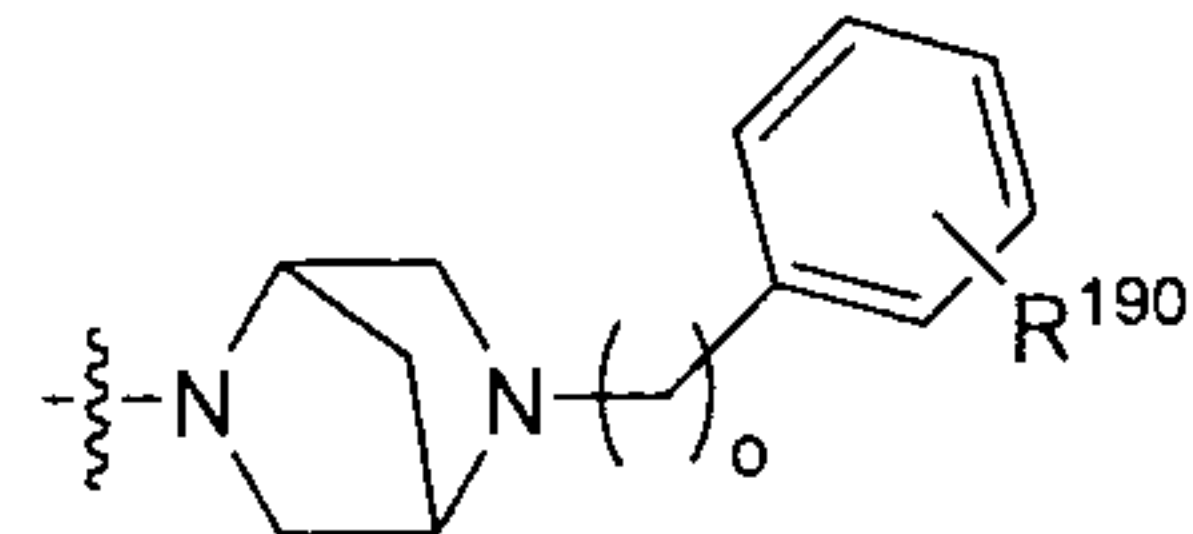
(B.21.)



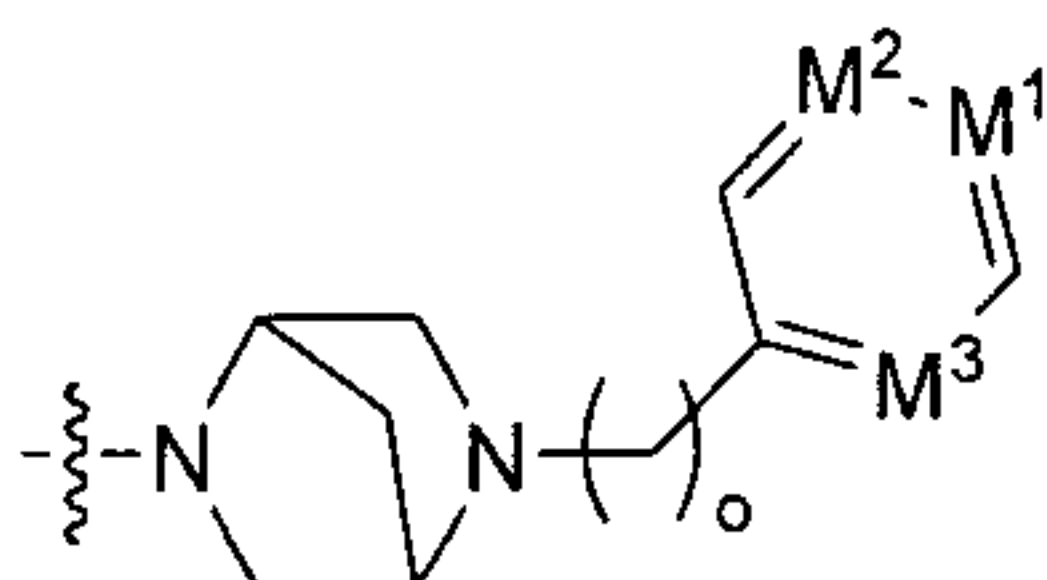
(B.22.)



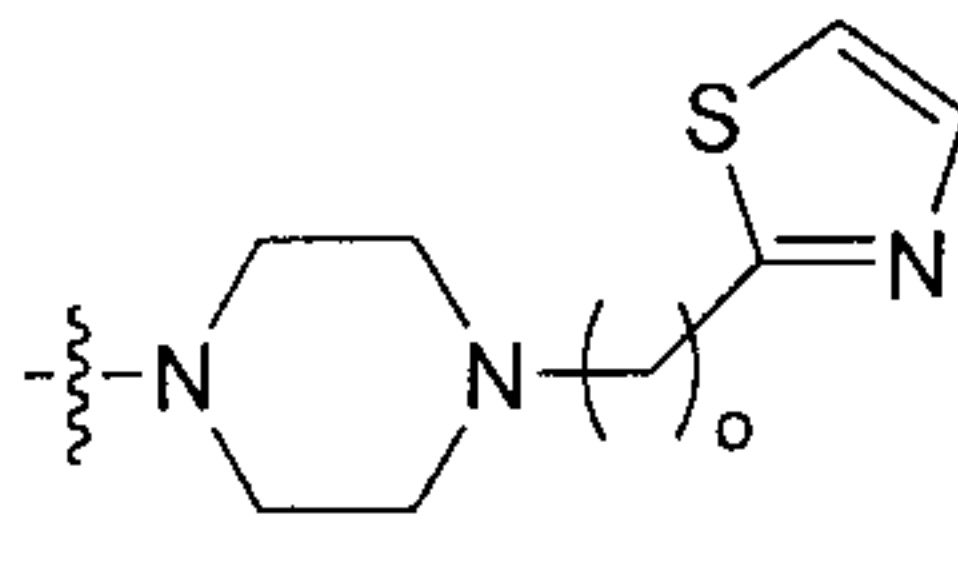
(B.23.)



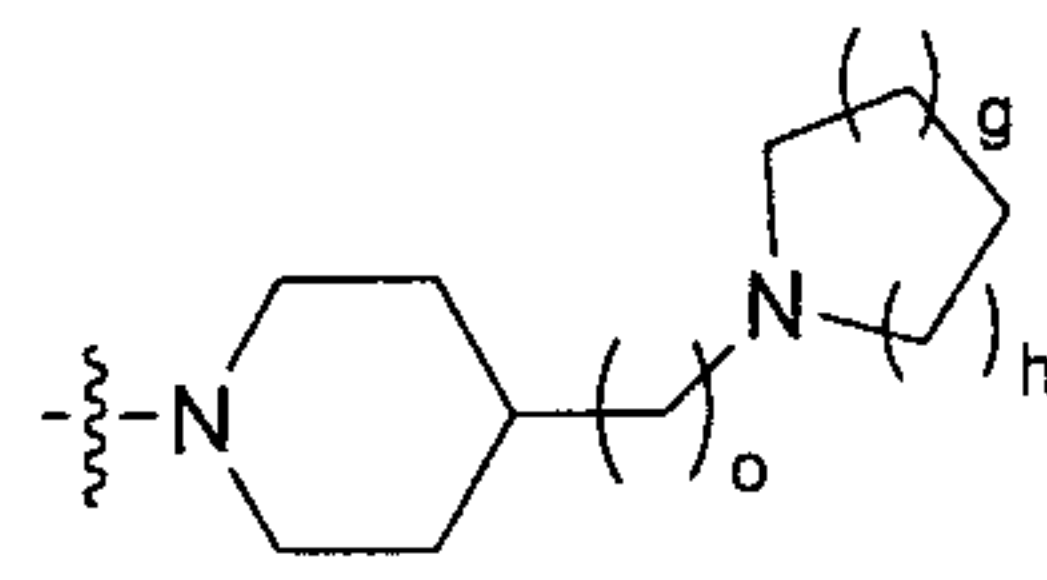
(B.24.)



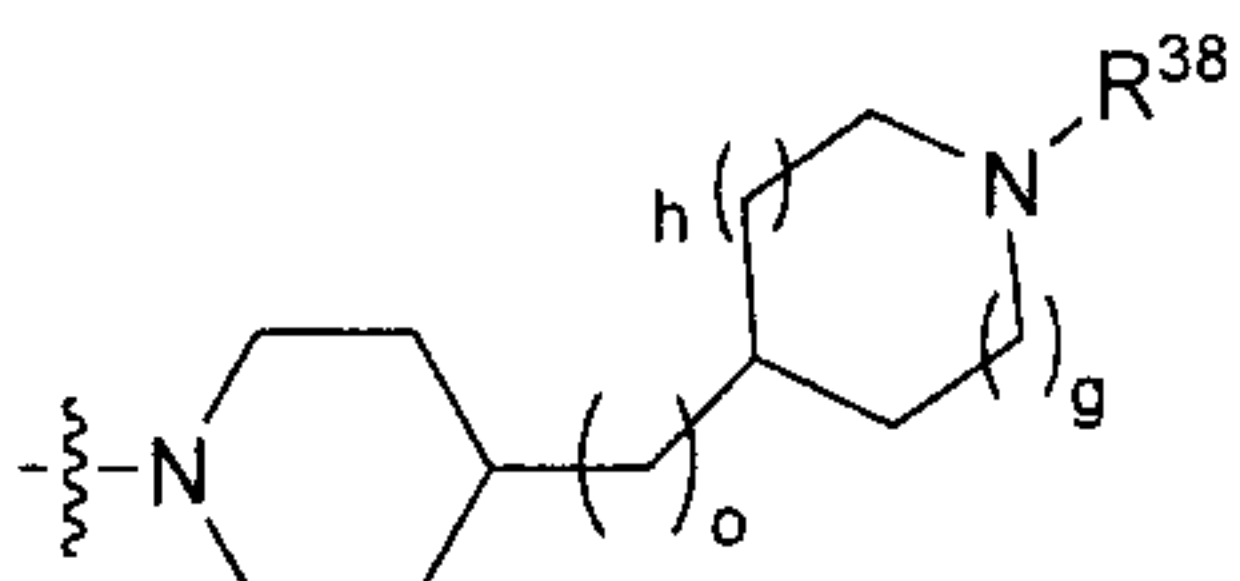
(B.25.)



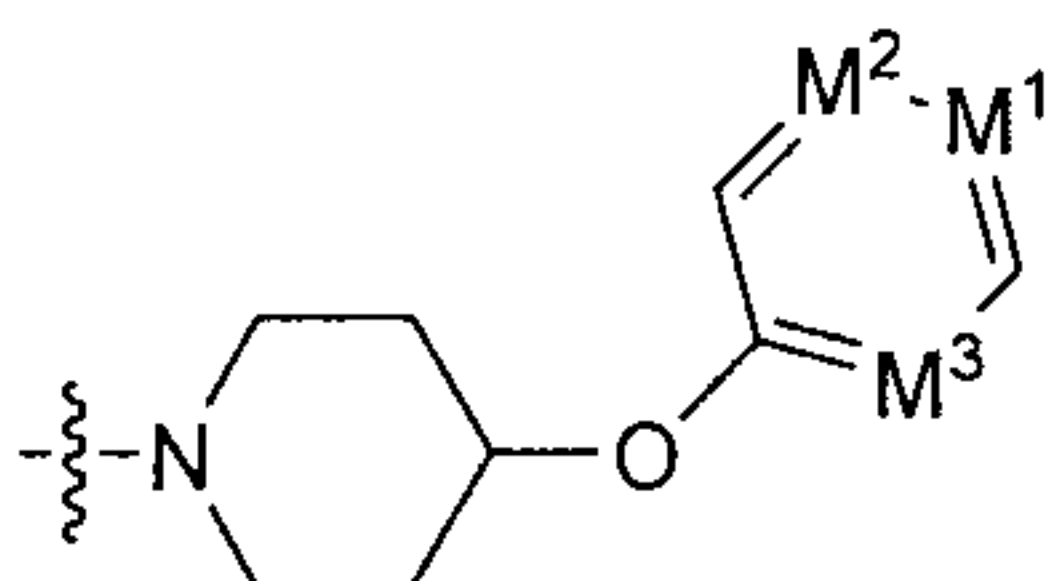
(B.26.)



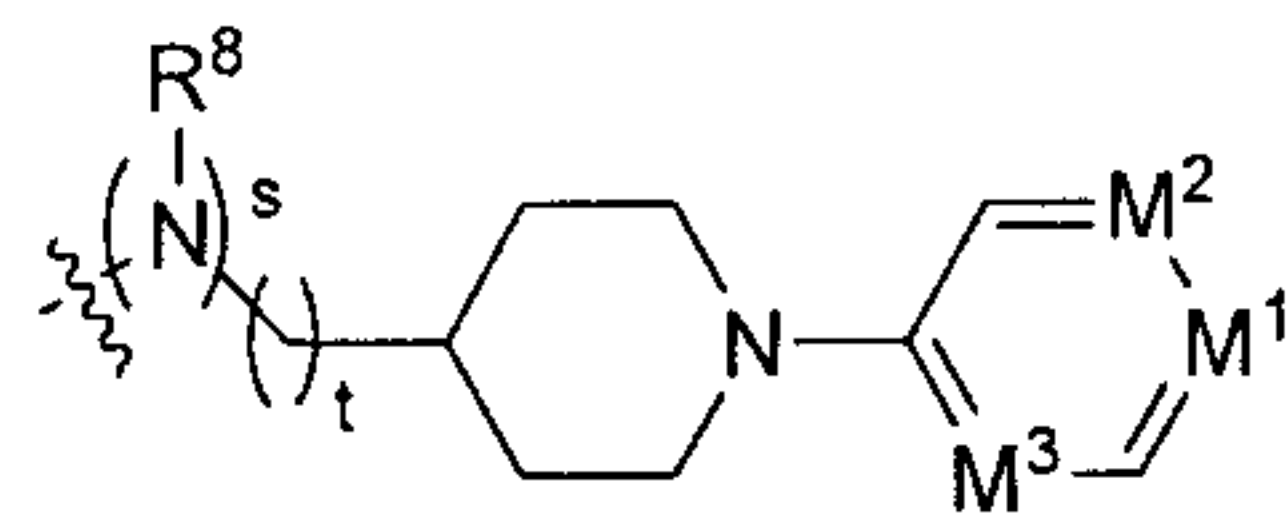
(B.27.)



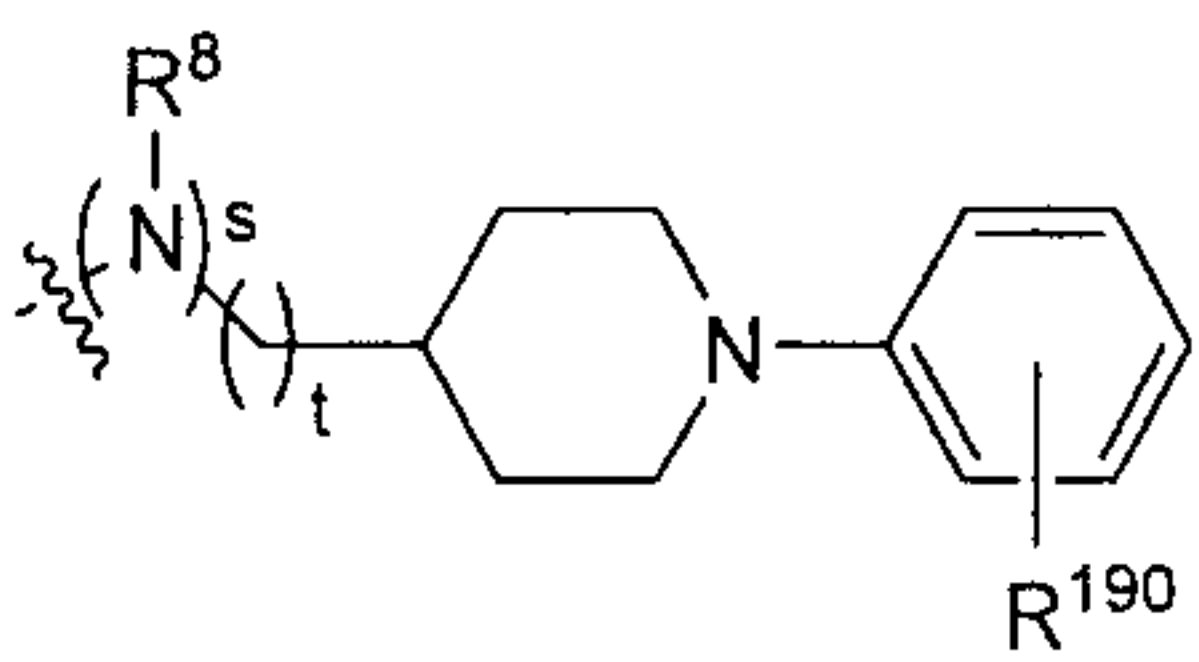
(B.28.)



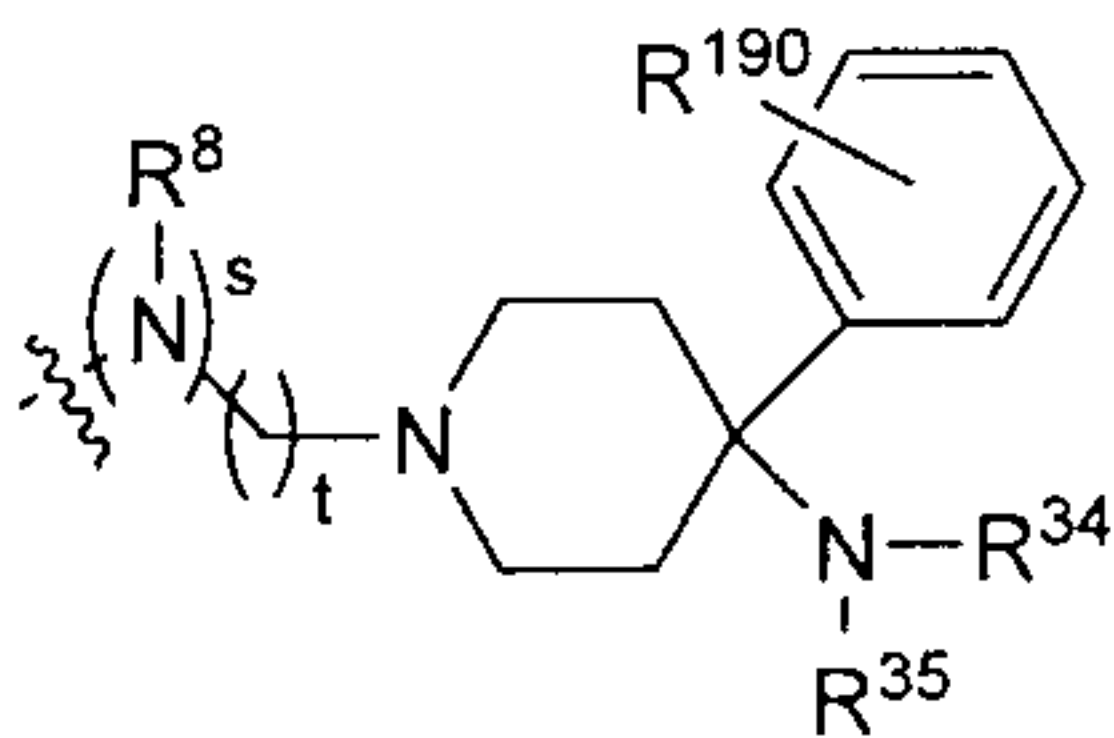
(B.29.)



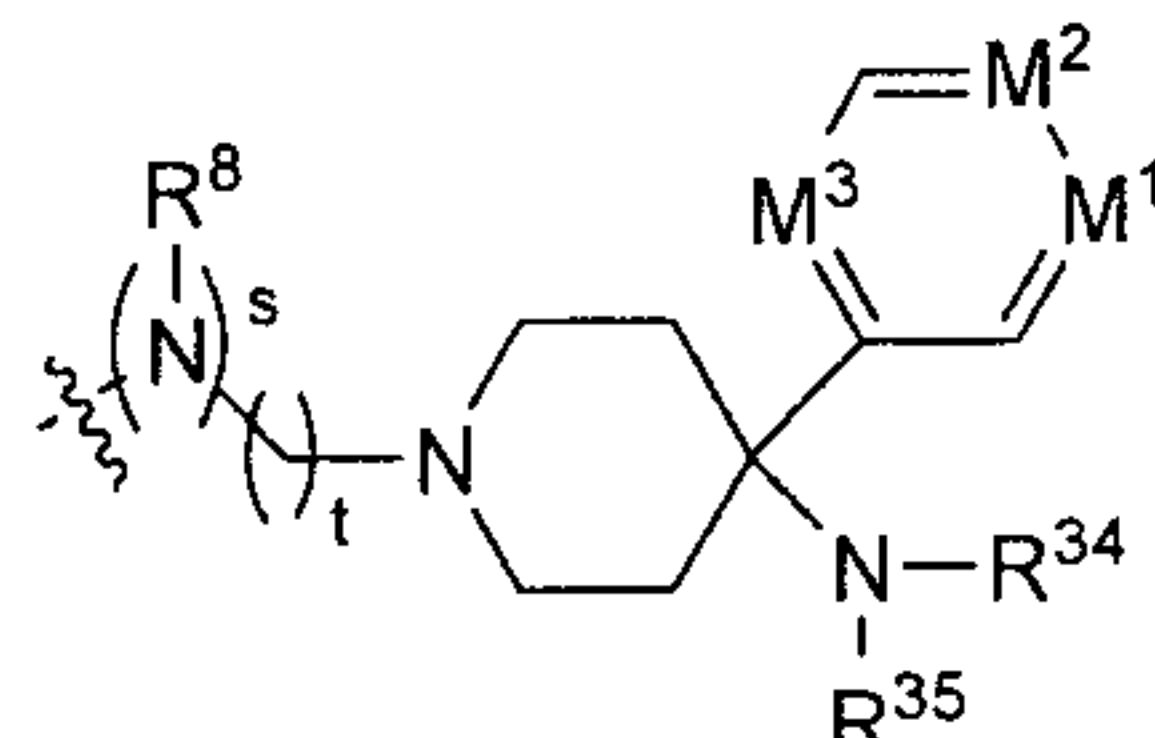
(B.30.)



(B.31.)

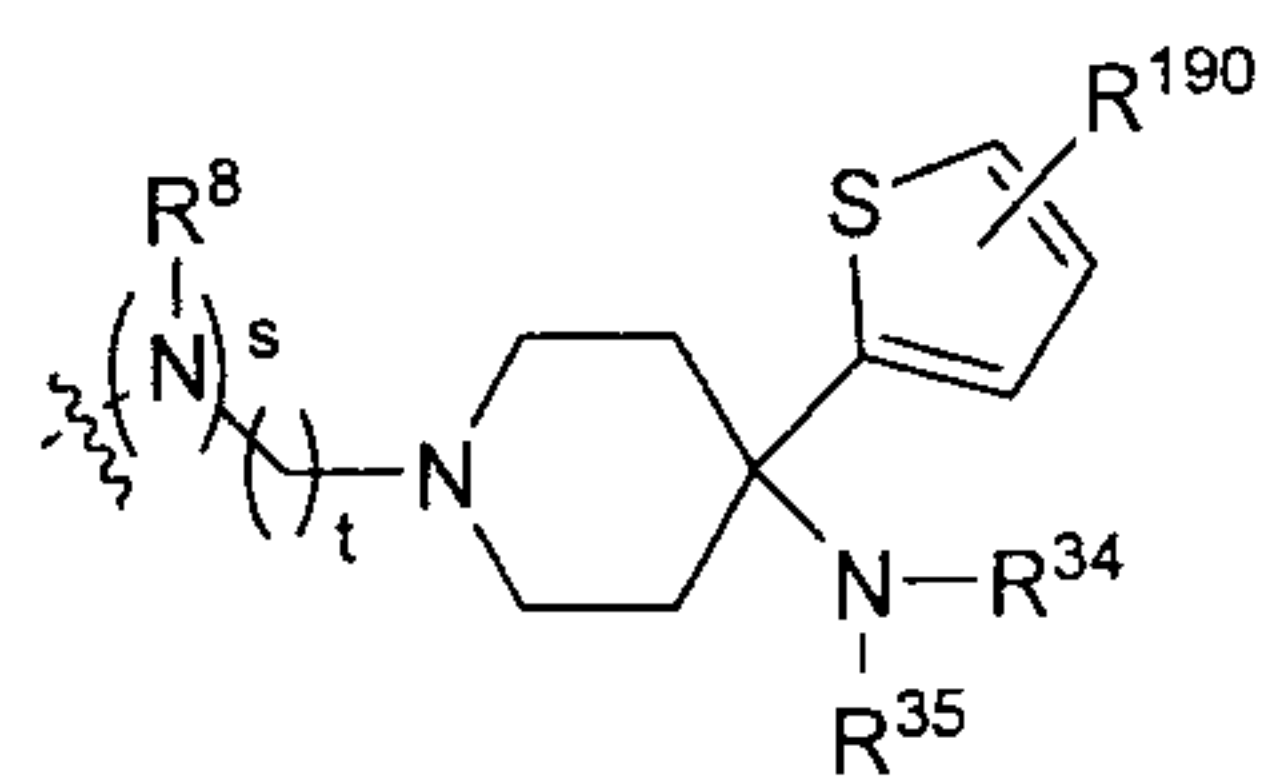


(B.32.)

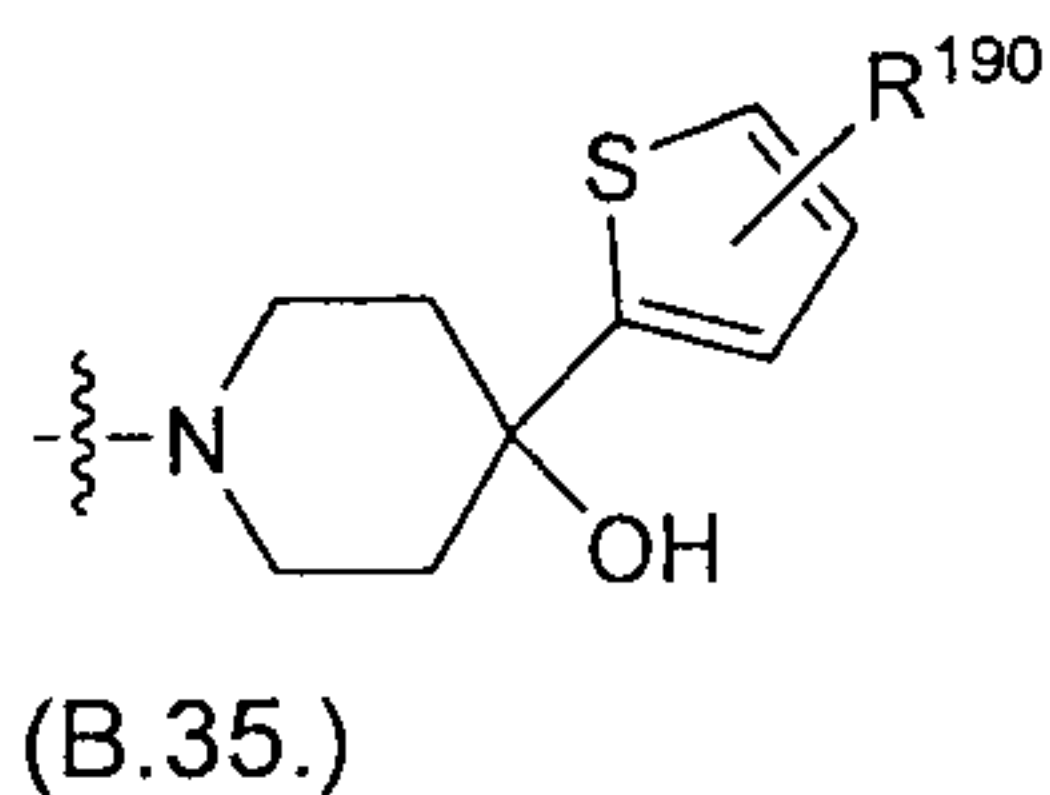


(B.33.)

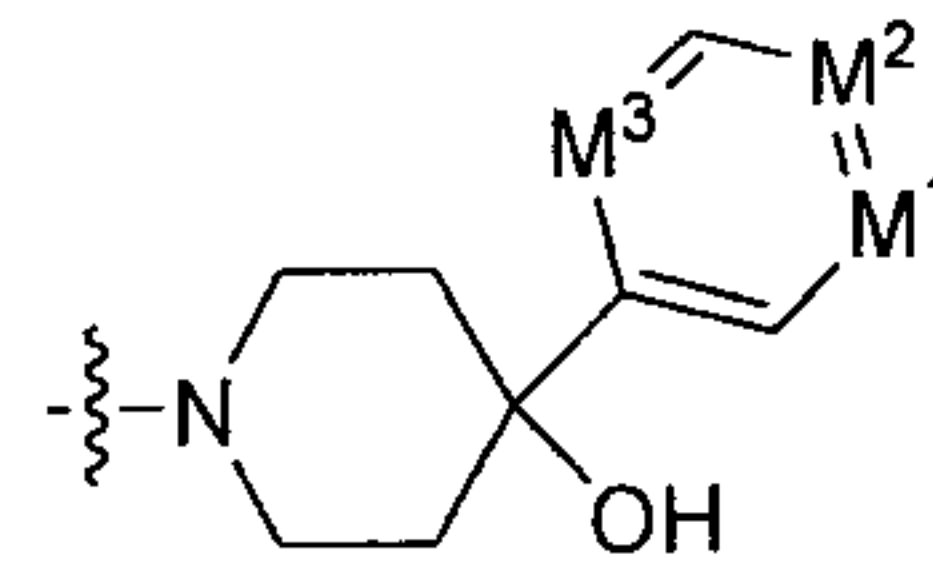
GRA3454-WO
22nd December 2009



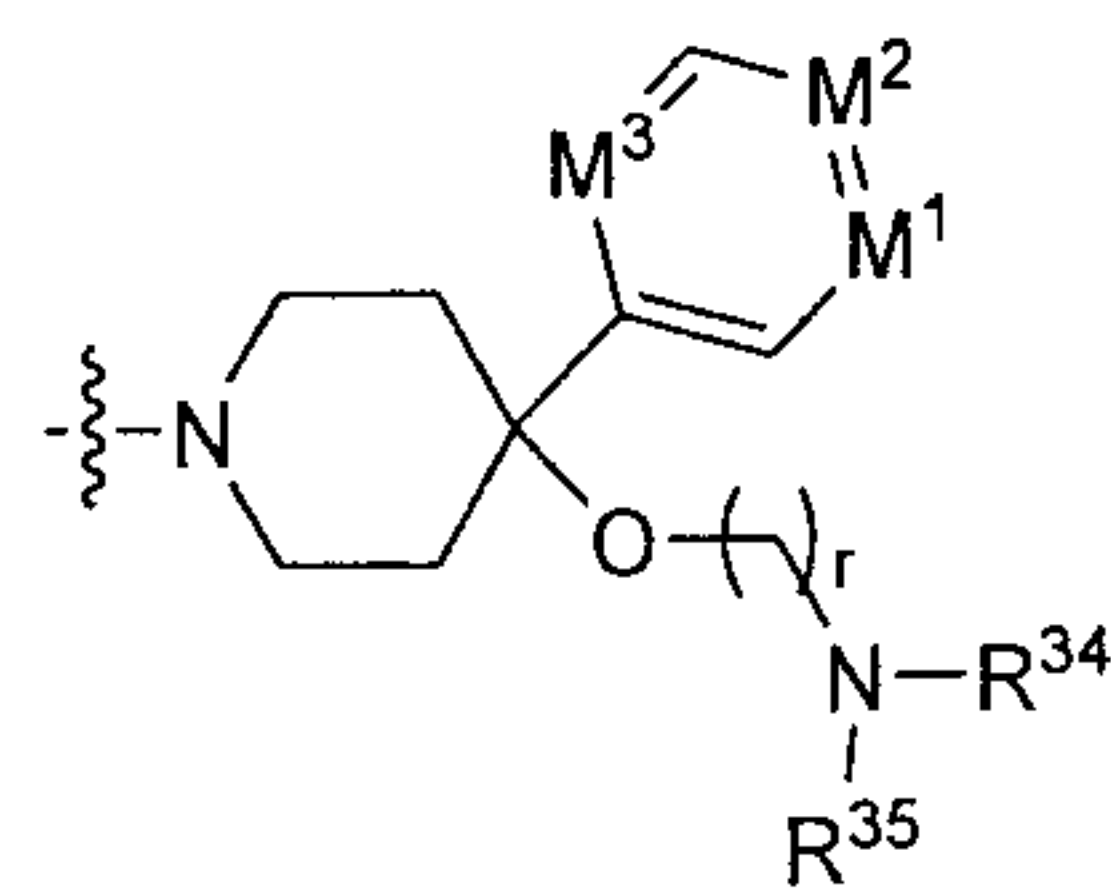
(B.34.)



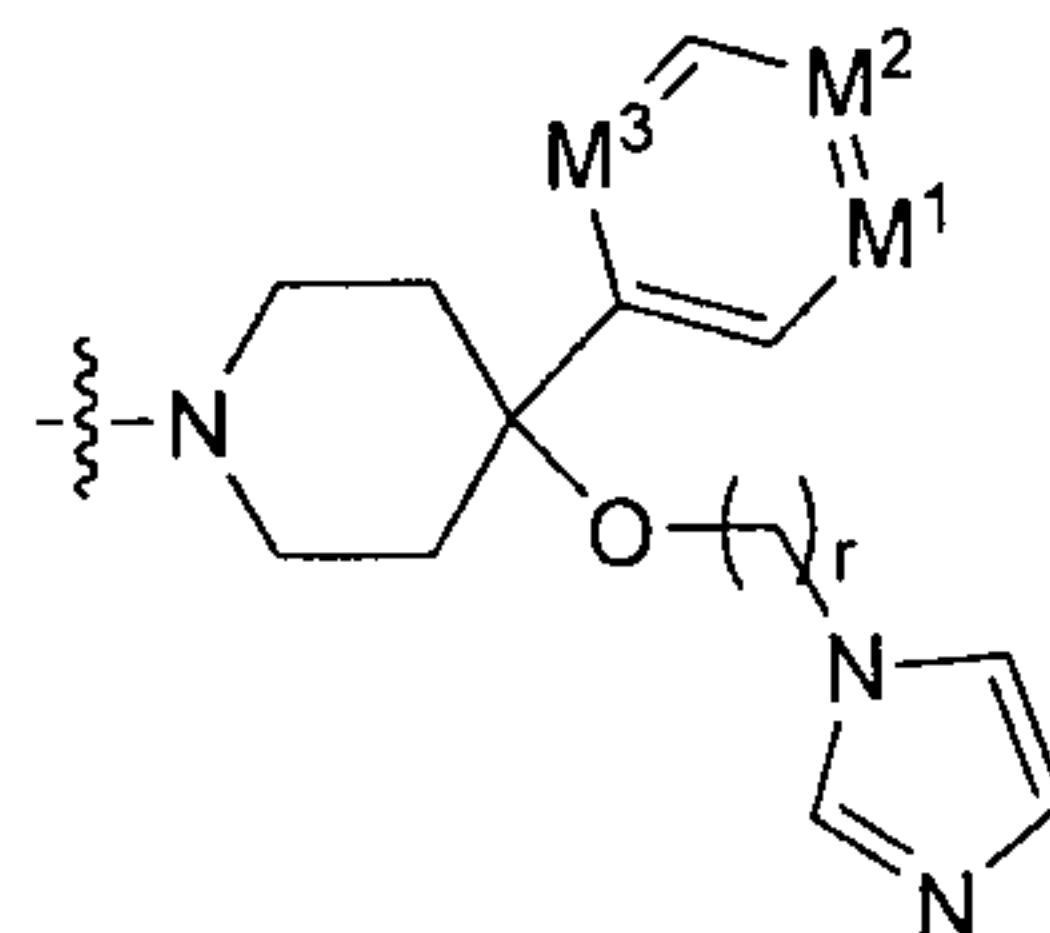
(B.35.)



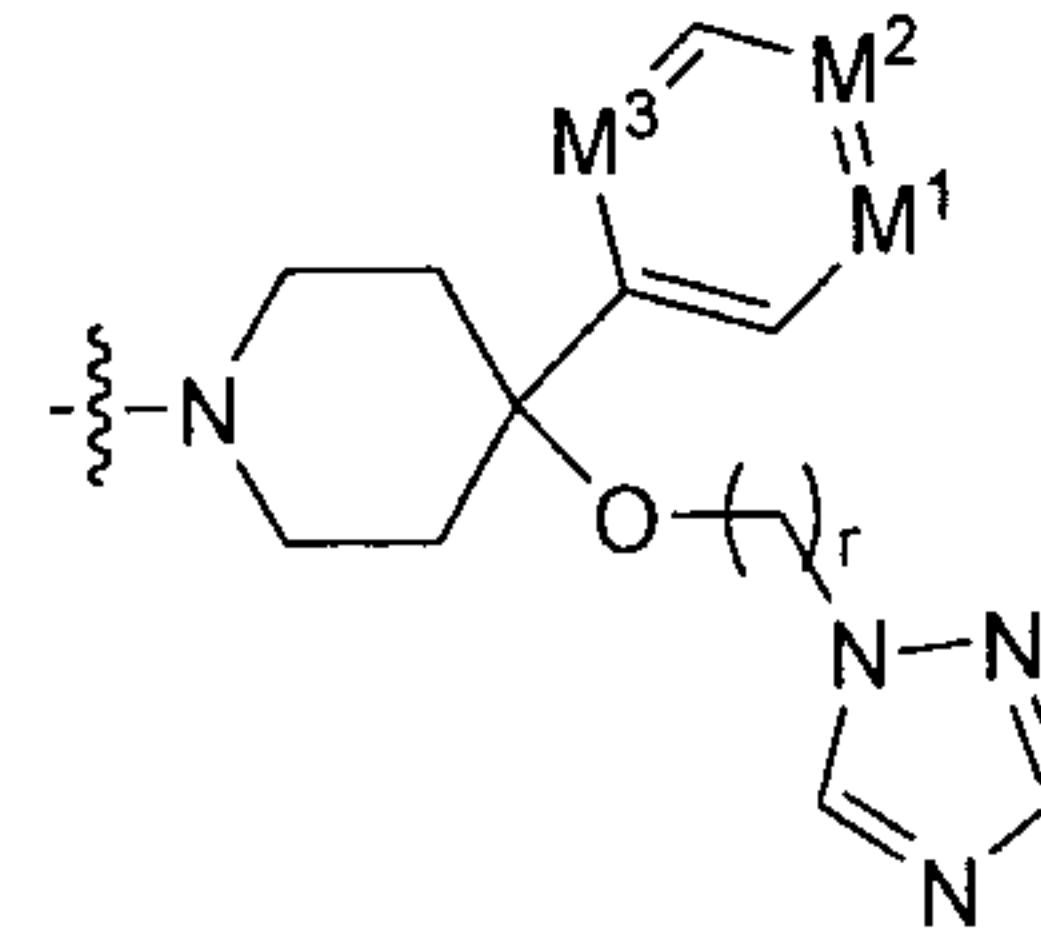
(B.36.)



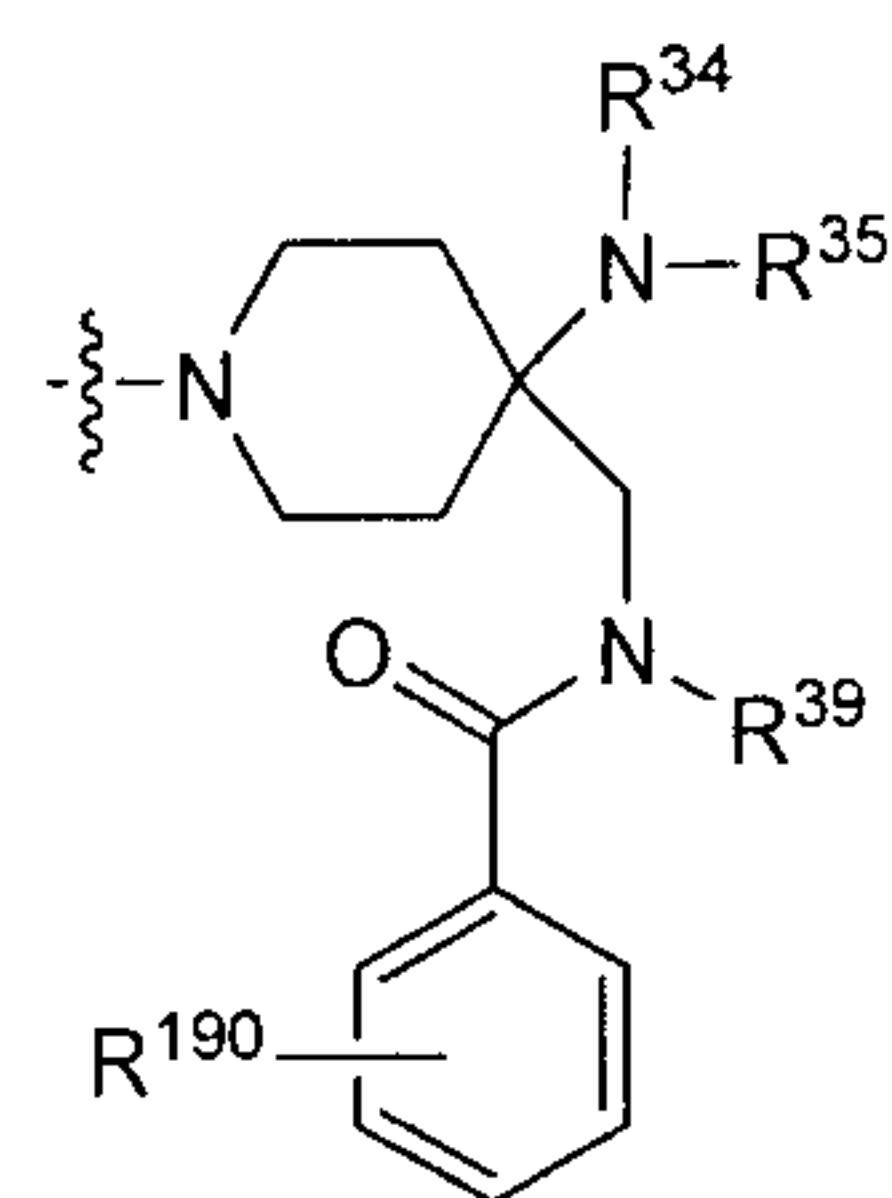
(B.37.)



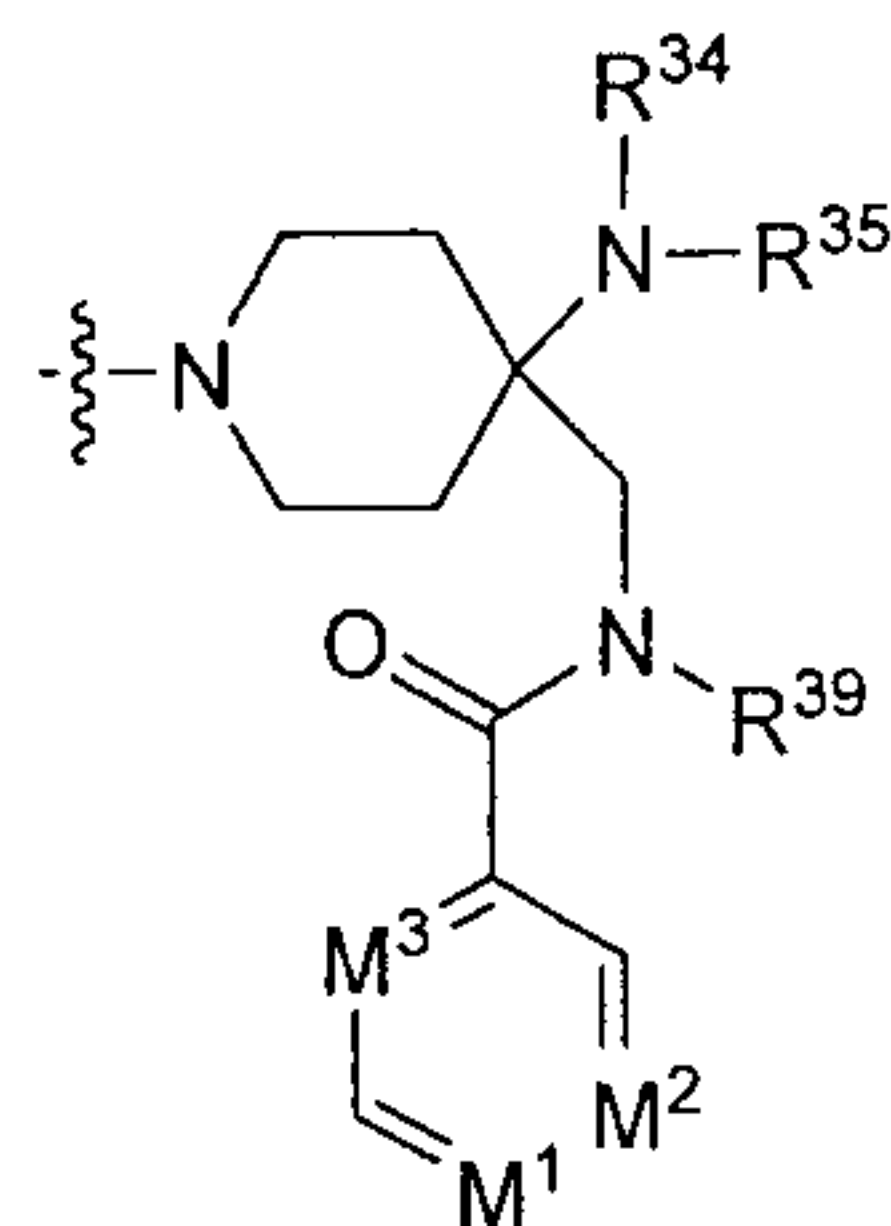
(B.38.)



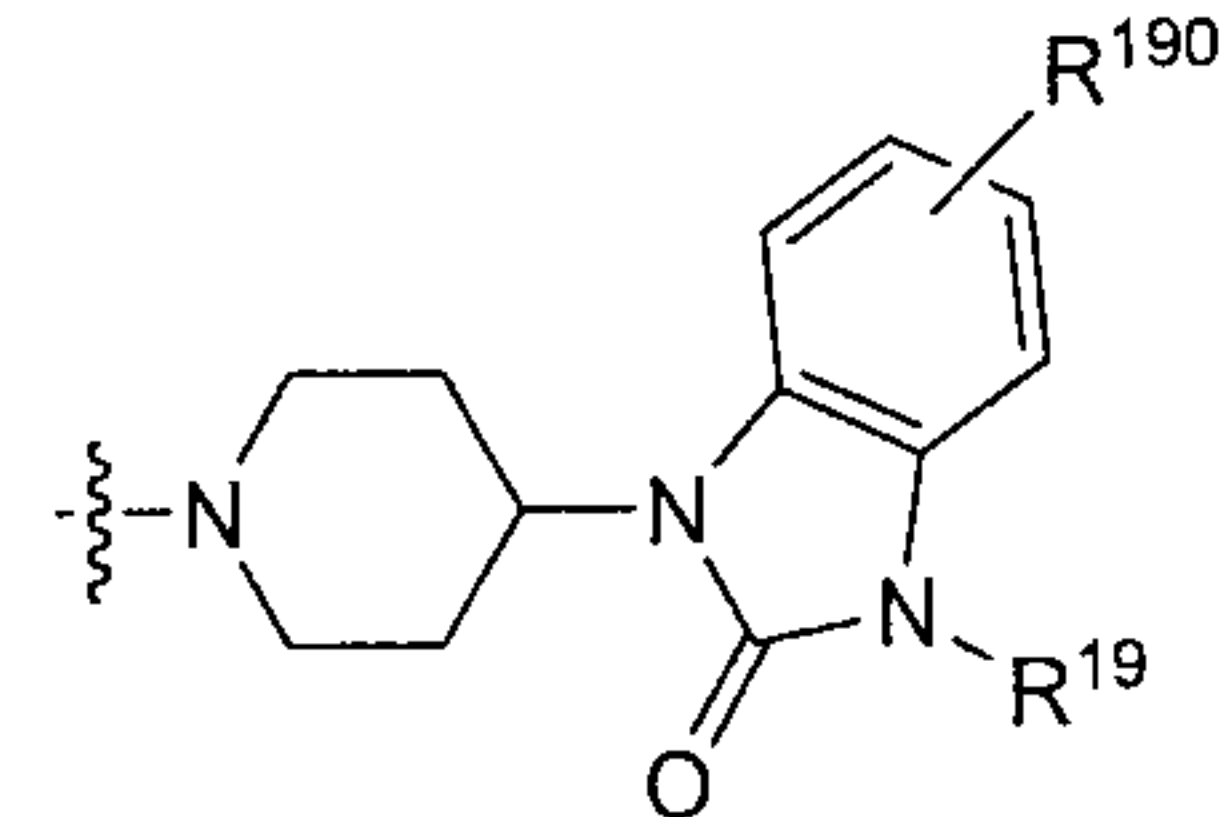
(B.39.)



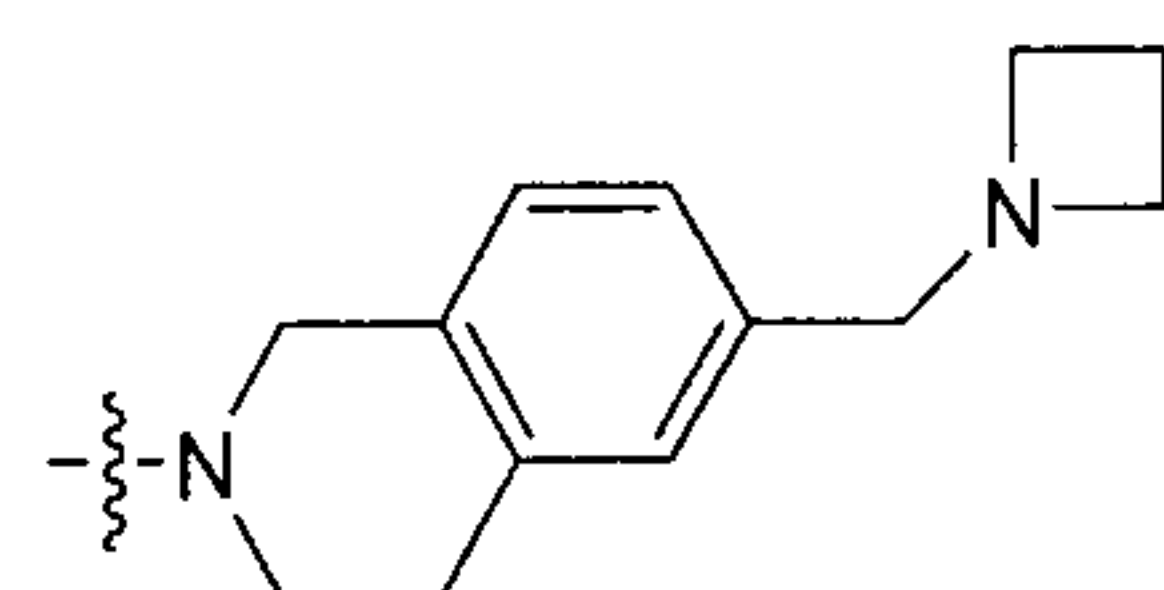
(B.40.)



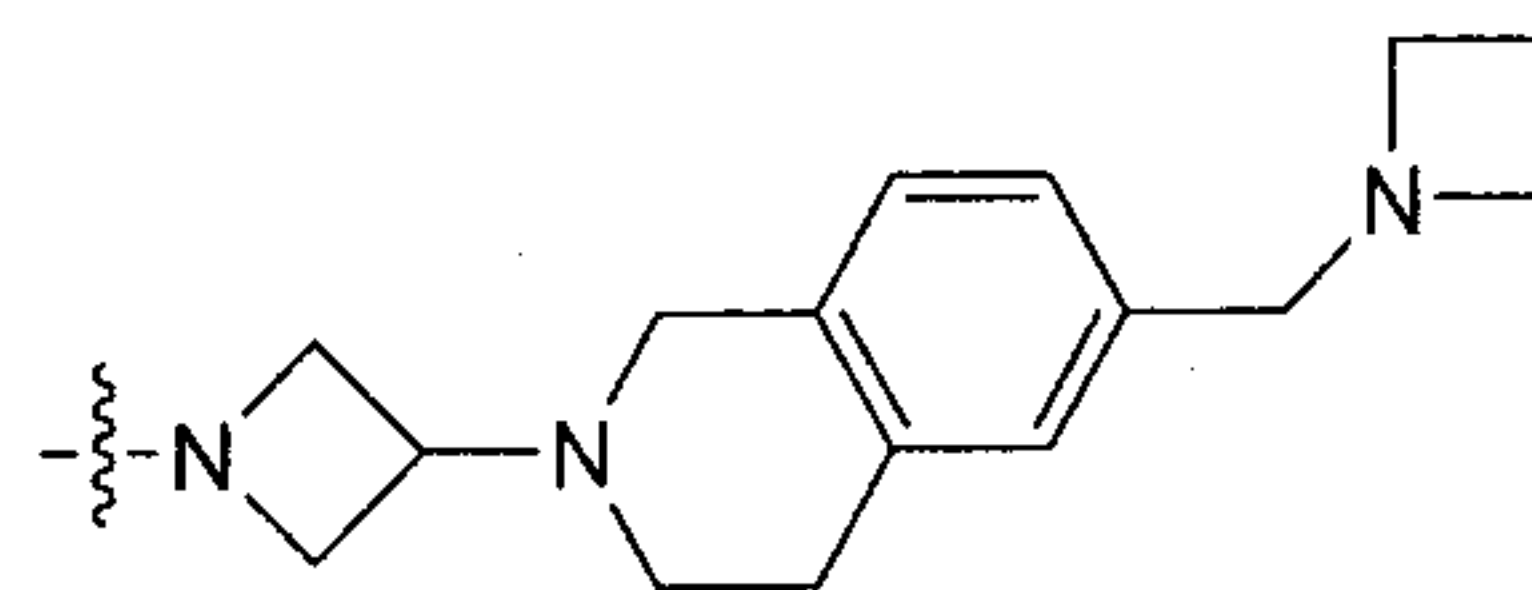
(B.40.)



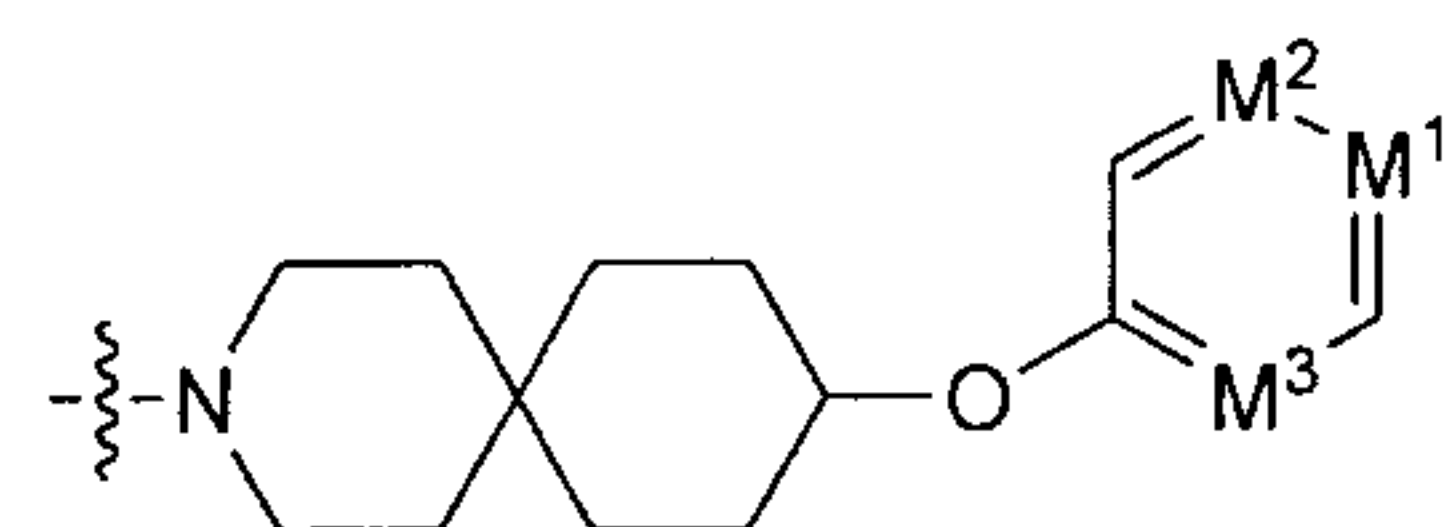
(B.41.)



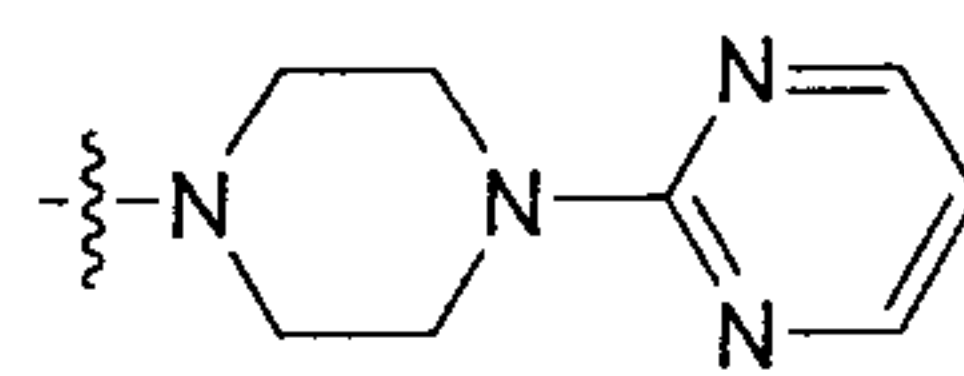
(B.42.) or



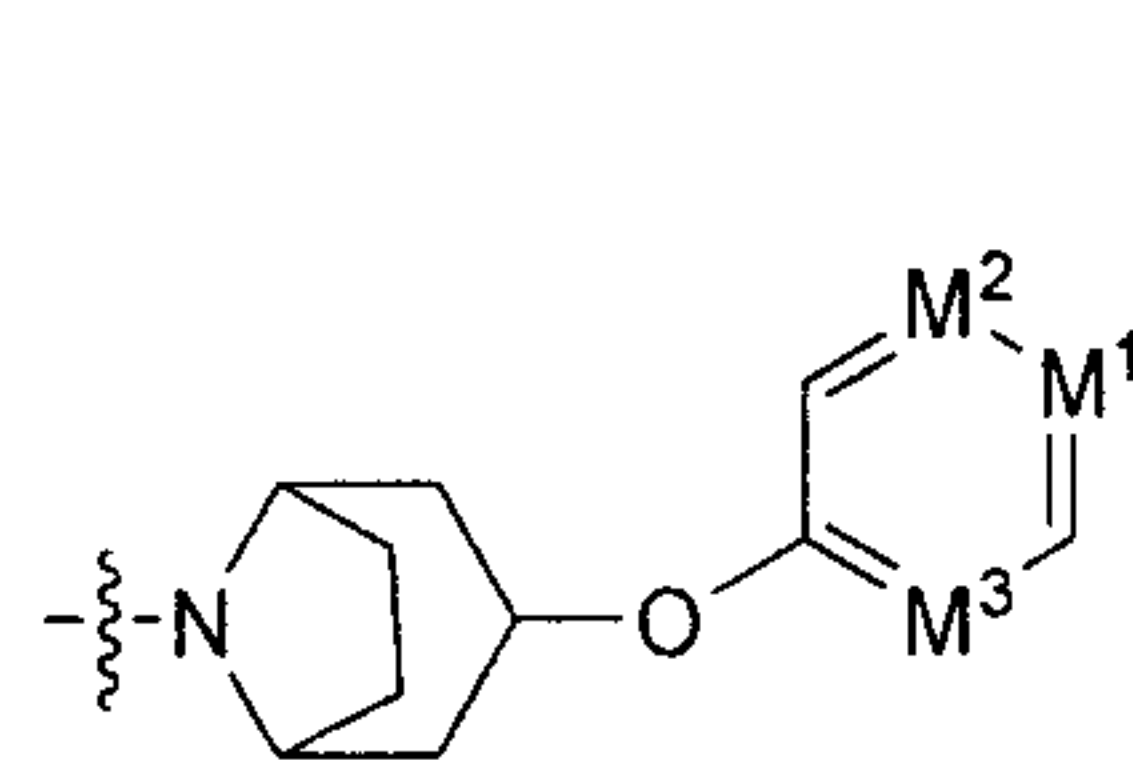
(B.43.)



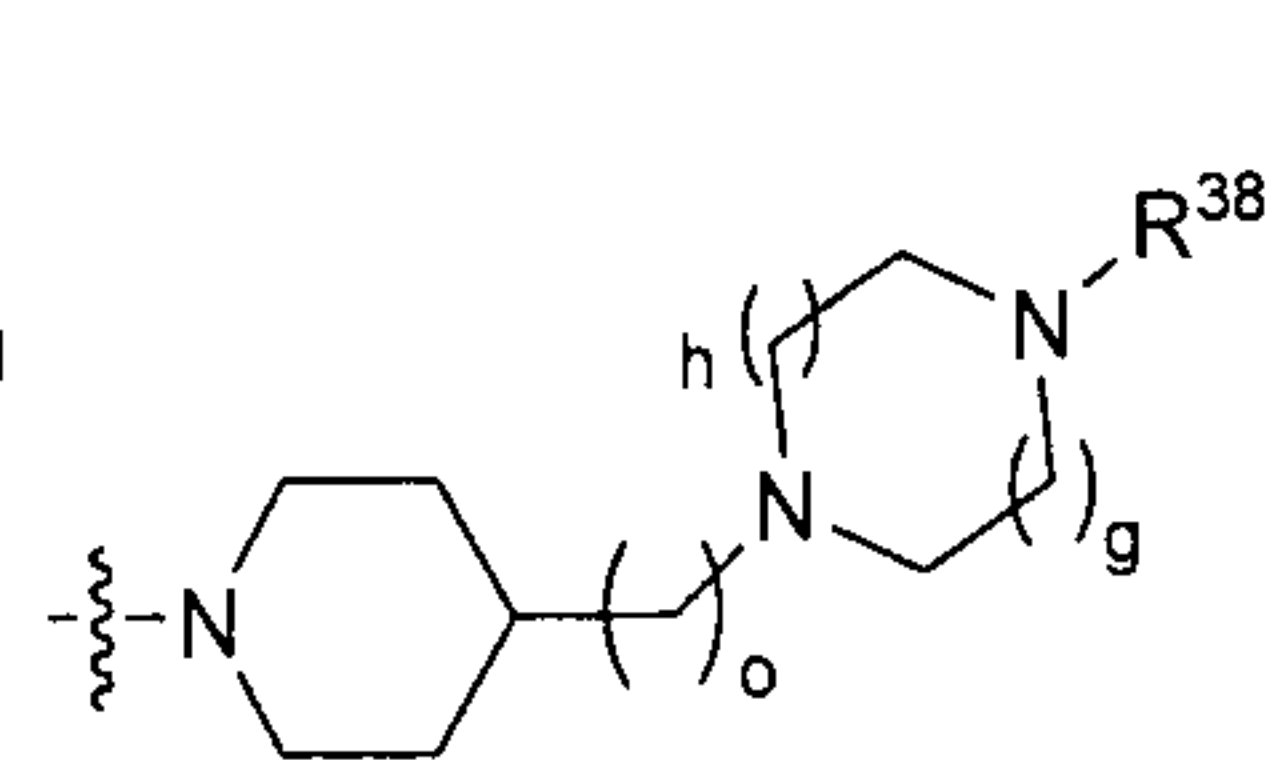
(B.44.)



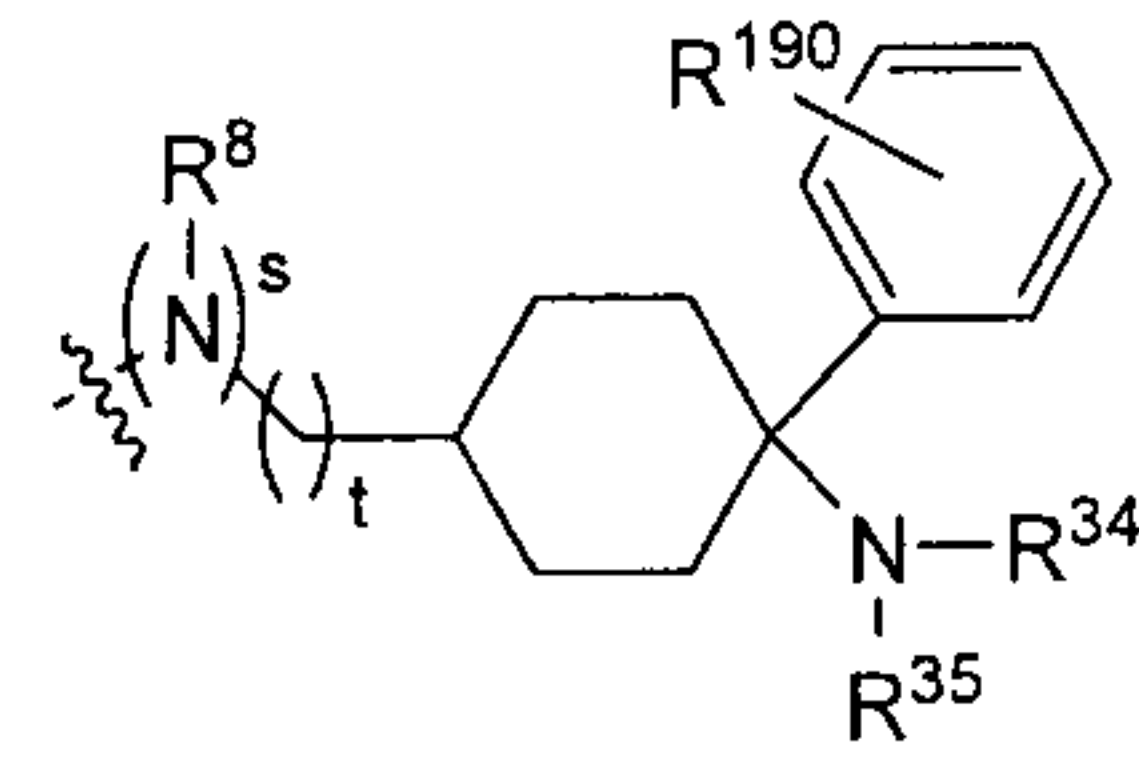
(B.45.)



(B.46.)

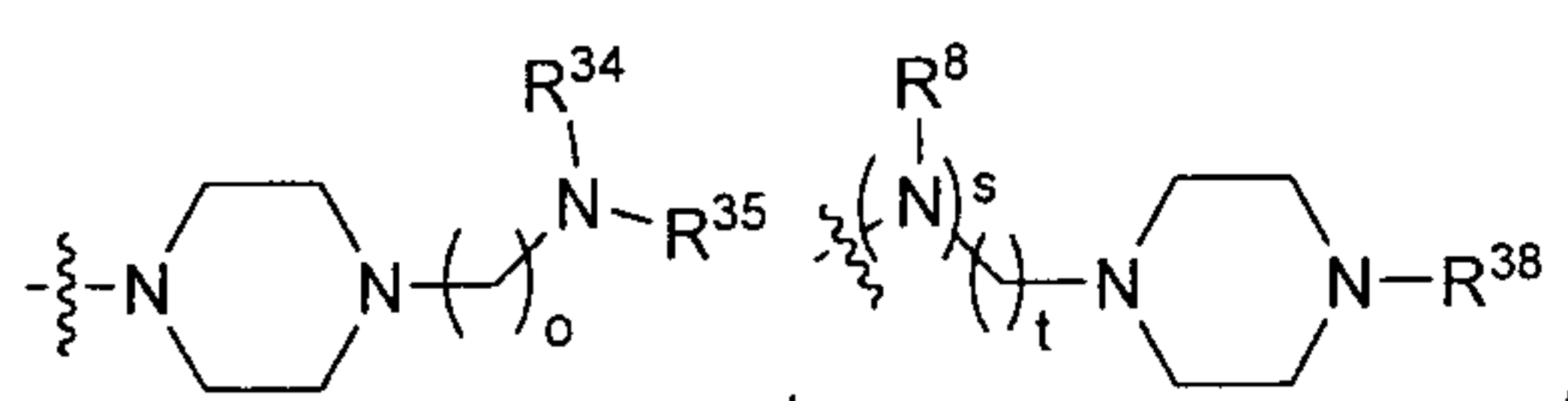


(B.47.)

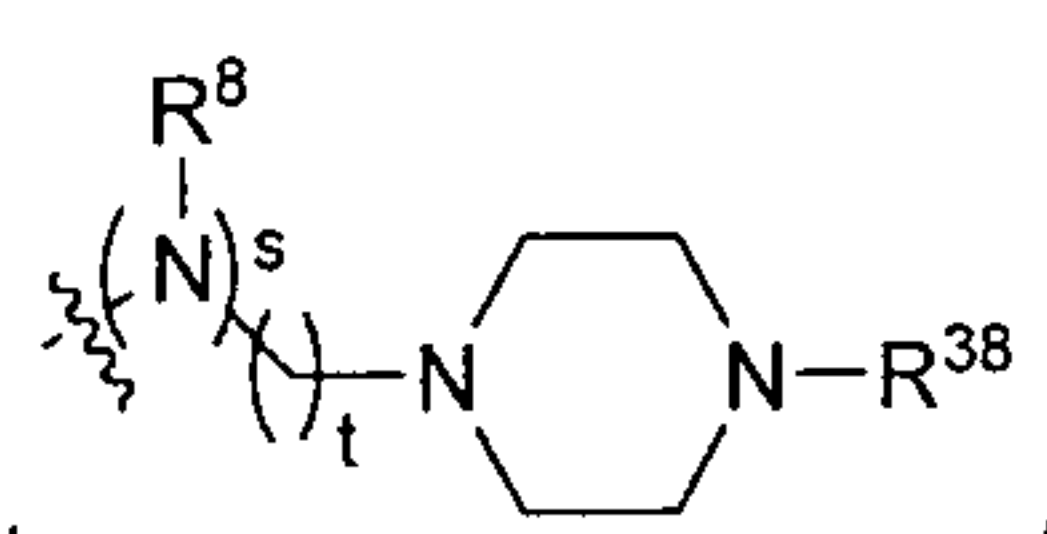


(B.48.)

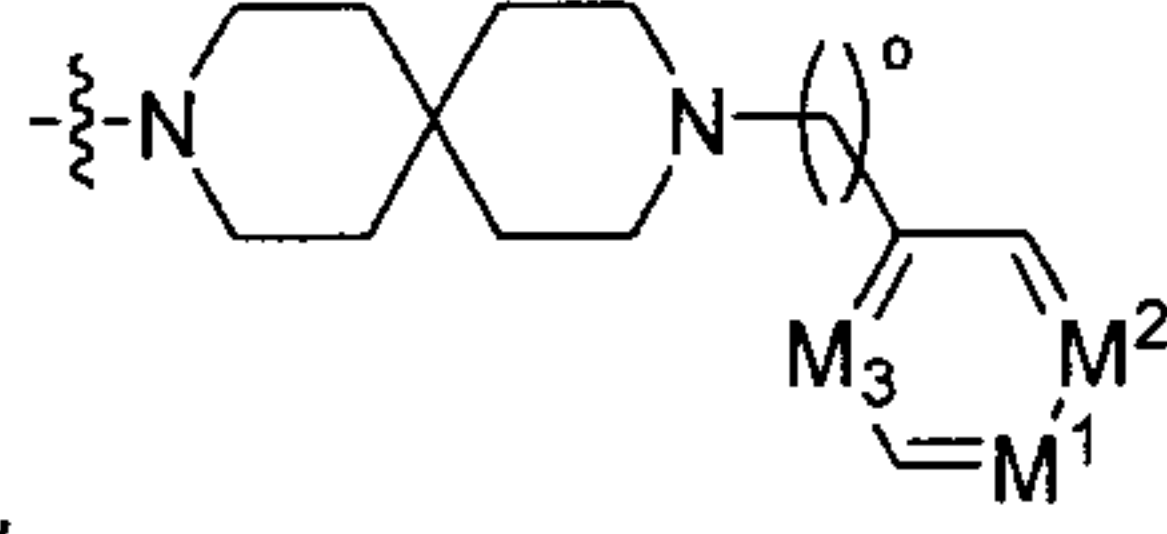
GRA3454-WO
22nd December 2009



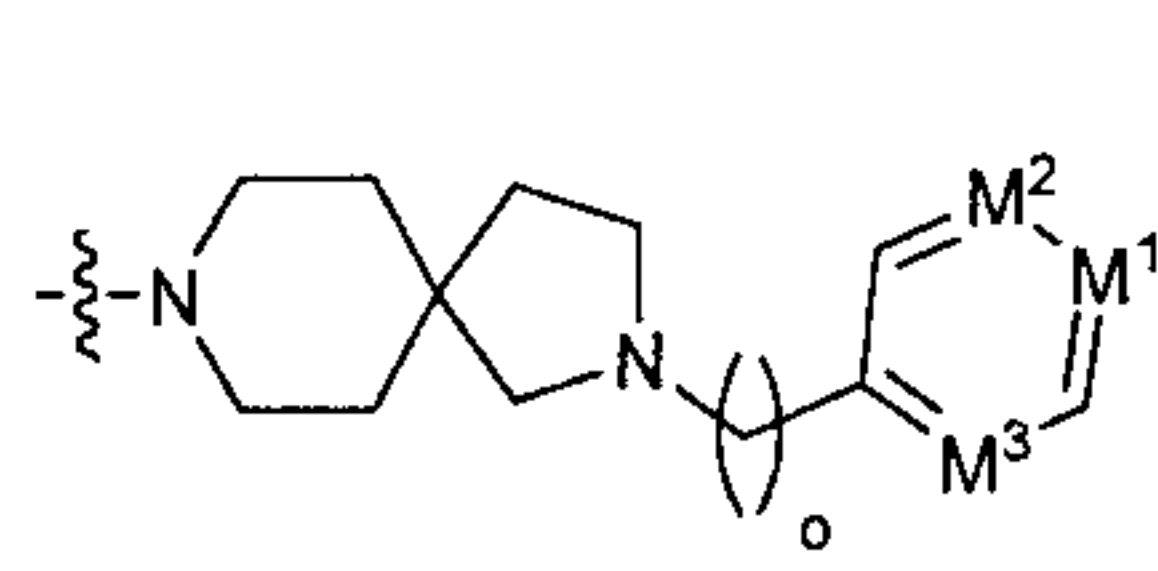
(B.49.)



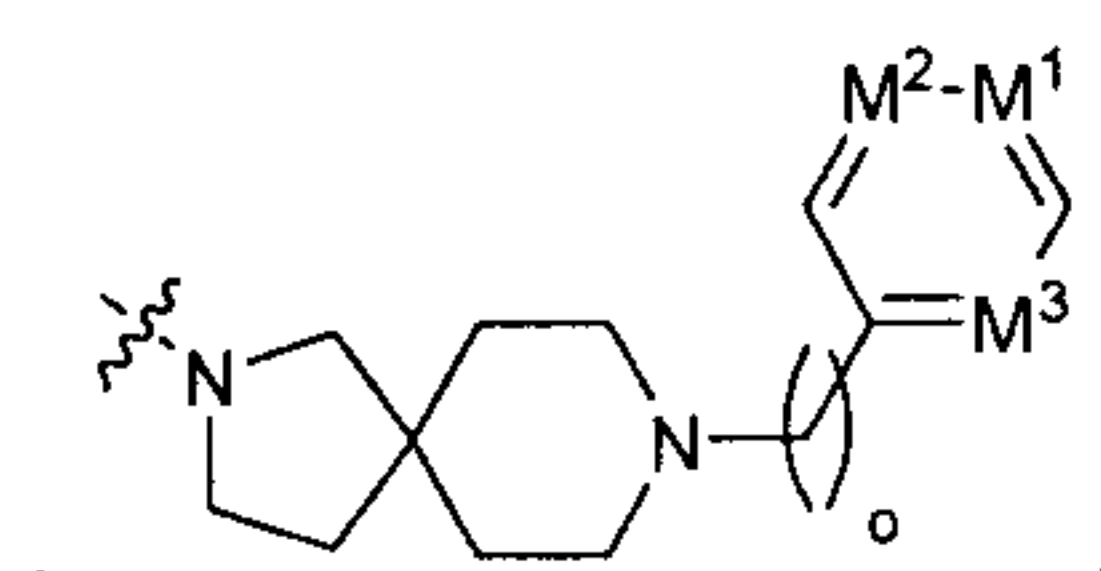
(B.50.)



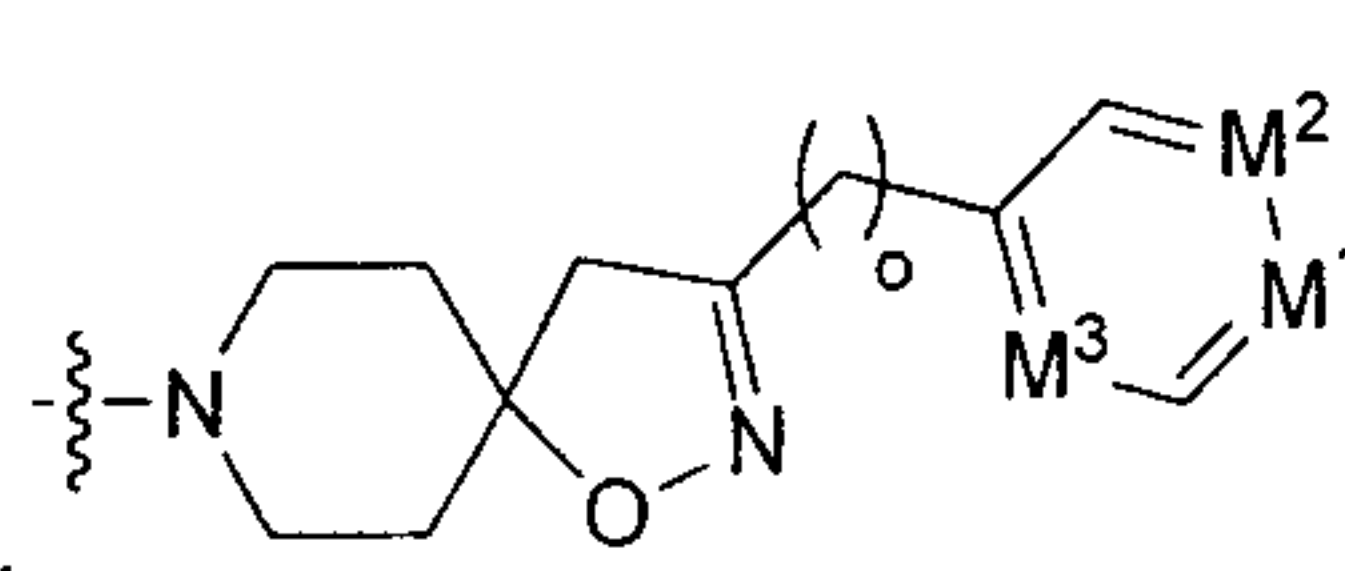
(B.51.)



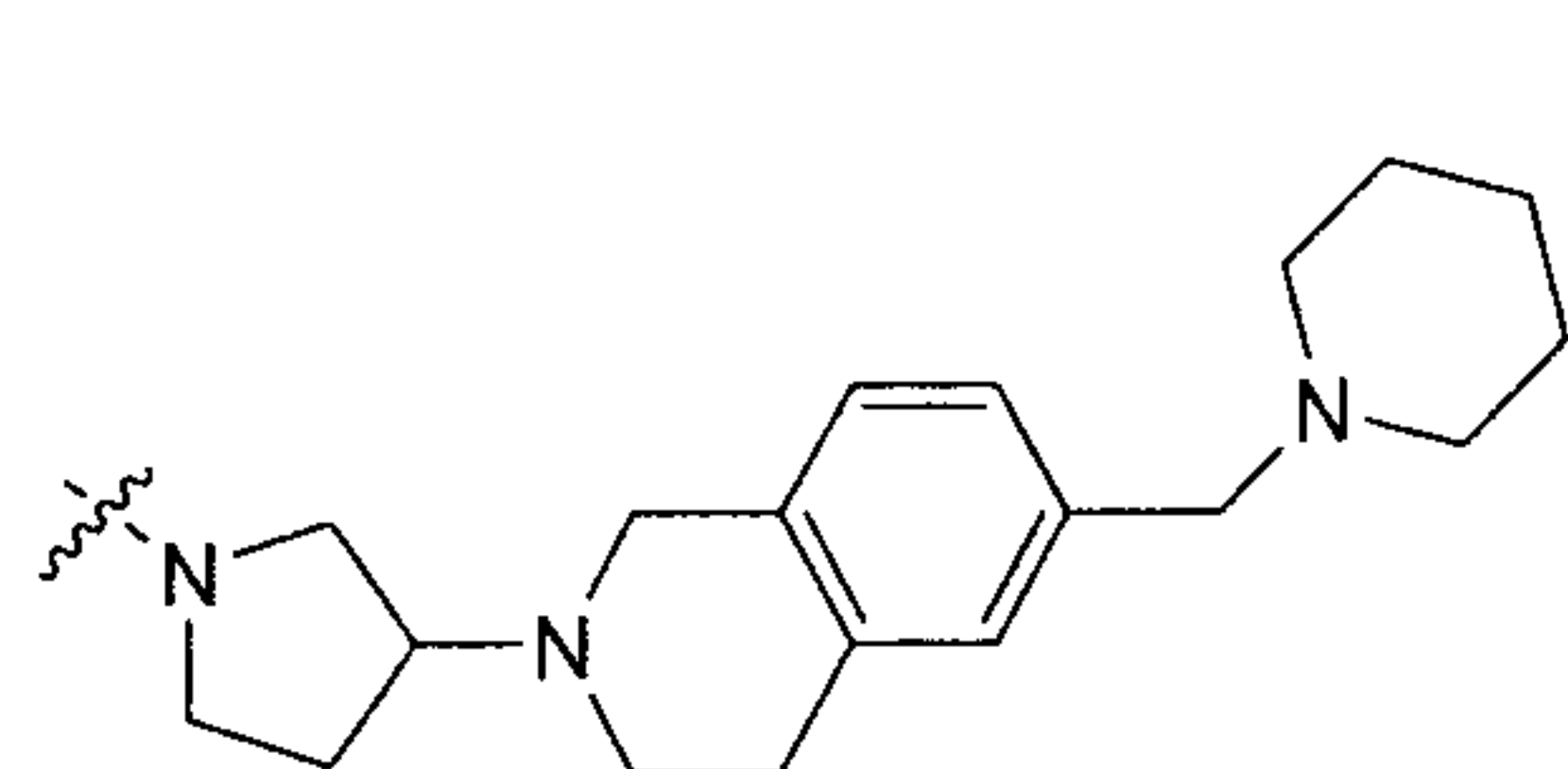
(B.52.)



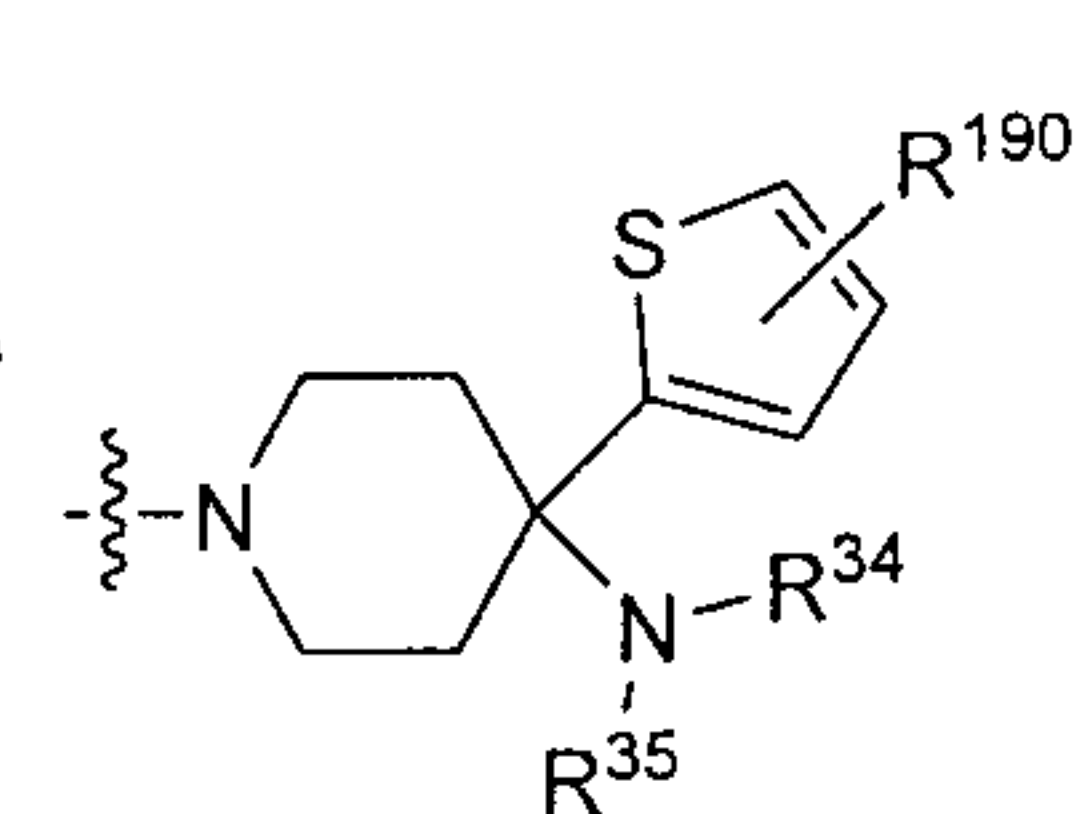
(B.53.)



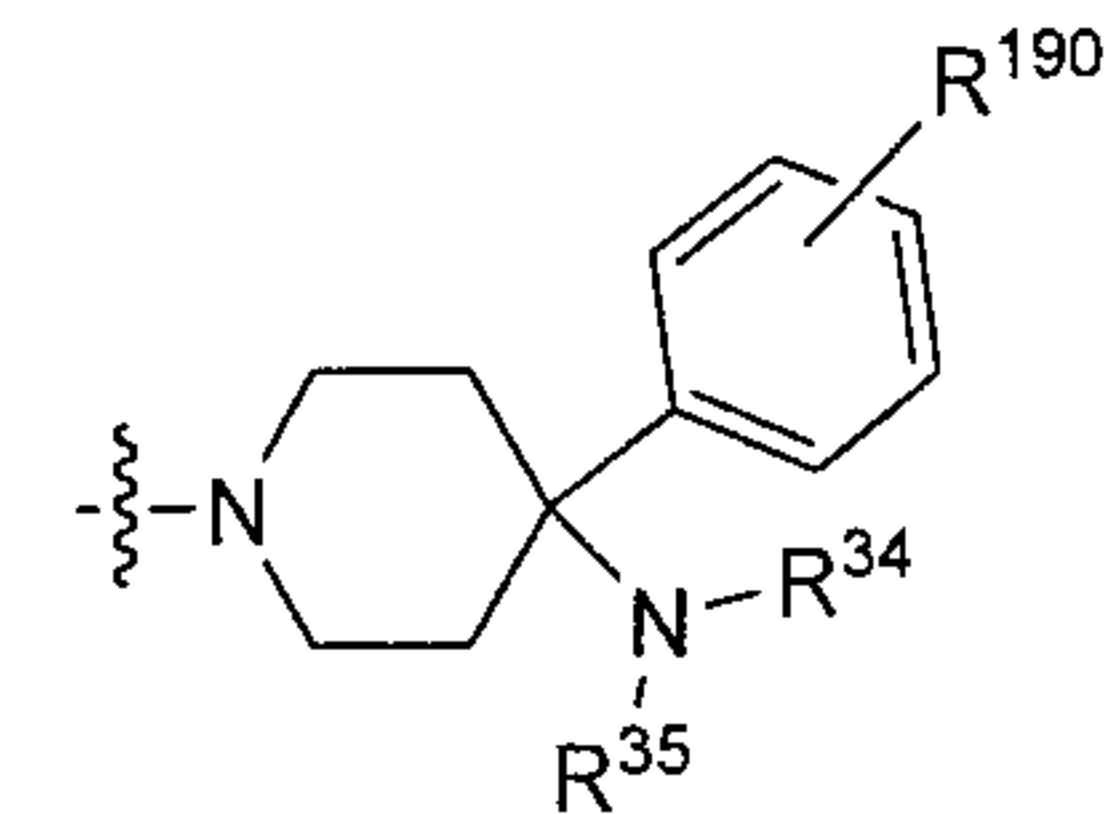
(B.54.)



(B.55.)



(B.56)



(B.57)

wherein

$h = 0$ or 1 ;

$g = 0$ or 1 ;

$m = 0$ or 1 ;

$n = 0$ or 1 ;

$o = 0, 1, 2$ or 3 ;

$r = 1, 2$ or 3 , in particular 1 or 2 ;

$s = 0$ or 1 ;

$t = 0, 1, 2$ or 3 , in particular $0, 1$ or 2 , with the proviso that if s stands for 0 then t likewise stands for 0 ;

GRA3454-WO
22nd December 2009

M¹, M² and M³ can mutually independently stand for N or CH, wherein one variable out of M¹, M² and M³ stands for N and the other two each stand for CH;

R⁸ stands for H; C₁₋₆ alkyl, in particular methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl; C₃₋₆ cycloalkyl, in particular cyclopropyl, each unsubstituted or mono- or polysubstituted with identical or different substituents;

R¹⁹ stands for H; C₁₋₆ alkyl, in particular methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl; C₃₋₆ cycloalkyl, in particular cyclopropyl; each unsubstituted or mono- or polysubstituted with identical or different substituents;

R³⁴ and R³⁵ are preferably mutually independently methyl or ethyl or together with the N-atom linking them they form an azetidiny, pyrrolidinyl, piperidinyl, 4-(C₁₋₆ alkyl)-piperazinyl group, each unsubstituted or mono- or polysubstituted with identical or different substituents;

R³⁸ stands for H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or pyridyl;

R³⁹ stands for H; C₁₋₆ alkyl, in particular methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl; C₃₋₆ cycloalkyl, in particular cyclopropyl, each unsubstituted or mono- or polysubstituted with identical or different substituents; and

R⁴⁵ stands for H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or pyridyl;

R¹⁹⁰ represents 0 to 4 substituents, which are mutually independently selected from F, Cl, O-CF₃, CF₃ or CN.

GRA3454-WO
22nd December 2009

13. Compound according to one or more of claims 1 to 12, selected from the group consisting of

No.	Compound
G-01	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G-02	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G-03	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyridin-4-yloxy-piperidin-1-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G-04	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(1-oxo-4-phenyl-2,4,8-triazaspiro[4.5]decan-8-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G-05	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G-06	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-pyridin-3-yl-4-(2-pyrrolidin-1-yl-ethoxy)-piperidin-1-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G-07	7-Chloro-2-[1-[3-oxo-3-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G-08	7-Chloro-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G-10	7-Chloro-2-(1-(3-oxo-3-(9-pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl)-1H-indol-7-yl)isoindolin-1-one
G-11	7-Chloro-2-(1-(2-oxo-2-(9-pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-1H-indol-7-yl)isoindolin-1-one
G-12	7-Chloro-2-(1-(2-oxo-2-(8-pyridin-4-yl)-2,8-diazaspiro[4.5]decan-2-yl)ethyl)-1H-indol-6-yl)isoindolin-1-one
G-13	4-Methoxy-2,6-dimethyl-N-(1-(2-oxo-2-(3-(pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-8-yl)ethyl)-1H-indol-7-yl)benzenesulfonic acid amide
G-14	4-Methoxy-2,6-dimethyl-N-(1-(2-oxo-2-(8-pyridin-4-yl)-2,8-diazaspiro[4.5]decan-2-yl)ethyl)-1H-indol-7-yl)benzenesulfonic acid amide
G-15	7-Chloro-2-(1-(2-oxo-2-(3-(pyridin-4-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-8-yl)ethyl)-1H-indol-6-yl)isoindolin-1-one
G-16	4-Methoxy-2,6-dimethyl-N-(1-(2-oxo-2-(3-(6-(piperidin-1-yl)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)pyrrolidin-1-yl)ethyl)-1H-indol-7-yl)benzenesulfonic acid amide
G-17	4-Methoxy-2,6-dimethyl-N-(1-(2-oxo-2-(7-(pyridin-4-yl)-2,7-diazaspiro[4.4]nonan-2-yl)ethyl)-1H-indol-7-yl)benzenesulfonic acid amide
G-18	N-(1-(2-(9-(azetidin-1-yl)-3-azaspiro[5.5]undecan-3-yl)-2-oxoethyl)-1H-indol-7-yl)-4-methoxy-2,6-dimethylbenzenesulfonic acid amide
G-19	7-Chloro-2-(1-(2-oxo-2-(9-pyridin-4-yloxy)-3-azaspiro[5.5]undecan-3-yl)ethyl)-1H-indol-6-yl)isoindolin-1-one
G-20	7-Chloro-2-(1-(2-(9-(3,3-difluoroazetidin-1-yl)-3-azaspiro[5.5]undecan-3-yl)-2-oxoethyl)-1H-indol-6-yl)isoindolin-1-one
G-21	2-(1-(2-(9-(Azetidin-1-yl)-3-azaspiro[5.5]undecan-3-yl)-2-oxoethyl)-1H-indol-6-yl)-7-chloroisoindolin-1-one

GRA3454-WO
22nd December 2009

G-22	4-Methoxy-2,6-dimethyl-N-(1-(2-oxo-2-(9-(pyridin-4-yloxy)-3-azaspiro[5.5]undecan-3-yl)ethyl)-1H-indol-7-yl)benzenesulfonic acid amide
G-23	8-Chloro-4-methyl-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-3,4-dihydro-2H-pyrrolo[3,4-b]indol-1-one
G-24	4-Methoxy-2,6-dimethyl-N-[[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-7-yl]-methyl]-benzenesulfonic acid amide
G-26	7-Methyl-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G-27	5-Methyl-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-1,2-dihydro-pyrrolo[2,1-e]imidazol-3-one
G-31	10-Chloro-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one
G-33	8-Chloro-2-[1-[2-oxo-2-(9-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-3-yl)-ethyl]-1H-indol-6-yl]-3,4-dihydro-2H-pyrrolo[1,2-a]pyrazin-1-one
G_CC-1	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-2	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-3	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-4	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-5	N-[1-[2-[4-(4-fluorophenyl)-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-6	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-7	4-Methoxy-2,6-dimethyl-N-[1-[2-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-8	4-Chloro-2,5-dimethyl-N-[1-[2-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-9	2-[6-[[[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[(1-pyridin-4-yl-piperidin-4-yl)-methyl]-acetamide
G_CC-10	N-[1-[2-(3-Benzyl-3,7-diazaspiro[4.4]nonan-7-yl)-2-oxo-ethyl]-1H-indol-6-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-11	N-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-2-[6-[[[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide
G_CC-12	N-[1-[2-[3-(4-Fluorophenyl)-4-oxo-3,8-diazaspiro[4.5]decan-8-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-13	N-[1-[2-(3-Benzyl-3,7-diazaspiro[4.4]nonan-7-yl)-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-14	N-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-2-[7-[[[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide
G_CC-15	2-[6-[[[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[3-(4-dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-N-methyl-acetamide

GRA3454-WO
22nd December 2009

G_CC-16	N-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-N-methyl-2-[7-[(naphthalen-1-ylsulfonyl)amino]-1H-indol-1-yl]-acetamide
G_CC-17	N-[4-(Azetidin-1-yl)-4-phenyl-cyclohexyl]-2-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetamide
G_CC-18	N-[3-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-2-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide
G_CC-19	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-2-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetamide
G_CC-20	N-[1-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-21	2-[7-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide
G_CC-22	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-3-[6-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionamide
G_CC-23	3-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide
G_CC-24	2-[6-[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide
G_CC-25	N-[3-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-N-methyl-2-[7-[(naphthalen-1-ylsulfonyl)amino]-1H-indol-1-yl]-acetamide
G_CC-26	2-[7-[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[3-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-N-methyl-acetamide
G_CC-27	2-[7-[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-acetamide
G_CC-28	2-[7-[[4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide
G_CC-29	N-[3-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-2-[6-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide
G_CC-30	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-2-[6-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetamide
G_CC-31	N-[1-[2-[1-(4-Fluorophenyl)-3-methyl-4-oxo-3,8-diazaspiro[4.5]decan-8-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-32	N-[1-[2-(3-Benzyl-4-oxo-3,8-diazaspiro[4.5]decan-8-yl)-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-33	N-[1-[2-[2-[(4-Fluorophenyl)-methyl]-2,5-diazabicyclo[2.2.1]heptan-5-yl]-2-oxo-ethyl]-1H-indol-6-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-34	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[2-(pyridin-4-yl-methyl)-2,5-diazabicyclo[2.2.1]heptan-5-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-35	4-Methoxy-2,6-dimethyl-N-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-36	4-Chloro-2,5-dimethyl-N-[1-[2-oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-37	N-[1-[2-Oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-6-yl]-2-(trifluoromethyl)-benzenesulfonic acid amide

GRA3454-WO

22nd December 2009

G_CC-38	N-[1-[2-Oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-naphthalene-1-sulfonic acid amide
G_CC-39	4-Chloro-2,5-dimethyl-N-[1-[2-oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-40	4-Methoxy-2,6-dimethyl-N-[1-[3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-41	4-Methoxy-2,6-dimethyl-N-[1-[3-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-42	4-Methoxy-2,6-dimethyl-N-[1-[3-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-43	4-Methoxy-2,6-dimethyl-N-[1-[3-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-44	N-[1-[3-[4-(3-Dimethylamino-propyl)-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-45	N-[1-[3-(4-Hydroxy-4-pyridin-2-yl-piperidin-1-yl)-3-oxo-propyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-46	N-[3-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-propyl]-3-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide
G_CC-47	3-[7-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide
G_CC-48	N-[1-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-3-oxo-propyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide
G_CC-49	N-[3-(4-Dimethylamino-4-phenyl-piperidin-1-yl)-propyl]-3-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide
G_CC-50	N-[4-(Azetidin-1-yl)-4-phenyl-cyclohexyl]-3-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionamide
G_CC-51	N-[2-(4-Dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-3-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionamide
G_CC-52	N-[1-[3-Oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-7-yl]-2-(trifluoromethyl)-benzenesulfonic acid amide
G_CC-53	N-[1-[2-Oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-2-(trifluoromethyl)-benzenesulfonic acid amide
G_CC-54	4-Methoxy-2,6-dimethyl-N-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-56	N-[3-(4-Ethyl-piperazin-1-yl)-propyl]-3-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-propionamide
G_CC-57	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-pyridin-3-yl-4-(2-pyrrolidin-1-yl-ethoxy)-piperidin-1-yl]-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-59	4-Chloro-2,5-dimethyl-N-[1-[3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-60	4-Chloro-2,5-dimethyl-N-[1-[3-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-61	4-Chloro-2,5-dimethyl-N-[1-[3-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide
G_CC-62	4-Chloro-2,5-dimethyl-N-[1-[3-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-3-oxo-propyl]-1H-indol-7-yl]-benzenesulfonic acid amide

GRA3454-WO
22nd December 2009

G_CC-63	7-Chloro-2-[1-[3-oxo-3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G_CC-64	7-Chloro-2-[1-[3-[4-[(1-methyl-piperidin-4-yl)-methyl]-piperazin-1-yl]-3-oxo-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G_CC-65	4-Chloro-2,5-dimethyl-N-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-6-yl]-benzenesulfonic acid amide
G_CC-66	8-[3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-propanoyl]-3-[(4-fluorophenyl)-methyl]-3,8-diazaspiro[4.5]decan-4-one
G_CC-67	7-Chloro-2-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G_CC-68	7-Chloro-2-[1-[3-oxo-3-(4-pyridin-4-yloxy-piperidin-1-yl)-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G_CC-69	7-Chloro-2-[1-[3-(4-hydroxy-4-pyridin-3-yl-piperidin-1-yl)-3-oxo-propyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one
G_CC-70	3-[7-[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide
G_CC-71	3-[6-[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide
G_CC-72	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-propionamide
G_CC-73	3-[7-[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-propionamide
G_CC-74	3-[6-[(4-Chloro-2,5-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-thiophen-2-yl-piperidin-1-yl)-ethyl]-propionamide
G_CC-76	2-[6-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-acetamide (G_CC-76)
G_CC-77	N-[2-(4-Dimethylamino-4-phenyl-cyclohexyl)-ethyl]-2-[7-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-77)
G_CC-81	N-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-3-[6-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide (G_CC-81)
G_CC-84	N-[1-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl]-1H-indol-7-yl]-4-methoxy-2,6-dimethyl-benzenesulfonic acid amide (G_CC-84)
G_CC-88	2-[7-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-acetamide (G_CC-88)
G_CC-91	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-91)
G_CC-92	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-(4-pyridin-4-yloxy-piperidin-1-yl)-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-92)
G_CC-95	N-[2-(4-Dimethylamino-4-phenyl-cyclohexyl)-ethyl]-2-[6-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide

GRA3454-WO
22nd December 2009

	(G_CC-95)
G_CC-99	N-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-2-[6-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-99)
G_CC-102	N-[2-[4-(3-Fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-2-[7-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-acetamide (G_CC-102)
G_CC-103	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-(1-pyridin-4-yl-piperidin-4-yl)-ethyl]-acetamide (G_CC-103)
G_CC-106	7-Chloro-2-[1-[3-oxo-3-(3-pyridin-4-yl-3,9-diazaspiro[5.5]undecan-9-yl)-propyl]-1H-indol-7-yl]-2,3-dihydro-isoindol-1-one (G_CC-106)
G_CC-108	N-[[1-[2-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-acetyl]-4-(4-methyl-piperazin-1-yl)-piperidin-4-yl]-methyl]-pyridine-4-carboxylic acid amide (G_CC-108)
G_CC-111	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[(1-pyridin-4-yl-piperidin-4-yl)-methyl]-acetamide (G_CC-111)
G_CC-113	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-[4-(3-fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-ethyl]-N-methyl-acetamide (G_CC-113)
G_CC-116	3-[6-[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-propionamide (G_CC-116)
G_CC-117	N-[2-(4-Dimethylamino-4-phenyl-cyclohexyl)-ethyl]-3-[6-[[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]amino]-1H-indol-1-yl]-N-methyl-propionamide (G_CC-117)
G_CC-119	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-propionamide (G_CC-119)
G_CC-120	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-1H-indol-6-yl]-benzenesulfonic acid amide (G_CC-120)
G_CC-123	3-[7-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[(1-pyridin-4-yl-piperidin-4-yl)-methyl]-propionamide (G_CC-123)
G_CC-127	3-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-[2-(4-dimethylamino-4-phenyl-cyclohexyl)-ethyl]-N-methyl-propionamide (G_CC-127)
G_CC-128	7-Chloro-2-[1-[2-[4-(3-fluorophenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl]-1H-indol-6-yl]-2,3-dihydro-isoindol-1-one (G_CC-128)
G_CC-138	2-[6-(4-Chloro-3-oxo-1,2-dihydro-isoindol-2-yl)-1H-indol-1-yl]-N-methyl-N-[3-(4-pyridin-4-yl-piperazin-1-yl)-propyl]-acetamide (G_CC-138)

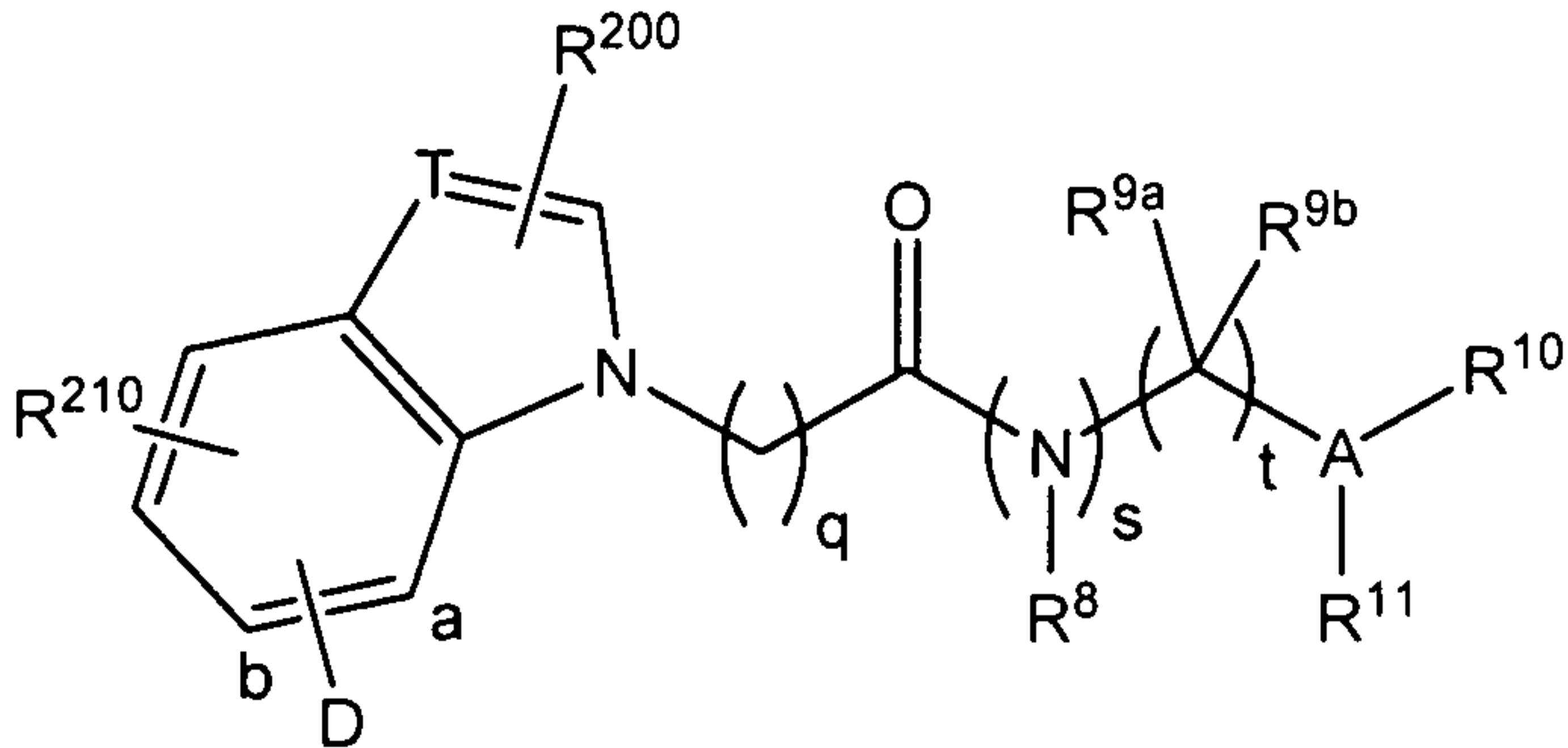
GRA3454-WO
22nd December 2009

G_CC-139	4-Methoxy-2,6-dimethyl-N-[1-[2-oxo-2-[4-(pyridin-3-carbonyl)-piperazin-1-yl]-ethyl]-1H-indol-7-yl]-benzenesulfonic acid amide (G_CC-139)
----------	--

optionally in the form of a single enantiomer or a single diastereomer, the racemate, the enantiomers, the diastereomers, mixtures of enantiomers or diastereomers, each in the form of their bases and/or physiologically compatible salts, in particular hydrochloride salts.

14. Medicinal product containing at least one compound according to one or more of claims 1 to 13.

15. Use of at least one compound according to one or more of claims 1 to 13 for the preparation of a medicinal product for the treatment of pain, in particular acute pain, visceral pain, neuropathic pain, chronic pain and/or inflammatory pain; migraine; diabetes; diseases of the respiratory tract; inflammatory bowel diseases; neurological diseases; inflammations of the skin; rheumatic diseases; septic shock; reperfusion syndrome; obesity, and/or as an angiogenesis inhibitor



(I)