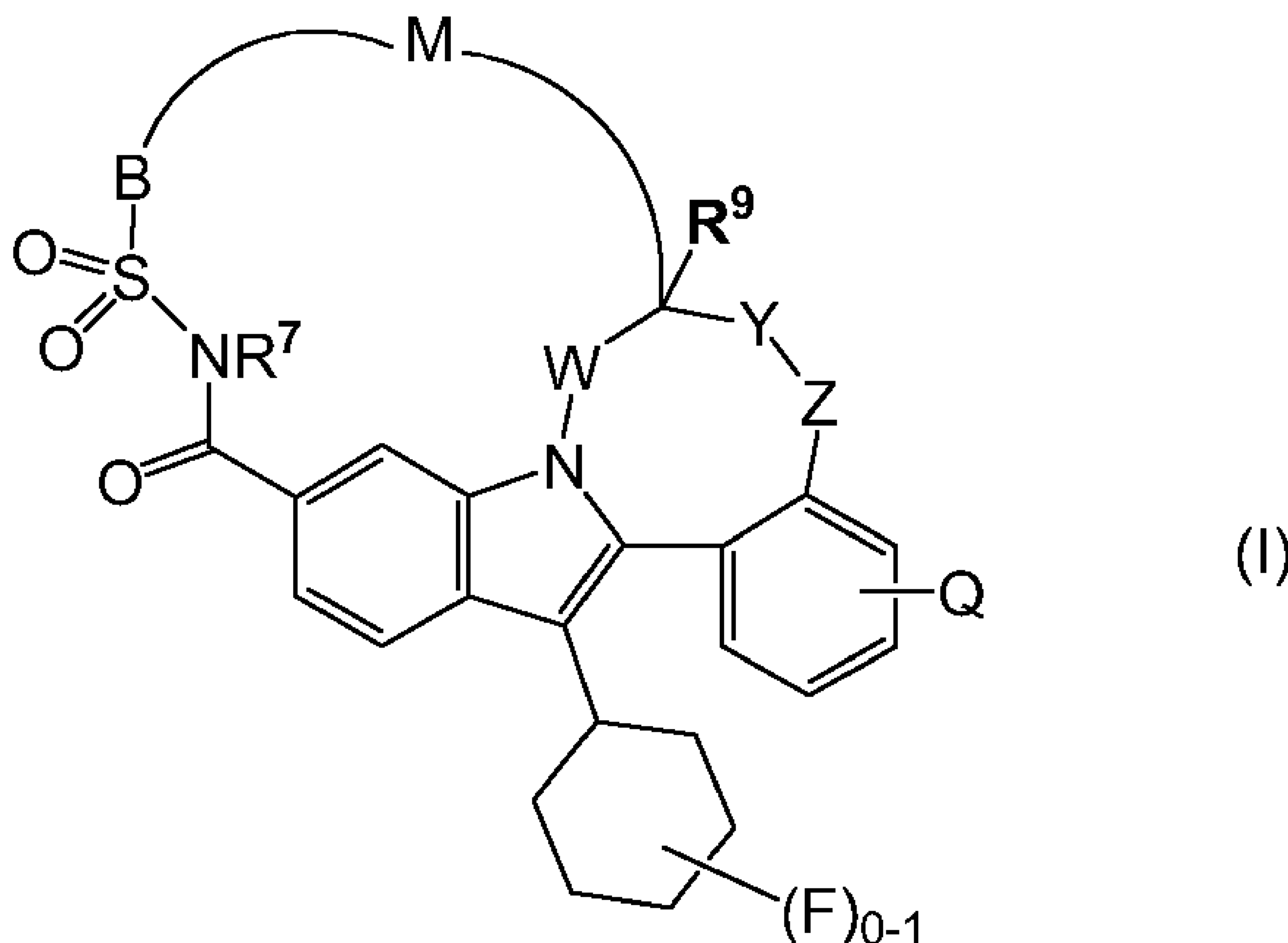




(86) Date de dépôt PCT/PCT Filing Date: 2008/07/09
(87) Date publication PCT/PCT Publication Date: 2009/01/22
(85) Entrée phase nationale/National Entry: 2010/01/14
(86) N° demande PCT/PCT Application No.: GB 2008/050551
(87) N° publication PCT/PCT Publication No.: 2009/010783
(30) Priorités/Priorities: 2007/07/17 (GB0713865.4);
2007/12/19 (GB0724635.8)

(51) Cl.Int./Int.Cl. *C07D 513/16* (2006.01),
A61K 31/407 (2006.01), *A61P 31/12* (2006.01),
C07D 515/16 (2006.01)
(71) Demandeur/Applicant:
ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE
P. ANGELETTI SPA, IT
(72) Inventeurs/Inventors:
CONTE, IMMACOLATA, IT;
HABERMANN, JOERG, IT;
MACKAY, ANGELA CLAIRE, IT;
NARJES, FRANK, IT;
RICO FERREIRA, MARIA DEL ROSARIO, IT;
STANSFIELD, IAN, IT
(74) Agent: OGILVY RENAULT LLP/S.E.N.C.R.L.,S.R.L.

(54) Titre : DERIVES MACROCYCLIQUES D'INDOLE POUR LE TRAITEMENT DES INFECTIONS D'HEPATITE C
(54) Title: MACROCYCLIC INDOLE DERIVATIVES FOR THE TREATMENT OF HEPATITIS C INFECTIONS



(57) Abrégé/Abstract:

A class of macrocyclic compounds of formula (I), wherein R^7 , R^9 , B, F, M, Q, W, Y and Z are defined herein, that are useful as inhibitors of viral proteases, particularly the hepatitis C virus (HCV) NS3 protease, are provided. Also provided are processes for the synthesis and use of such 5 macrocyclic compounds for treating or preventing HCV infection.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 January 2009 (22.01.2009)

PCT

(10) International Publication Number
WO 2009/010783 A1

(51) International Patent Classification:

C07D 513/16 (2006.01) *A61K 31/407* (2006.01)
C07D 515/16 (2006.01) *A61P 31/12* (2006.01)

(74) Agent: **ROLLINS, Anthony J.**; European Patent Department, Hertford Road, Hoddesdon Hertfordshire EN11 9BU, _____ + (GB).

(21) International Application Number:

PCT/GB2008/050551

(22) International Filing Date: 9 July 2008 (09.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0713865.4 17 July 2007 (17.07.2007) GB
0724635.8 19 December 2007 (19.12.2007) GB

(71) Applicant (for all designated States except US): **ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA** [IT/IT]; Via Pontina KM 30.600, I-00040 Pomezia (Rome) (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CONTE, Immacolata** [IT/IT]; IRBM, Via Pontina KM 30.600, I-00040 Pomezia (Rome) (IT). **HABERMANN, Joerg** [DE/IT]; IRBM, Via Pontina KM 30.600, I-00040 Pomezia (Rome) (IT). **MACKAY, Angela Claire** [IT/IT]; IRBM, Via Pontina KM 30.600, I-00040 Pomezia (Rome) (IT). **NARJES, Frank** [DE/IT]; IRBM, Via Pontina KM 30.600, I-00040 Pomezia (Rome) (IT). **RICO FERREIRA, Maria del Rosario** [ES/IT]; IRBM, Via Pontina KM 30.600, I-00040 Pomezia (Rome) (IT). **STANSFIELD, Ian** [GB/IT]; IRBM, Via Pontina KM 30.600, I-00040 Pomezia (Rome) (IT).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

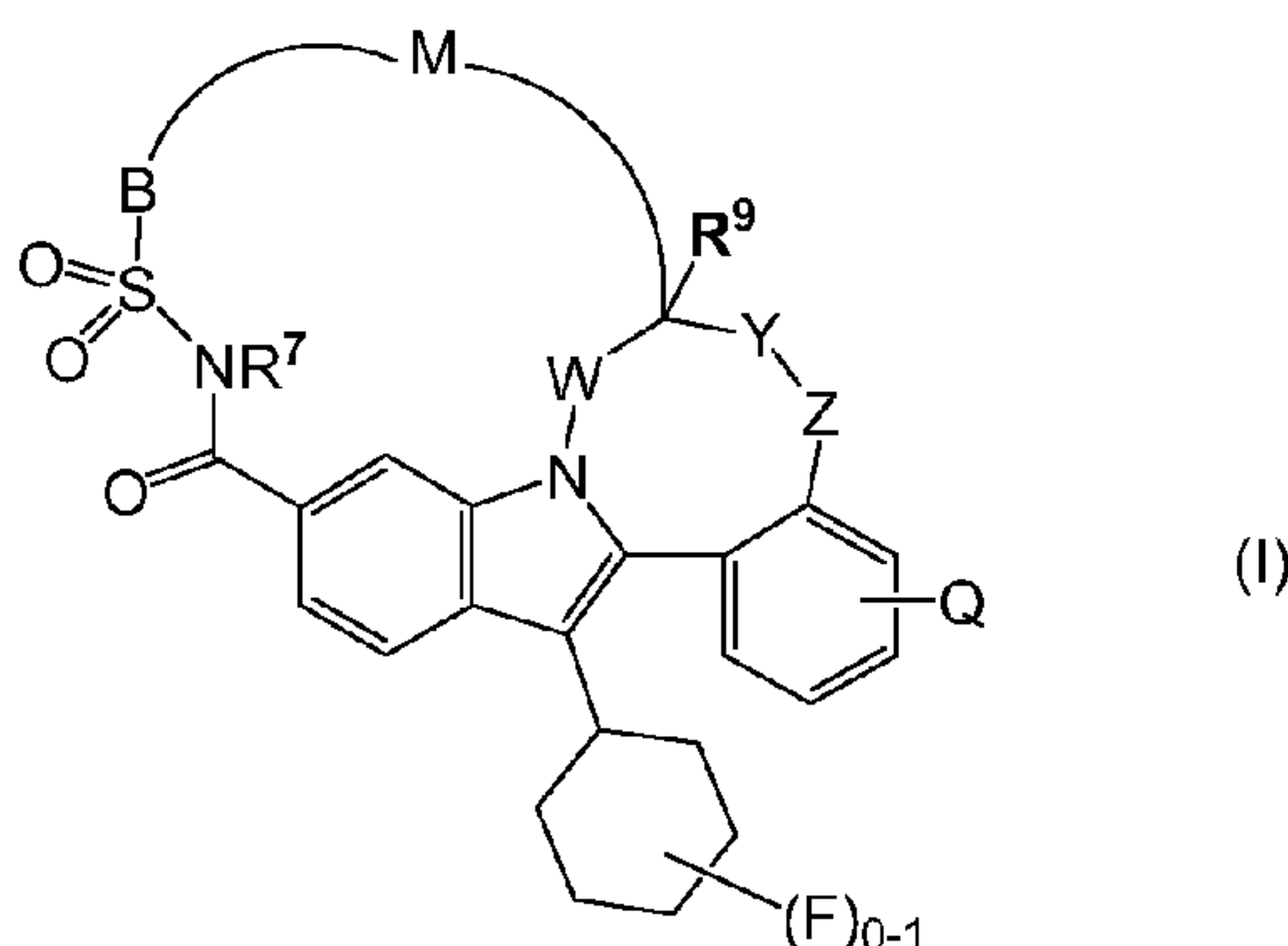
Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report

(54) Title: MACROCYCLIC INDOLE DERIVATIVES FOR THE TREATMENT OF HEPATITIS C INFECTIONS



(57) Abstract: A class of macrocyclic compounds of formula (I), wherein R^7 , R^9 , B, F, M, Q, W, Y and Z are defined herein, that are useful as inhibitors of viral proteases, particularly the hepatitis C virus (HCV) NS3 protease, are provided. Also provided are processes for the synthesis and use of such 5 macrocyclic compounds for treating or preventing HCV infection.

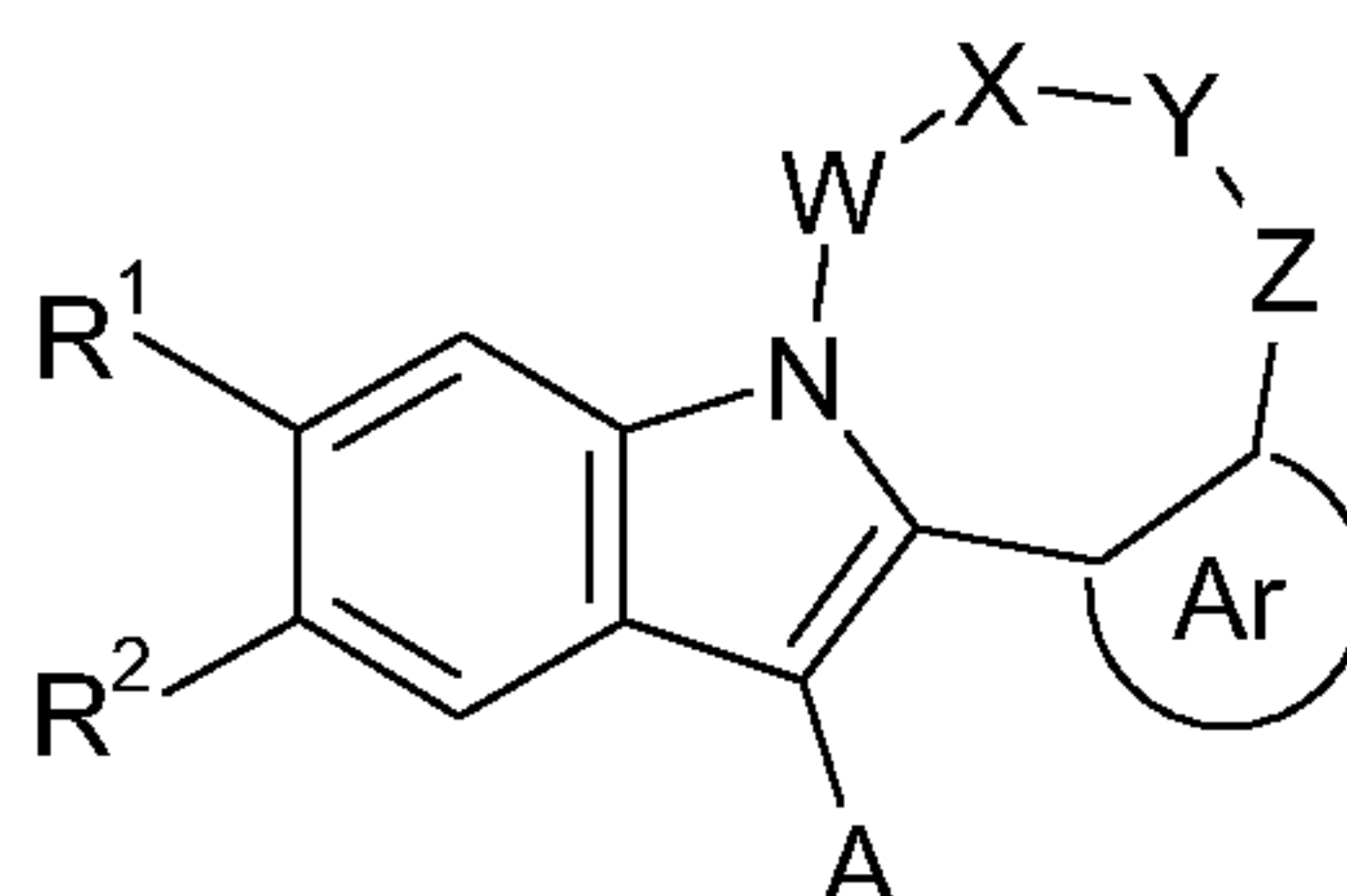
WO 2009/010783 A1

MACROCYCLIC INDOLE DERIVATIVES FOR THE TREATMENT OF HEPATITIS C INFECTIONS

The present invention relates to macrocyclic indole compounds, to pharmaceutical compositions containing them, to their use in the prevention and treatment of hepatitis C infections and to methods of preparation of such compounds and compositions.

Hepatitis C (HCV) is a cause of viral infections. There is as yet no adequate treatment for HCV infection but it is believed that inhibition of its RNA polymerase in mammals, particularly humans, would be of benefit.

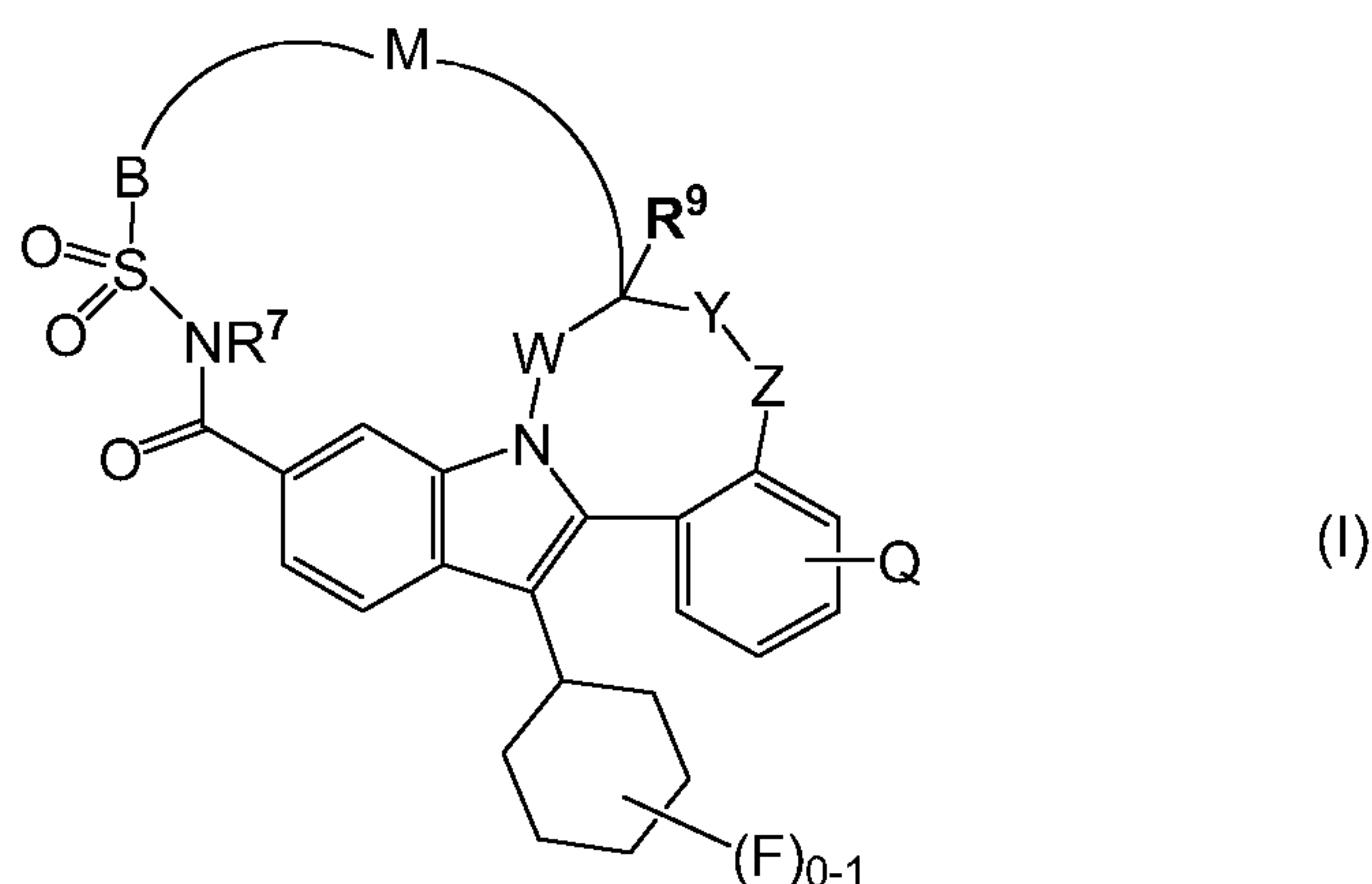
Published International applications WO2006/046030 and WO2006/046039 (both Istituto Di Ricerche Di Biologia Molecolare P. Angeletti SpA) disclose certain tetracyclic indole derivatives:



wherein R^1 , R^2 , A, Ar, W, X, Y, and Z are defined therein, useful for the treatment or prevention of infection by hepatitis C virus. Published International applications WO2007/029029 and WO2007/054741 (both Istituto Di Ricerche Di Biologia Molecolare P. Angeletti SpA) disclose structurally related tetracyclic indole derivatives, useful for the treatment or prevention of infection by hepatitis C virus.

We have now discovered a class of macrocyclic indole derivatives useful for the treatment or prevention of infection by hepatitis C virus.

Thus, the present invention provides the compound of the formula (I):



wherein Q is hydrogen, halogen, hydroxy, a group $(O)_{0-1} (CR^e R^f)_{0-3} R^8$ wherein R^e is hydrogen or C_{1-6} alkyl; R^f is hydrogen or C_{1-6} alkyl; and R^8 is hydrogen, C_{1-5} alkyl optionally substituted by C_{3-6} cycloalkyl, or R^8 is aryl, C_{1-6} alkoxy, heteroaryl or a 4-, 5-, 6- or 7-membered heteroaliphatic ring optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy, or a

- 2 -

- group NR^aR^b , or CONR^aR^b , wherein R^a and R^b are each independently selected from hydrogen, C_{1-4} alkyl and $\text{C}(\text{O})\text{C}_{1-4}$ alkyl; or R^a , R^b and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy; and wherein said C_{1-4} alkyl, C_{1-4} alkoxy and aryl groups are optionally substituted by
- 5 halogen or hydroxy;
- W is a bond, $\text{C}=\text{O}$, O, $\text{S}(\text{O})_{0-2}$ or $-(\text{CR}^{10}\text{R}^{11})-(\text{CR}^{12}\text{R}^{13})_{0-1}-$;
- Y is a bond, $\text{C}=\text{O}$, O, $-\text{CR}^{14}\text{R}^{15}-$ or NR^{14} ;
- Z is a bond, $\text{C}=\text{O}$, O, $\text{S}(\text{O})_{0-2}$, $-(\text{CR}^{10}\text{R}^{11})-(\text{CR}^{12}\text{R}^{13})_{0-1}-$ or NR^{10} ;
- and none, one or two of W, Y and Z are a bond;
- 10 R^9 is a bond, hydrogen, fluoro or hydroxyl;
- R^{10} , R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, $\text{C}(\text{O})\text{C}_{1-6}$ alkyl, a heteroaliphatic ring of 4 to 7 ring atoms containing 1, 2 or 3 heteroatoms selected from N, O or S or a group $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, NH or NC_{1-4} alkyl, or R^{10} , R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from $(\text{CH}_2)_{0-3}\text{NR}^{16}\text{R}^{17}$,
- 15 $\text{C}(\text{O})(\text{CH}_2)_{0-3}\text{NR}^{16}\text{R}^{17}$, $\text{NHC}(\text{O})(\text{CH}_2)_{0-3}\text{NR}^{16}\text{R}^{17}$, $\text{O}(\text{CH}_2)_{1-3}\text{NR}^{16}\text{R}^{17}$, $\text{S}(\text{O})_{0-2}(\text{CH}_2)_{0-3}\text{NR}^{16}\text{R}^{17}$, $\text{NMeC}(\text{O})(\text{CH}_2)_{0-3}\text{NR}^{16}\text{R}^{17}$ and $\text{C}(\text{O})(\text{CH}_2)_{0-3}\text{OR}^{16}$; or one of R^{10} , R^{14} and R^9 is linked to R^{20} or R^{21} to form a 4-10 membered carbocyclic ring, where said ring is optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy; or, when Z is $-\text{CR}^{10}\text{R}^{11}-$ or NR^{10} , R^{10} is joined to R^9 to form a $-(\text{CH}_2)_{1-4}$ group, optionally substituted by C_{1-4} alkyl; or R^9 is joined with an atom of the
- 20 linker M to form an aliphatic ring of 4-7 ring atoms, said aliphatic ring optionally containing one or two heteroatoms selected from O, N or S or a group $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, NH or NC_{1-4} alkyl;
- R^{16} and R^{17} are independently selected from hydrogen, C_{1-6} alkyl and $(\text{CH}_2)_{0-4}\text{NR}^{18}\text{R}^{19}$; or R^{16} , R^{17} and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, which ring may optionally contain 1 or 2 more heteroatoms selected from O or S or a
- 25 group $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, NH or NC_{1-4} alkyl, and which ring is optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy;
- R^{18} and R^{19} are independently selected from hydrogen and C_{1-6} alkyl; or R^{18} , R^{19} and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, which ring may optionally contain 1 or 2 more heteroatoms selected from O or S or a group $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, NH or
- 30 NC_{1-4} alkyl, and which ring is optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy;
- R^7 is hydrogen or C_{1-6} alkyl;
- B is $\text{NR}^{20}-$ and R^{20} is hydrogen, C_{1-6} alkyl optionally substituted by 1-3 fluoro, C_{2-6} alkenyl, $(\text{CH}_2)_{0-3}\text{C}_{3-6}$ cycloalkyl, $(\text{CH}_2)_{1-3}\text{OH}$, C_{1-6} alkoxy, $\text{C}(\text{O})\text{C}_{1-6}$ alkyl, $(\text{CH}_2)_{0-3}$ aryl, $(\text{CH}_2)_{0-3}\text{Het}$,
- 35 $(\text{CH}_2)_{0-3}$ heteroaryl, $(\text{CH}_2)_{1-3}\text{NR}^{16}\text{R}^{17}$, $\text{C}(\text{O})(\text{CH}_2)_{1-3}\text{NR}^{16}\text{R}^{17}$, $\text{S}(\text{O})_{0-2}(\text{CH}_2)_{1-3}\text{NR}^{16}\text{R}^{17}$, $\text{C}(\text{O})(\text{CH}_2)_{1-3}\text{OR}^{16}$, $(\text{CH}_2)_{1-3}\text{O}(\text{CH}_2)_{0-3}$ aryl, or R^{20} is linked to one of R^{10} , R^{14} and R^9 to form a ring of 4 to 10 atoms as hereinbefore described, or the R^{20} and a R^{21} group can be joined to form a $-(\text{CH}_2)_{1-3}$ group, optionally substituted by C_{1-2} alkyl;

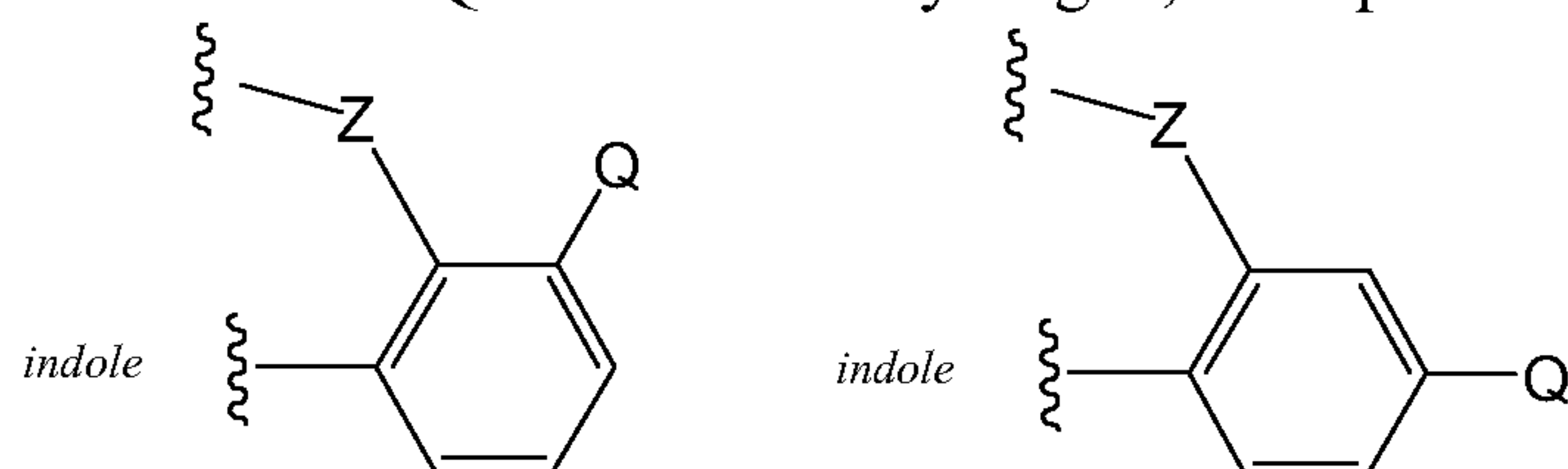
and M is C₃₋₇alkylene or C₃₋₇alkenylene, optionally substituted by one or two groups R²¹ which can be substituents on the same carbon atom where R²¹ is halo, C₁₋₄alkyl optionally substituted by 1-3 fluoro, (CH₂)₀₋₃C₃₋₈cycloalkyl, (CH₂)₀₋₃aryl, (CH₂)₀₋₃heteroaryl, (CH₂)₀₋₃Het, oxo or (CH₂)₀₋₃NR¹⁶R¹⁷, or R²¹ is linked to one of R¹⁰, R¹⁴ and R⁹ to form a ring of 4 to 10 atoms as

hereinbefore described; and 1, 2 or 3 of the carbon atoms in the C₃₋₇alkylene or C₃₋₇alkenylene groups is optionally replaced by O, NR²², S, SO, SO₂, piperidinyl, piperazinyl, homopiperazinyl or pyrrolidinyl;

and each group R²² is independently hydrogen, C₁₋₆alkyl optionally substituted with 1-3 fluoro, C₂₋₆alkenyl, (CH₂)₀₋₃C₃₋₆cycloalkyl, (CH₂)₁₋₃OH, C₁₋₆alkoxy, C(O)C₁₋₆alkyl, (CH₂)₀₋₃aryl, (CH₂)₀₋₃Het, (CH₂)₀₋₃heteroaryl, (CH₂)₁₋₃NR¹⁶R¹⁷, C(O)(CH₂)₁₋₃NR¹⁶R¹⁷, (CH₂)₁₋₃C(O)NR¹⁶R¹⁷, S(O)₀₋₂(CH₂)₁₋₃NR¹⁶R¹⁷, C(O)(CH₂)₁₋₃OR¹⁶, (CH₂)₁₋₃O(CH₂)₀₋₃aryl, or where 1, 2 or 3 of the carbon atoms in the C₃₋₇alkylene or C₃₋₇alkenylene group are replaced by NR²², then the R²⁰ and R²² groups can be joined to form a -(CH₂)₁₋₃ group, optionally substituted by C₁₋₂alkyl; and pharmaceutically acceptable salts thereof.

Preferably, Q is hydrogen, halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy or O₀₋₁(CH₂)₀₋₃R²³ where R²³ is a 5- or 6- membered heteroaliphatic ring, such as pyrrolidine or piperidine, or heteroaryl, such as pyridyl. More preferably, Q is O-CH₂-(2-pyridyl), O-CH₂CH₂-(1-pyrrolidine), halogen, hydroxy, C₁₋₄alkyl or C₁₋₄alkoxy. Most preferably, Q is O-CH₂-(2-pyridyl), O-CH₂CH₂-(1-pyrrolidine), fluorine, chlorine, methyl or methoxy. Suitable examples of Q groups are O-CH₂-(2-pyridyl), O-CH₂CH₂-(1-pyrrolidine), methoxy, methyl and fluorine.

When Q is other than hydrogen, examples of preferred Q positions are:



In a further embodiment, W is a bond, C=O or -(CR¹⁰R¹¹)-(CR¹²R¹³)₀₋₁- where R¹⁰, R¹¹, R¹² and R¹³ are as hereinbefore defined. Preferably, W is -(CR¹⁰R¹¹)-(CR¹²R¹³)₀₋₁. More preferably, W is -CH₂- or -CH₂CH₂-. Most preferably, W is -CH₂-.

In a further embodiment, Z is a bond, C=O, O, -(CR¹⁰R¹¹)-(CR¹²R¹³)₀₋₁- or NR¹⁰ where R¹⁰, R¹¹, R¹² and R¹³ are as hereinbefore defined. Preferably, Z is a bond, O or -(CR¹⁰R¹¹)-(CR¹²R¹³)₀₋₁. More preferably, Z is a bond, O, -CH₂- or -CH₂CH₂-. Most preferably, Z is O. Suitable examples of Z groups are O, NCH₃ and CH₂.

In a further embodiment, Y is a bond, C=O, O, -CR¹⁴R¹⁵- or NR¹⁴ where R¹⁴ and R¹⁵ are as hereinbefore defined. Preferably, Y is C=O, O, CR¹⁴R¹⁵ or -NR¹⁴. More preferably, Y is O, -CR¹⁴R¹⁵- or NR¹⁴. Most preferably, Y is -CH₂-, NH, N(C₁₋₆alkyl), NCH₂CH₂N(C₁₋₆alkyl)₂ or NC(O)(CH₂)₁₋₂N(C₁₋₆alkyl)₂. Especially, Y is -CH₂-, NH, N(C₁₋₄alkyl), N(CH₂)₂N(C₁₋₄alkyl)₂

- 4 -

or NC(O)CH₂N(C₁₋₄alkyl)₂. More especially, Y is -CH₂-, NCH₃ or N(CH₂)₂N(CH₃)₂. Most especially, Y is -CH₂-. Suitable examples of Y groups are CH₂ and a bond.

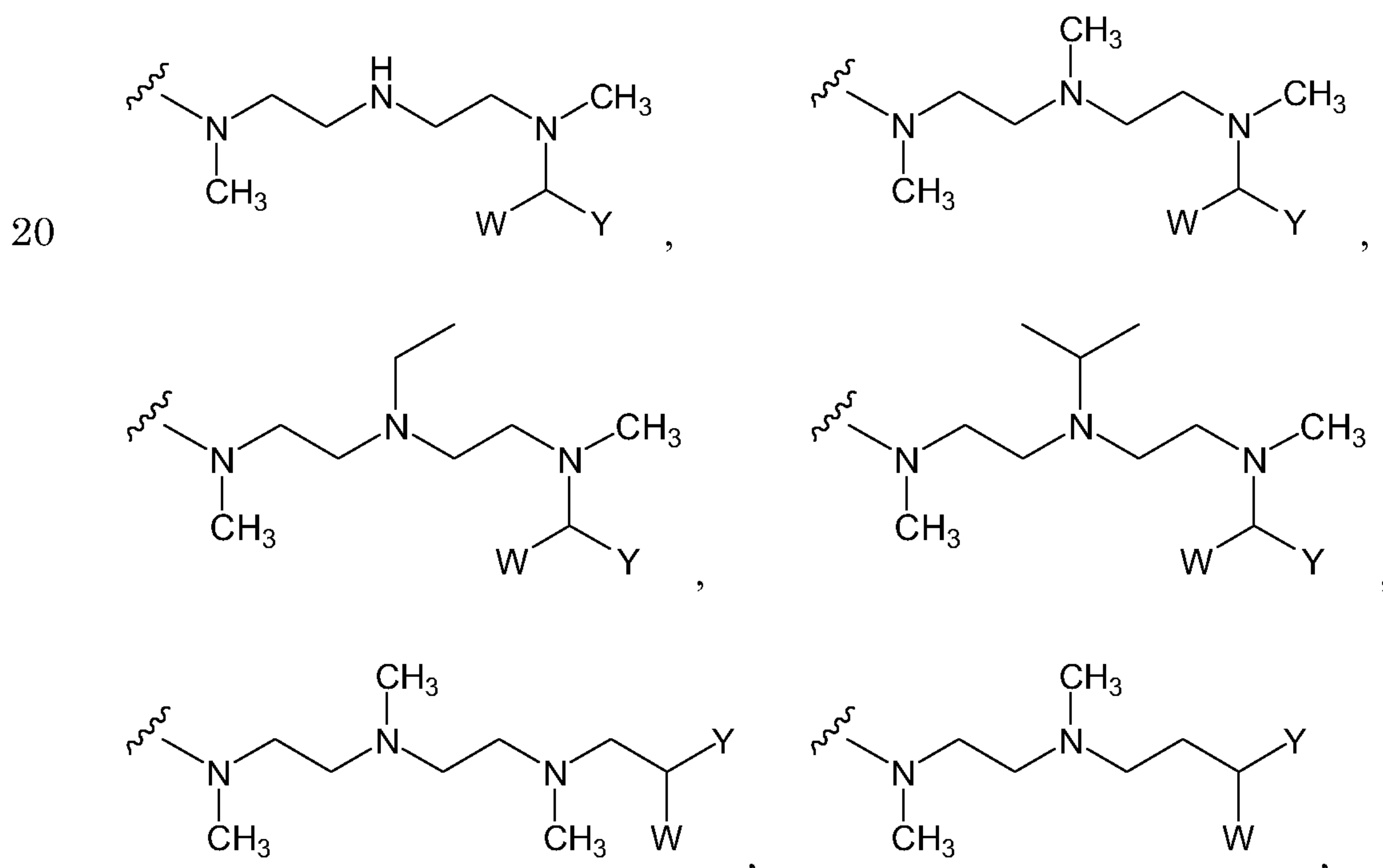
In a further embodiment, M is C₃₋₇ alkylene, optionally substituted by one or two halo such as fluoro, C₁₋₄ alkyl or oxo, and where one or two of the carbon atoms in the C₃₋₇ alkylene group is optionally replaced by O, NR²², S, SO or SO₂, where R²² is as hereinbefore defined.

5 Preferably, M is C₃₋₇alkylene, optionally substituted by one or two halo, such as fluoro, C₁₋₄alkyl, such as methyl, or oxo, and where one or two of the carbon atoms in the C₃₋₇ alkylene group is optionally replaced by O, NR²², S, SO or SO₂, where R²² is hydrogen, C₁₋₆alkyl optionally substituted by one, two or three fluoro, (CH₂)₀₋₃C₃₋₆cycloalkyl, (CH₂)₁₋₃OH, (CH₂)₀₋₃aryl,

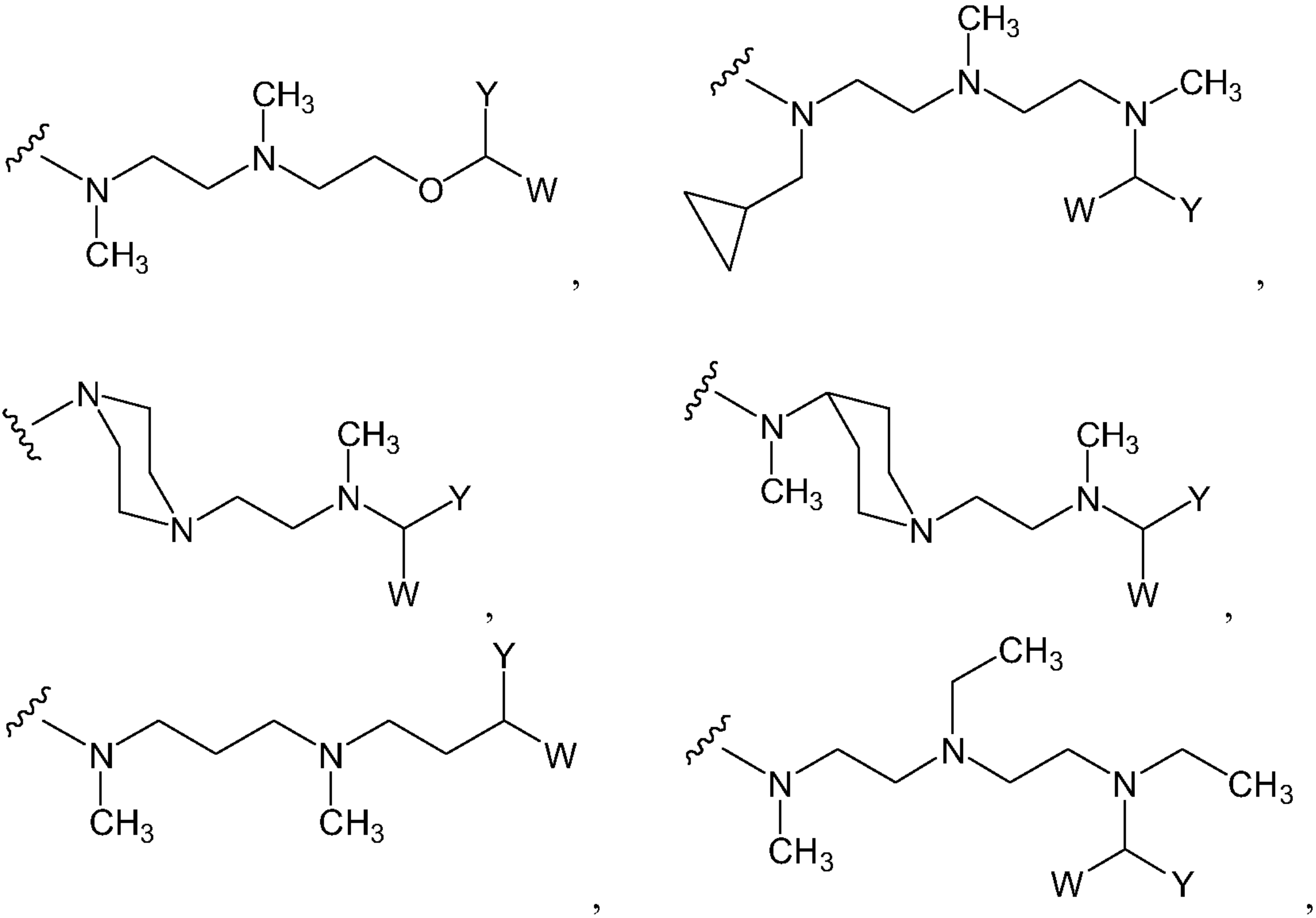
10 (CH₂)₀₋₃heteroaryl such as pyrazolyl, (CH₂)₁₋₃NR¹⁶R¹⁷, C(O)(CH₂)₁₋₃NR¹⁶R¹⁷, (CH₂)₁₋₃C(O)NR¹⁶R¹⁷ or (CH₂)₁₋₃O(CH₂)₀₋₃aryl, where R¹⁶ and R¹⁷ are as hereinbefore defined. More preferably, M is C₃₋₇ alkylene, optionally substituted by methyl or gem dimethyl or gem difluoro, and where one or two of the carbon atoms in the C₃₋₇alkylene group is replaced by O or NR²², where R²² is hydrogen, C₁₋₄ alkyl, (CH₂)C₃₋₆ cycloalkyl, (CH₂)₂OH, CH₂phenyl, CH₂pyridyl,

15 (CH₂)₂NR¹⁶R¹⁷, C(O)CH₂NR¹⁶R¹⁷ or (CH₂)₂OCH₂phenyl, where R¹⁶ and R¹⁷ are each hydrogen or C₁₋₄ alkyl or R¹⁶ and R¹⁷ are linked to form a nitrogen containing heteroaliphatic ring containing 4 to 7 ring members.

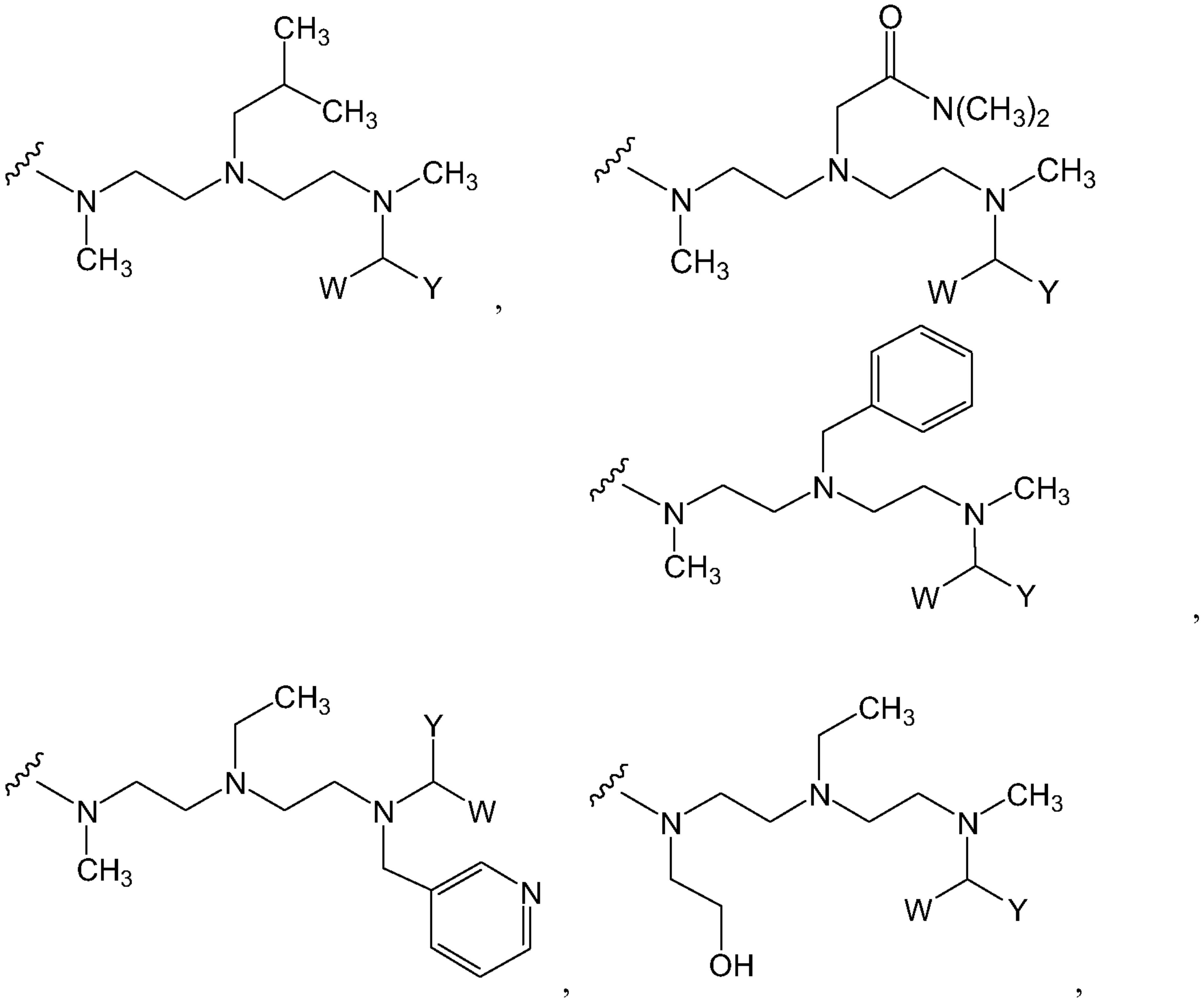
Examples of suitable B-M combinations (where R⁹ is hydrogen) are:



- 5 -

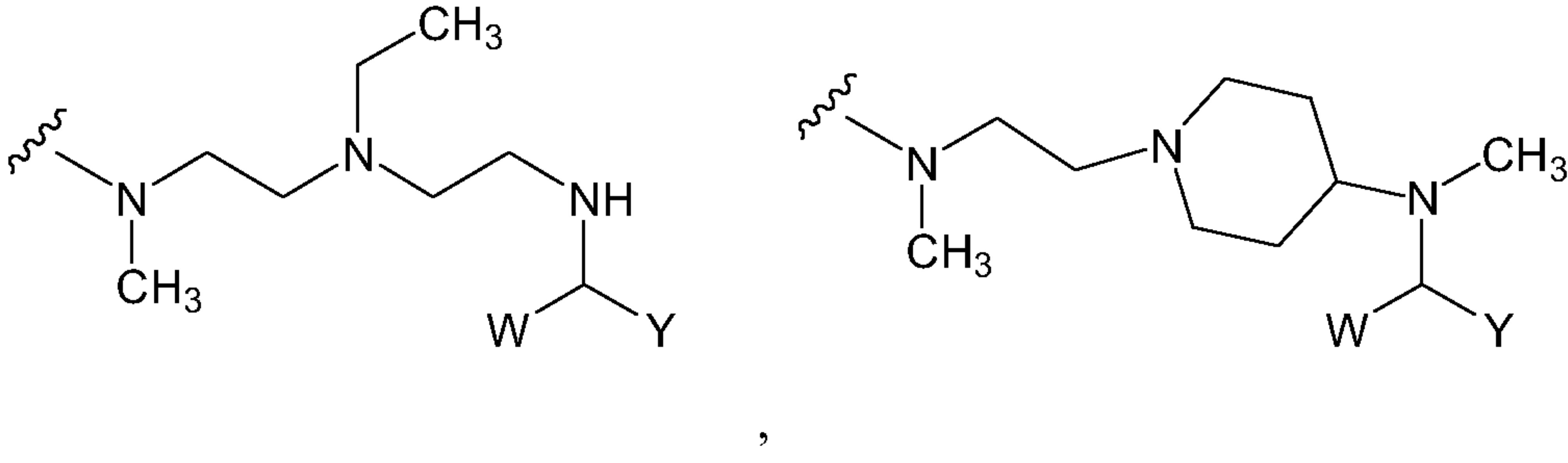
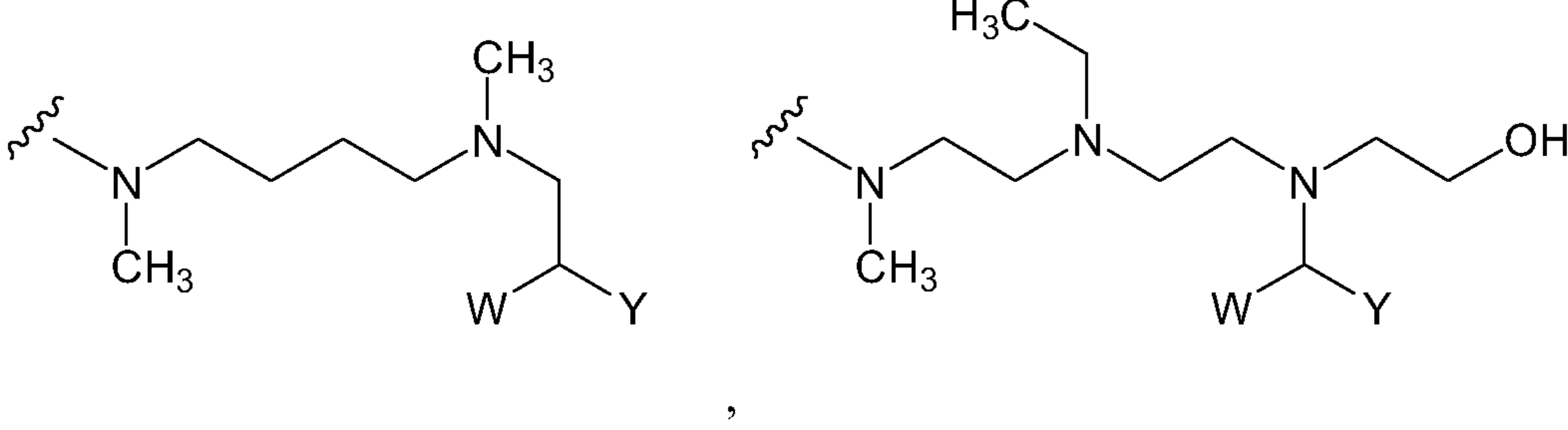
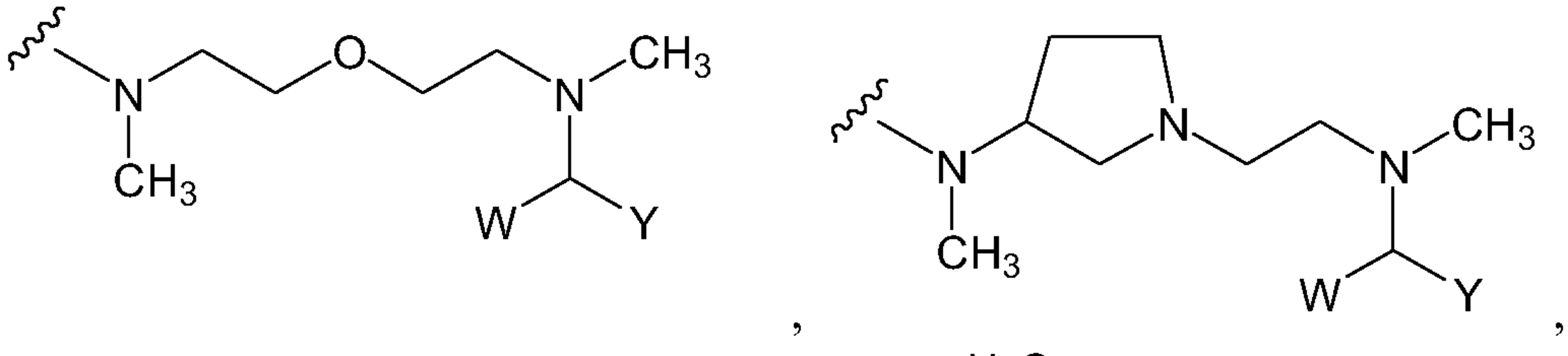
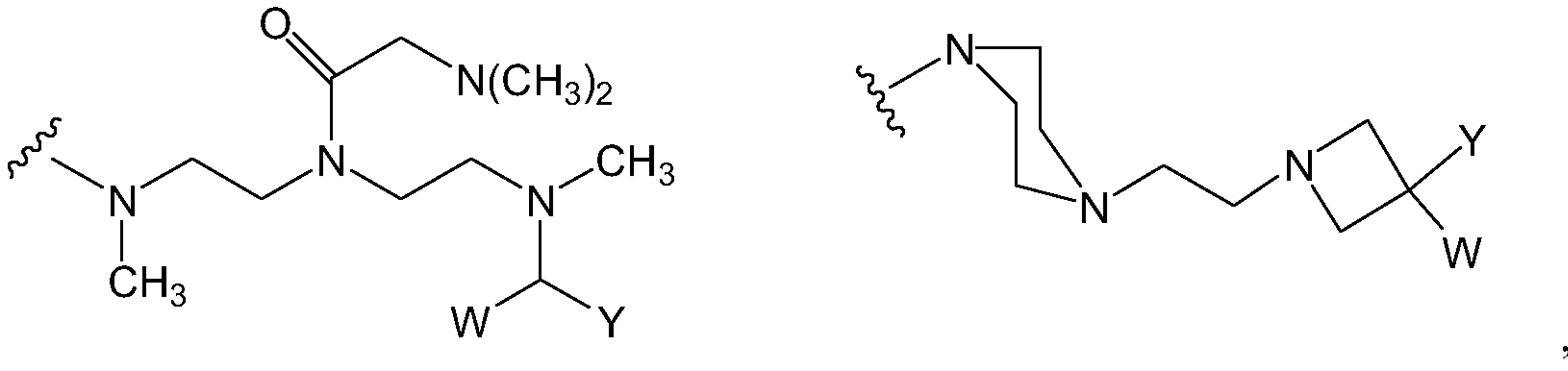
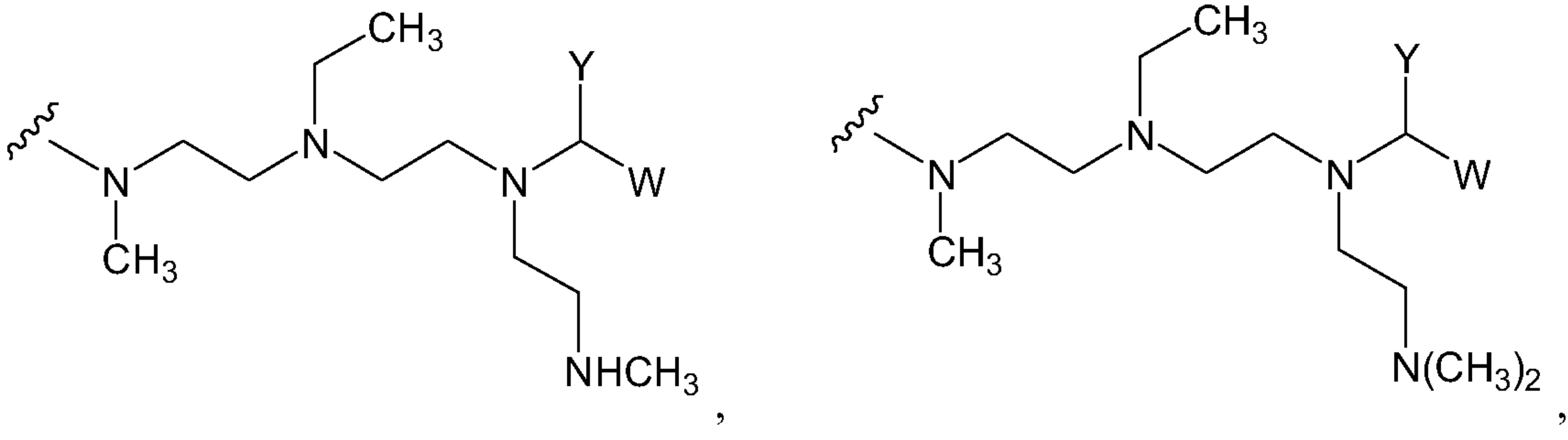
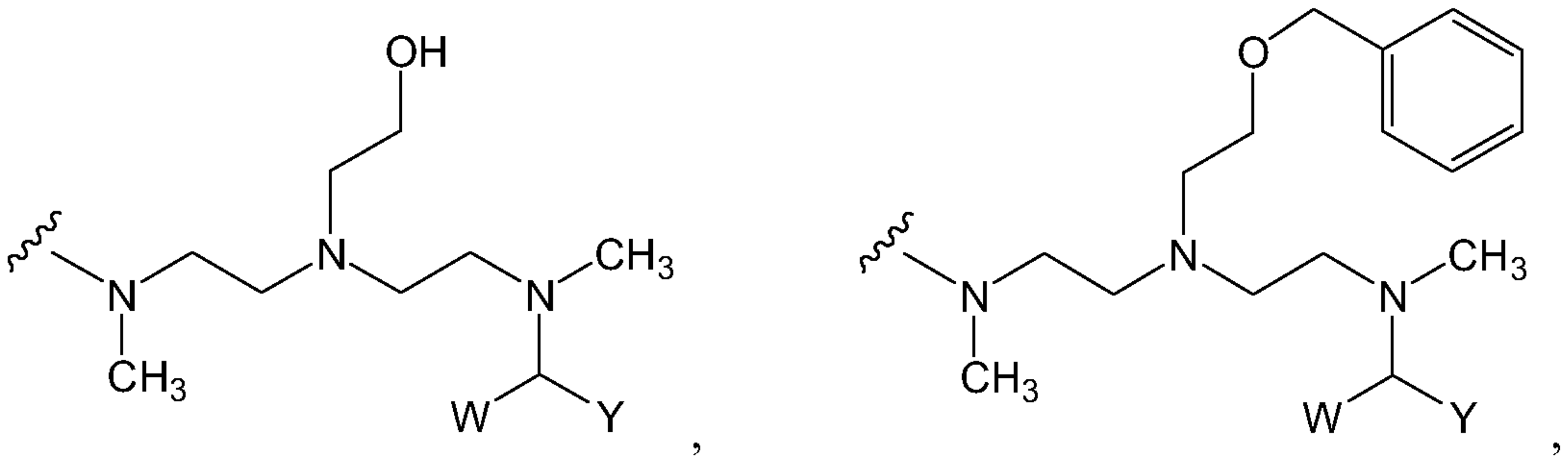


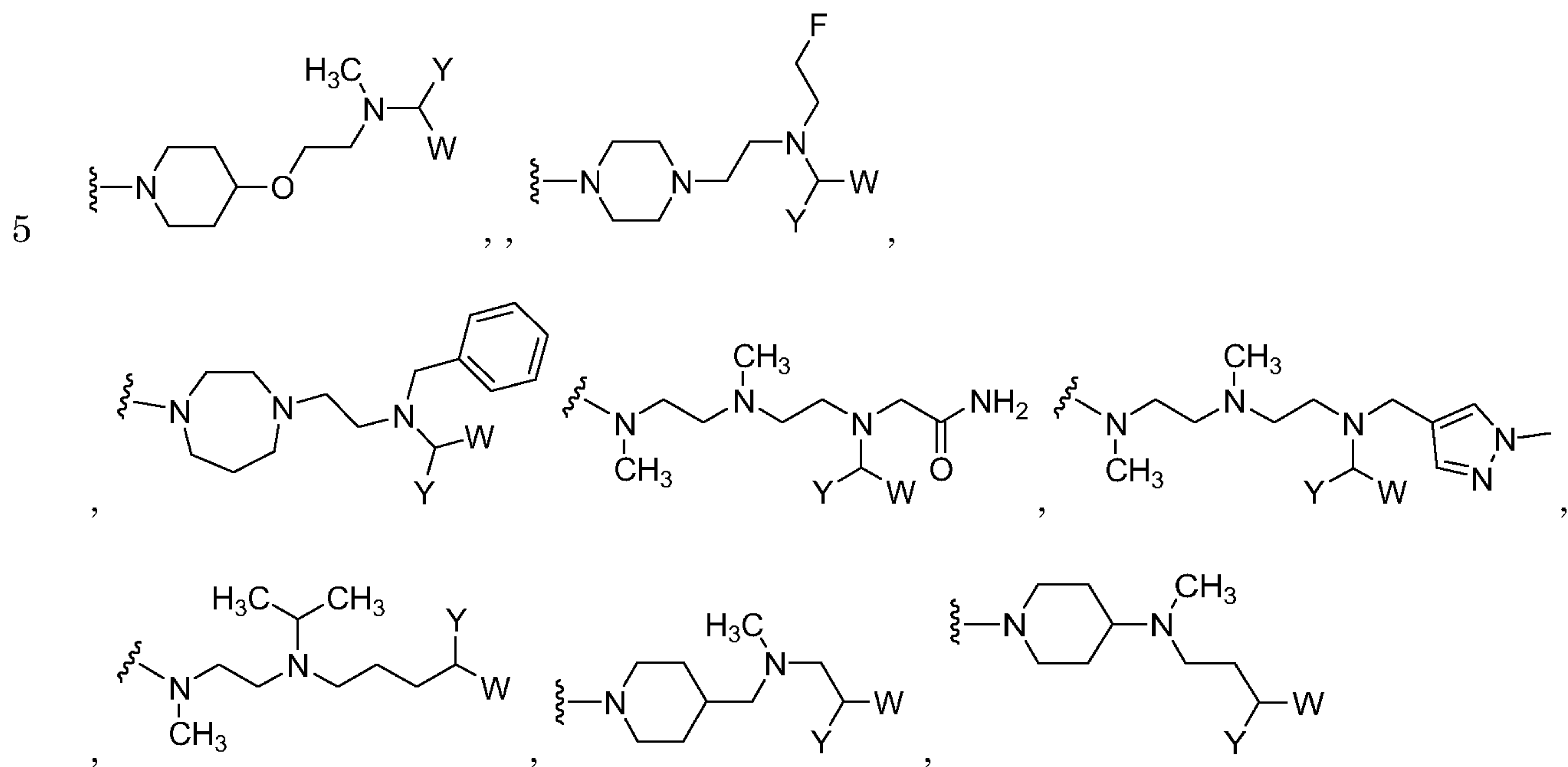
5

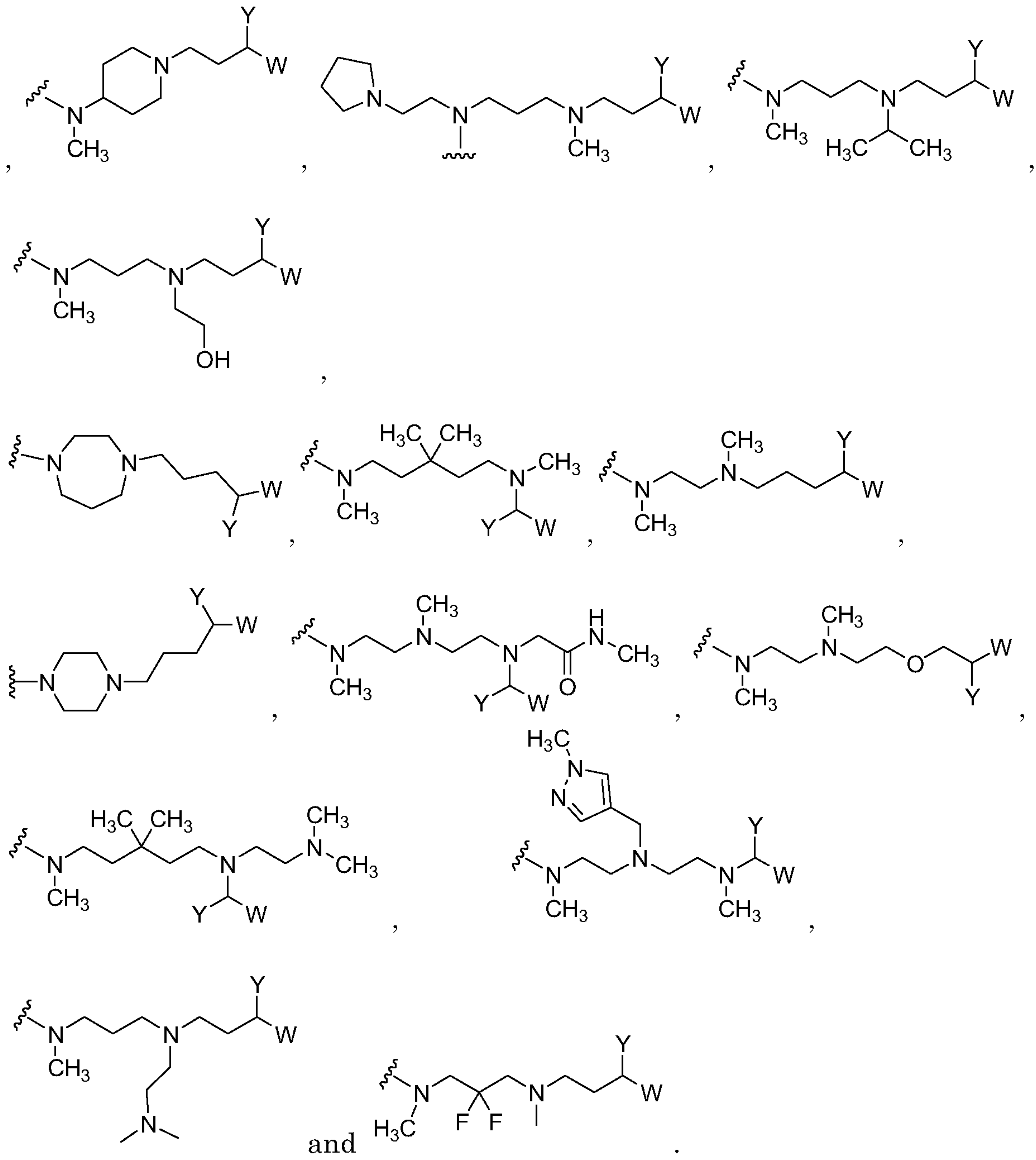


10

- 6 -

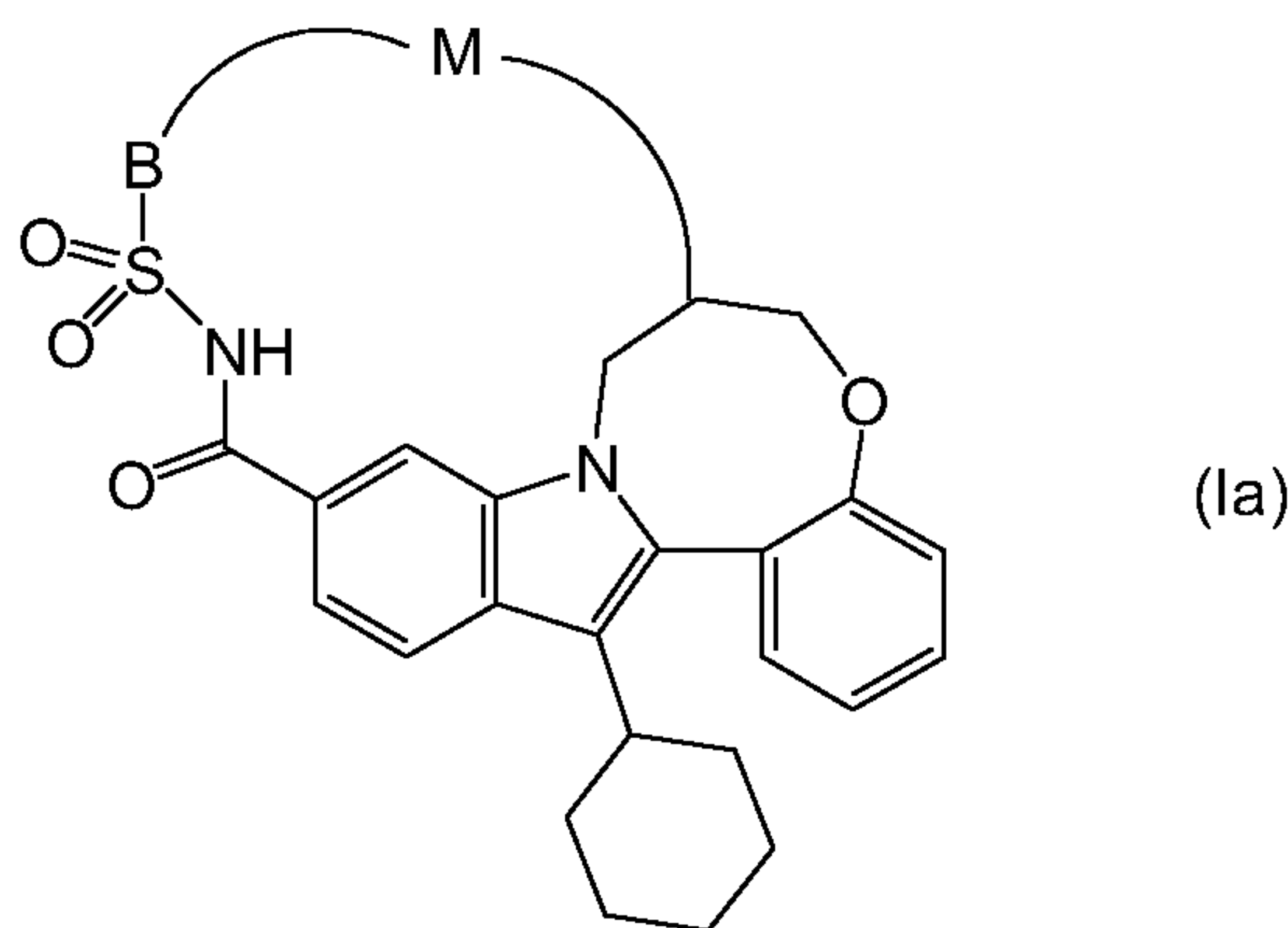






10 In another embodiment of the present invention, there is provided the compound of formula (Ia):

- 9 -



or a pharmaceutically acceptable salt thereof, wherein M and B are as defined in relation to formula (I).

When any variable occurs more than one time in formula (I) or in any substituent, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term “alkyl”, “alkenyl”, “alkynyl” or “alkoxy” as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is propargyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

As used herein, the term “alkylene” means that the alkyl group links two separate groups and may be straight or branched. Examples of suitable alkylene groups include ethylene [–CH₂–CH₂–] and propylene [–CH₂–CH₂–CH₂–, –CH(CH₃)–CH₂– or –CH₂–CH(CH₃)–]. The terms “alkenylene” and “alkynylene” shall be construed in an analogous manner.

When used herein, the term “halogen” means fluorine, chlorine, bromine and iodine.

When used herein, the term “aryl” as a group or part of a group means a carbocyclic aromatic ring. Examples of suitable aryl groups include phenyl and naphthyl.

When used herein, the term “heteroaryl” as a group or part of a group means a 5- to 10-membered heteroaromatic ring system containing 1 to 4 heteroatoms selected from N, O and S. Particular examples of such groups include pyrrolyl, furanyl, thienyl, pyridyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, oxadiazolyl, thiadiazolyl, triazinyl, tetrazolyl, indolyl, benzothienyl, benzimidazolyl, benzofuryl, quinolinyl and isoquinolinyl.

Where a compound or group is described as “optionally substituted” none, one or more substituents may be present. Furthermore, optional substituents may be attached to the compounds or groups which they substitute in a variety of ways, either directly or through a connecting group of which the following are examples: amine, amide, ester, ether, thioether, sulfonamide, sulfamide, sulfoxide, urea, thiourea and urethane. As appropriate an optional

substituent may itself be substituted by another substituent, the latter being connected directly to the former or through a connecting group such as those exemplified above.

Specific compounds within the scope of this invention include:

- (7*R*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-isopropyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 15 (7*R*)-14-cyclohexyl-18-(cyclopropylmethyl)-21,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (20*R*)-30-cyclohexyl-21-methyl-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- 20 (7*S*)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(epoxyethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 25 (7*R*)-14-cyclohexyl-18,21,24-trimethyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 13-cyclohexyl-5,17,20,23-tetramethyl-6,7-dihydro-5*H*-10,6-(methanoiminothioiminoethanoiminoethanoiminomethano)indolo[1,2-*d*][1,4]benzodiazepin-14-one 16,16-dioxide;
- 30 13-cyclohexyl-3-methoxy-17,20-dimethyl-6,7-dihydro-5*H*-6,10-(ethanoiminoethanoiminothioiminomethano)indolo[2,1-*a*][2]benzazepin-14-one 16,16-dioxide;
- (7*R*)-14-cyclohexyl-3-fluoro-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 35 (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-21-ethyl-3-fluoro-18-methyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)-indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;

- 11 -

- (+)-14-cyclohexyl-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 5 (-)-14-cyclohexyl-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*S*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 (7*R,S*)-14-[(1*R,2S*) or (1*S,2R*)-2-fluorocyclohexyl]-18,23-dimethyl-7,8-dihydro-6*H*-11,7-(methanoiminothioiminobutanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (20*S*)-31-cyclohexyl-10-methyl-19,22-dioxa-9-thia-1,8,10,13-tetraazahexacyclo[18.9.1.1^{2,6}.1^{3,29}.0^{13,17}.0^{23,28}]dotriaconta-2(32),3,5,23,25,27,29(31)-heptaen-7-one 9,9-dioxide;
- 15 (18*R*)-29-cyclohexyl-10,17-dimethyl-20-oxa-9-thia-1,8,10,14,17-pentaazahexacyclo[16.9.1.1^{2,6}.1^{3,27}.1^{11,14}.0^{21,26}]hentriaconta-2(31),3,5,21,23,25,27(29)-heptaen-7-one 9,9-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-4,18,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 20 (7*R*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanooxyethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 25 (16*S,18R*)-29-cyclohexyl-10,17-dimethyl-20-oxa-9-thia-1,8,10,13,17-pentaazahexacyclo[16.9.1.1^{2,6}.1^{3,27}.1^{13,16}.0^{21,26}]hentriaconta-2(31),3,5,21,23,25,27(29)-heptaen-7-one 9,9-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-4-propyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 30 31-cyclohexyl-8-oxa-24-thia-1,4,16,23,25-pentaazaheptacyclo[23.2.2.1^{4,6}.1^{6,16}.1^{15,18}.1^{17,21}.0^{9,14}]tritriaconta-9,11,13,15(31),17(30),18,20-heptaen-22-one 24,24-dioxide;
- (7*R*)-14-cyclohexyl-18,19,19,21,24-pentamethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 35

- 12 -

- (7*R*)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 5 (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-methoxy-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 (7*R*)-14-cyclohexyl-21-ethyl-4-methoxy-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-methoxy-18,24-dimethyl-21-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-
15 *e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 2-[(7*R*)-14-cyclohexyl-18,21-dimethyl-17,17-dioxido-15-oxo-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-24-yl]-*N*-methylacetamide;
- (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-18,21,21-trimethyl-7,8-dihydro-6*H*-7,11-(epiminopentanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 20 (7*R*)-14-cyclohexyl-18,21,24-trimethyl-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-methoxy-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
25 dioxide;
- 30-cyclohexyl-18-oxa-2-thia-1,3,10,24-tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- 30 (-)-14-cyclohexyl-3-methoxy-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (+)-14-cyclohexyl-3-methoxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
35 dioxide;
- (-)-14-cyclohexyl-3-methoxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;

- 13 -

- 14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-3-methoxy-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
(7*R* or 7*S*)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6*H*-7,11-
- 5 (methanooxyethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
(7*R*)-14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 14-cyclohexyl-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
(7*R*)-21-[2-(benzyloxy)ethyl]-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
- 15 17,17-dioxide;
(7*R*)-14-cyclohexyl-21-(2-hydroxyethyl)-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
(7*R*)-14-cyclohexyl-21-isobutyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-
- 20 (epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
(7*R*)-14-cyclohexyl-21-(*N,N*-dimethylglycyl)-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 25 (7*R*)-14-cyclohexyl-21-ethyl-18-(2-hydroxyethyl)-24-methyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
(7*R*)-14-cyclohexyl-21,24-diethyl-18-methyl-7,8-dihydro-6*H*-7,11-
- 30 (epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
20-benzyl-13-cyclohexyl-17,23-dimethyl-6,7-dihydro-5*H*-6,10-(epiminoethanoiminoethanoiminothioiminomethano)indolo[2,1-*a*][2]benzazepin-14-one 16,16-dioxide;
(7*R*)-14-cyclohexyl-2-fluoro-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-
- 35 (epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;

- 14 -

- (7*R*)-14-cyclohexyl-21-ethyl-3-fluoro-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 5 (7*R*)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-2-fluoro-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 (7*R*)-14-cyclohexyl-21-ethyl-2-fluoro-18-methyl-24-(pyridin-3-ylmethyl)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-3-fluoro-21-isopropyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 15 (7*R*)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-24-[2-(methylamino)ethyl]-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-2-fluoro-21-isopropyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 20 (7*R*)-14-cyclohexyl-21-ethyl-3-methoxy-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 25 (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-18,21,24-trimethyl-4-propyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 30 (7*R*)-14-cyclohexyl-21-isopropyl-18,24-dimethyl-4-propyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-24-(2-hydroxyethyl)-3,18-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 35

- 15 -

- (7*R*)-14-cyclohexyl-21-ethyl-3,18,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 5 (7*R*)-14-cyclohexyl-3,18,21,24-tetramethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-21-ethyl-18-methyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 (7*R*)-14-cyclohexyl-21-isopropyl-3,18,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-21-ethyl-4,18-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 15 (7*R*)-14-cyclohexyl-21-[2-(dimethylamino)ethyl]-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (18*R*)-29-cyclohexyl-10,17-dimethyl-20-oxa-9-thia-1,8,10,13,17-pentaazahexacyclo[16.9.1.1^{2,6}.1^{3,27}.1^{13,16}.0^{21,26}]hentriaconta-2(31),3,5,21,23,25,27(29)-heptaen-7-one 9,9-dioxide;
- 20 (3*R*)-31-cyclohexyl-2,22-dimethyl-5-oxa-21-thia-2,13,20,22,25-pentaazahexacyclo[23.2.2.1^{3,13}.1^{12,15}.1^{14,18}.0^{6,11}]dotriaconta-6,8,10,12(31),14(30),15,17-heptaen-19-one 21,21-dioxide;
- 25 (5*R*)-31-cyclohexyl-4,24-dimethyl-7-oxa-23-thia-1,4,15,22,24-pentaazahexacyclo[23.2.2.1^{5,15}.1^{14,17}.1^{16,20}.0^{8,13}]dotriaconta-8,10,12,14(31),16(30),17,19-heptaen-21-one 23,23-dioxide;
- (20*R*)-31-cyclohexyl-21-methyl-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.3.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide;
- 30 (5*R*)-31-cyclohexyl-4,24-dimethyl-7-oxa-23-thia-1,4,15,22,24-pentaazahexacyclo[23.2.2.1^{5,15}.1^{14,17}.1^{16,20}.0^{8,13}]dotriaconta-8,10,12,14(31),16(30),17,19-heptaen-21-one 23,23-dioxide;
- (20*R*)-31-cyclohexyl-21-methyl-18,24-dioxa-2-thia-1,3,10,21-tetraazahexacyclo[23.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide;
- 35

- 16 -

- (20*R*)-31-cyclohexyl-21-[2-(dimethylamino)ethyl]-18,24-dioxa-2-thia-1,3,10,21-tetraazahexacyclo[23.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide;
- 5 (20*R*)-30-cyclohexyl-21-(2-fluoroethyl)-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- (20*R*)-21-benzyl-31-cyclohexyl-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.3.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide;
- 10 (7*S*)-14-cyclohexyl-21-isopropyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-18-methyl-7,8-dihydro-6*H*-7,11-(epiminoethanoxyethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 15 (7*R*)-4-allyl-14-cyclohexyl-21-ethyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-4-fluoro-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 20 (7*R*)-14-cyclohexyl-4-fluoro-21-isopropyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-4-(trifluoromethyl)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 25 (7*R*)-14-cyclohexyl-4-(cyclopropylmethyl)-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 30 2-[(7*R*)-14-cyclohexyl-18,21-dimethyl-17,17-dioxido-15-oxo-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-24-yl]acetamide;
- (7*R*)-14-cyclohexyl-18,21-dimethyl-24-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 35

- 17 -

- (7*R*)-14-cyclohexyl-18,24-dimethyl-4-(morpholin-4-ylmethyl)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 5 (7*R*)-4-(benzyloxy)-14-cyclohexyl-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-methoxy-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 (7*R*)-14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
- 15 dioxide;
- 30-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-23-methyl-18-oxa-2-thia-1,3,10,23-tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- 30-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-22-methyl-18-oxa-2-thia-1,3,10,22-
- 20 tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- 30-cyclohexyl-23-methyl-6-oxa-22-thia-1,14,21,23-tetraazahexacyclo[22.2.2.1^{4,14}.1^{13,16}.1^{15,19}.0^{7,12}]hentriaconta-7,9,11,13(30),15(29),16,18-heptaen-20-one 22,22-dioxide;
- 25 (7*R*) or (7*S*)-14-cyclohexyl-22-methyl-18-(2-pyrrolidin-1-ylethyl)-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*) or (7*S*)-14-cyclohexyl-22-isopropyl-18-methyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
- 30 dioxide;
- (7*R*) or (7*S*)-14-cyclohexyl-22-(2-hydroxyethyl)-18-methyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 31-cyclohexyl-18-oxa-2-thia-1,3,10,24-
- 35 tetraazahexacyclo[22.3.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide;

- 14-cyclohexyl-21-isopropyl-18-methyl-7,8-dihydro-6*H*-7,11-
(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
dioxide;
- 5 (7*R*)-14-cyclohexyl-4-methoxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-
(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
dioxide;
- (7*R*)-14-cyclohexyl-18,21-dimethyl-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6*H*-7,11-
(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
dioxide;
- 10 (7*R*)-14-cyclohexyl-18,21,21,24-tetramethyl-7,8-dihydro-6*H*-7,11-
(epiminopentanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-18,22-dimethyl-7,8-dihydro-6*H*-7,11-
(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
dioxide;
- 15 30-[(1*R*,2*S*)-2-fluorocyclohexyl]-23-methyl-18-oxa-2-thia-1,3,10,23-
tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-
one 2,2-dioxide;
- 30-[(1*R*,2*S*)-2-fluorocyclohexyl]-22-methyl-18-oxa-2-thia-1,3,10,22-
tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-
20 one 2,2-dioxide;
- 30-cyclohexyl-23-methyl-6-oxa-22-thia-1,14,21,23-
tetraazahexacyclo[22.2.2.1^{4,14}.1^{13,16}.1^{15,19}.0^{7,12}]hentriaconta-7,9,11,13(30),15(29),16,18-heptaen-
20-one 22,22-dioxide;
- (7*R*) or (7*S*)-14-cyclohexyl-22-methyl-18-(2-pyrrolidin-1-ylethyl)-7,8-dihydro-6*H*-7,11-
25 (ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
dioxide;
- (7*R*) or (7*S*)-14-cyclohexyl-22-isopropyl-18-methyl-7,8-dihydro-6*H*-7,11-
(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
dioxide;
- 30 (7*R*) or (7*S*)-14-cyclohexyl-22-(2-hydroxyethyl)-18-methyl-7,8-dihydro-6*H*-7,11-
(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
dioxide;
- 31-cyclohexyl-18-oxa-2-thia-1,3,10,24-
tetraazahexacyclo[22.3.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-
35 one 2,2-dioxide;
- 14-cyclohexyl-21-isopropyl-18-methyl-7,8-dihydro-6*H*-7,11-
(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
dioxide;

- (7*R*)-14-cyclohexyl-4-methoxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 5 (7*R*)-14-cyclohexyl-18,21-dimethyl-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-18,21,21,24-tetramethyl-7,8-dihydro-6*H*-7,11-(epiminopentanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 (7*R*)-14-[(1*R*,2*S*)-2-fluorocyclohexyl]-4,18,21-trimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 2-[(7*R*)-14-cyclohexyl-4,18,24-trimethyl-17,17-dioxido-15-oxo-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-21-yl]-*N,N*-dimethylacetamide;
- 15 (7*R*)-14-cyclohexyl-4,18,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4,18,21,24-tetramethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
- 20 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4,18,24-trimethyl-21-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclopentyl-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
- 25 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-methoxy-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoxyethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 30 (7*R*)-14-cyclohexyl-4,18,21-trimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4,18,22-trimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
- 35 dioxide;
- (7*R*)-14-cyclohexyl-22-[2-(dimethylamino)ethyl]-4,18-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;

(20*R*)-30-cyclohexyl-15-methoxy-23-methyl-18-oxa-2-thia-1,3,10,23-tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;

(7*R*)-14-cyclohexyl-20,20-difluoro-3-methoxy-18,22-dimethyl-7,8-dihydro-6*H*-7,11-

5 (ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;

and pharmaceutically acceptable salts thereof.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulfonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulfuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulfate ester, or reduction or oxidation of a susceptible functionality.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

- 21 -

The present invention also includes within its scope any enantiomers, diastereomers, geometric isomers and tautomers of the compounds of formula (I). It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the invention.

5 The present invention further provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in therapy.

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for treatment or prevention of infection by hepatitis C virus in a human or animal.

10 In another aspect, the invention provides the use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of infection by hepatitis C virus in a human or animal.

15 A further aspect of the invention provides a pharmaceutical composition comprising a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier. The composition may be in any suitable form, depending on the intended method of administration. It may for example be in the form of a tablet, capsule or liquid for oral administration, or of a solution or suspension for administration parenterally.

20 The pharmaceutical compositions optionally also include one or more other agents for the treatment of viral infections such as an antiviral agent, or an immunomodulatory agent such as α -, β - or γ -interferon.

25 In a further aspect, the invention provides a method of inhibiting hepatitis C virus polymerase and/or of treating or preventing an illness due to hepatitis C virus, the method involving administering to a human or animal (preferably mammalian) subject suffering from the condition a therapeutically or prophylactically effective amount of the pharmaceutical composition described above or of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof. "Effective amount" means an amount sufficient to cause a benefit to the subject or at least to cause a change in the subject's condition.

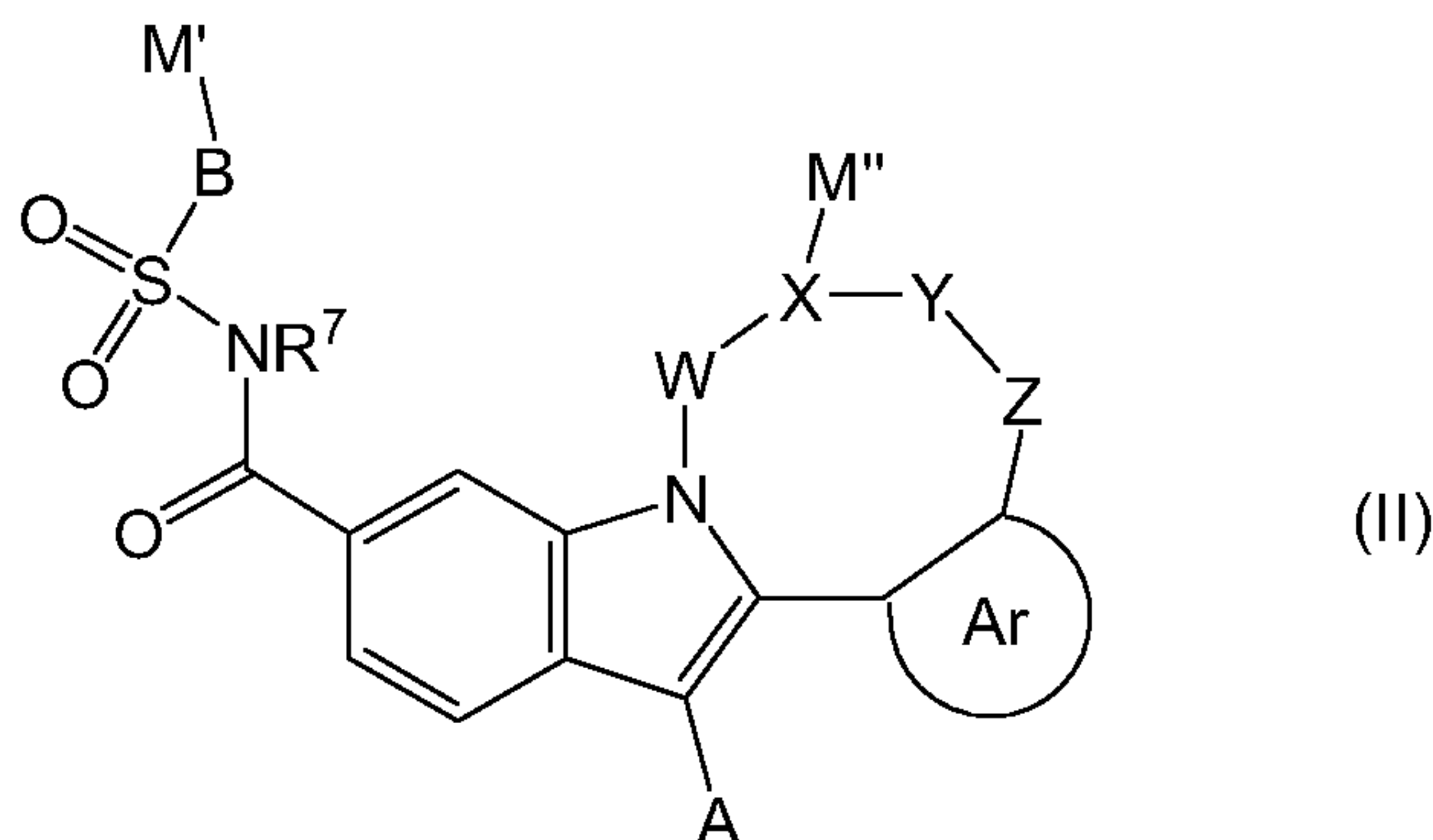
30 The dosage rate at which the compound is administered will depend on a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age of the patient, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition and the host undergoing therapy. Suitable dosage levels may be of the order of 0.02 to 5 or 10 g per day, with oral dosages two to five times higher. For instance, administration of from 1 to 50 mg of the compound per kg of body weight from one to three
35 times per day may be in order. Appropriate values are selectable by routine testing. The compound may be administered alone or in combination with other treatments, either simultaneously or sequentially. For instance, it may be administered in combination with effective amounts of antiviral agents, immunomodulators, anti-infectives or vaccines known to

those of ordinary skill in the art. It may be administered by any suitable route, including orally, intravenously, cutaneously and subcutaneously. It may be administered directly to a suitable site or in a manner in which it targets a particular site, such as a certain type of cell. Suitable targeting methods are already known.

5 An additional aspect of the invention provides a method of preparation of a pharmaceutical composition, involving admixing at least one compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable adjuvants, diluents or carriers and/or with one or more other therapeutically or prophylactically active agents.

10 The present invention also provides a process for the preparation of compounds of formula (I).

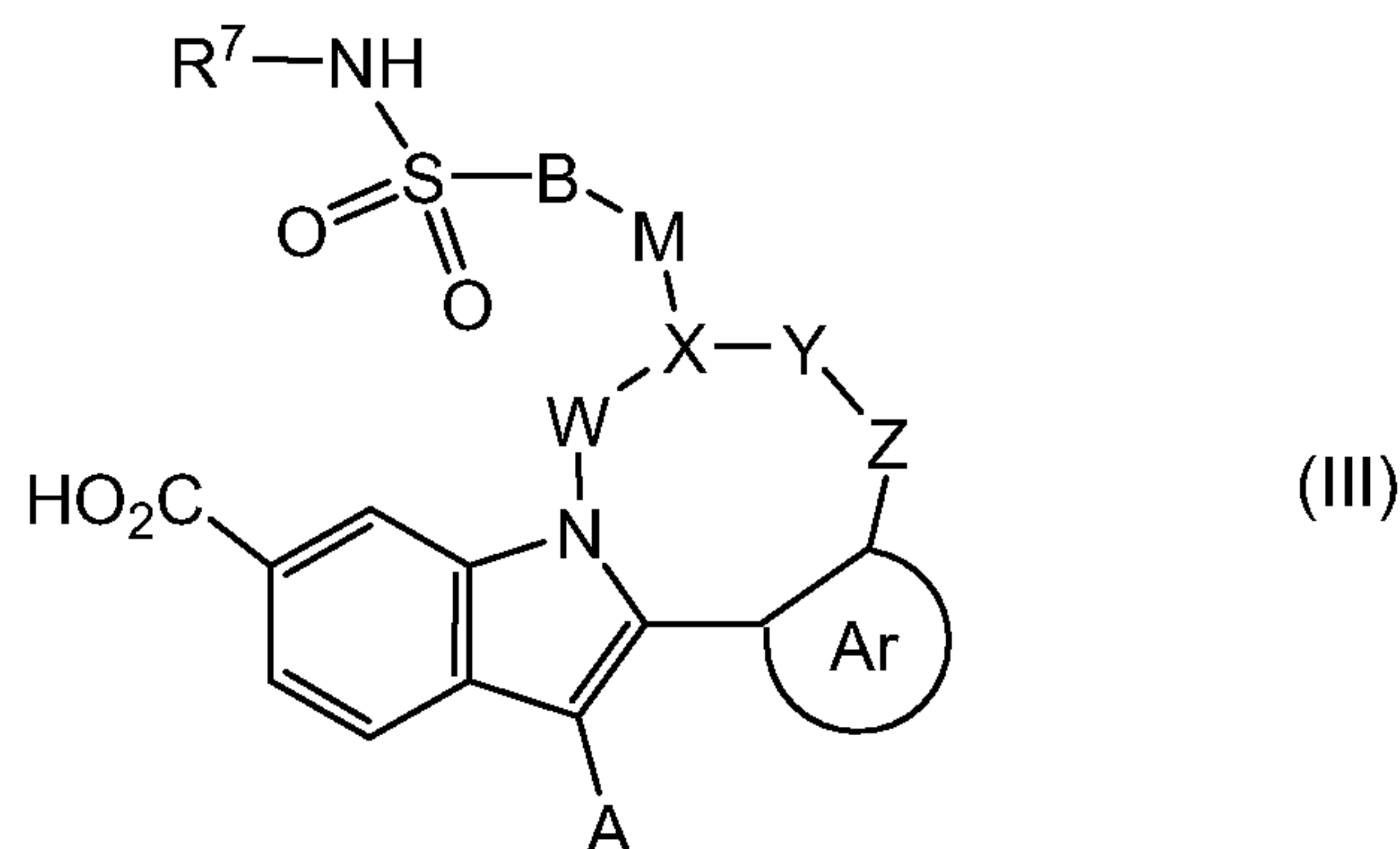
According to a general process (a), compounds of formula (I) may be prepared by internal ring closure of the compound of formula (II):



15 where A is cyclohexyl optionally substituted by a fluorine, Ar is a phenyl ring optionally substituted by Q. Q, B, R⁷, W, Y and Z are as defined in relation to formula (I), X is CR⁹ and M' and M'' have suitable precursor functionality to form group M as defined in relation to formula (I). For instance, when M is -CH₂-CH₂-NH-CH₂-CH₂-N(CH₃)-, M' can be -CH₂-CHO and M'' can be -N(CH₃)-CH₂-CH₂-NH₂, where the reaction is carried out in the presence of a mild
20 reducing agent, such as sodium cyanoborohydride, in a suitable solvent mixture, such as aqueous methanol, at pH 5-6.

According to a general process (b), compounds of formula (I) may be prepared by internal ring closure of the compound of formula (III):

- 23 -



where A is cyclohexyl optionally substituted by a fluorine, Ar is a phenyl ring optionally substituted by Q. Q, B, M, R¹, W, Y and Z are as defined in relation to formula (I) and X is CR⁹. The reaction is conveniently carried out in the presence of a coupling reagent, such as EDC, and an additive, such as DMAP, in a suitable solvent such as DMF, DCM and mixtures thereof.

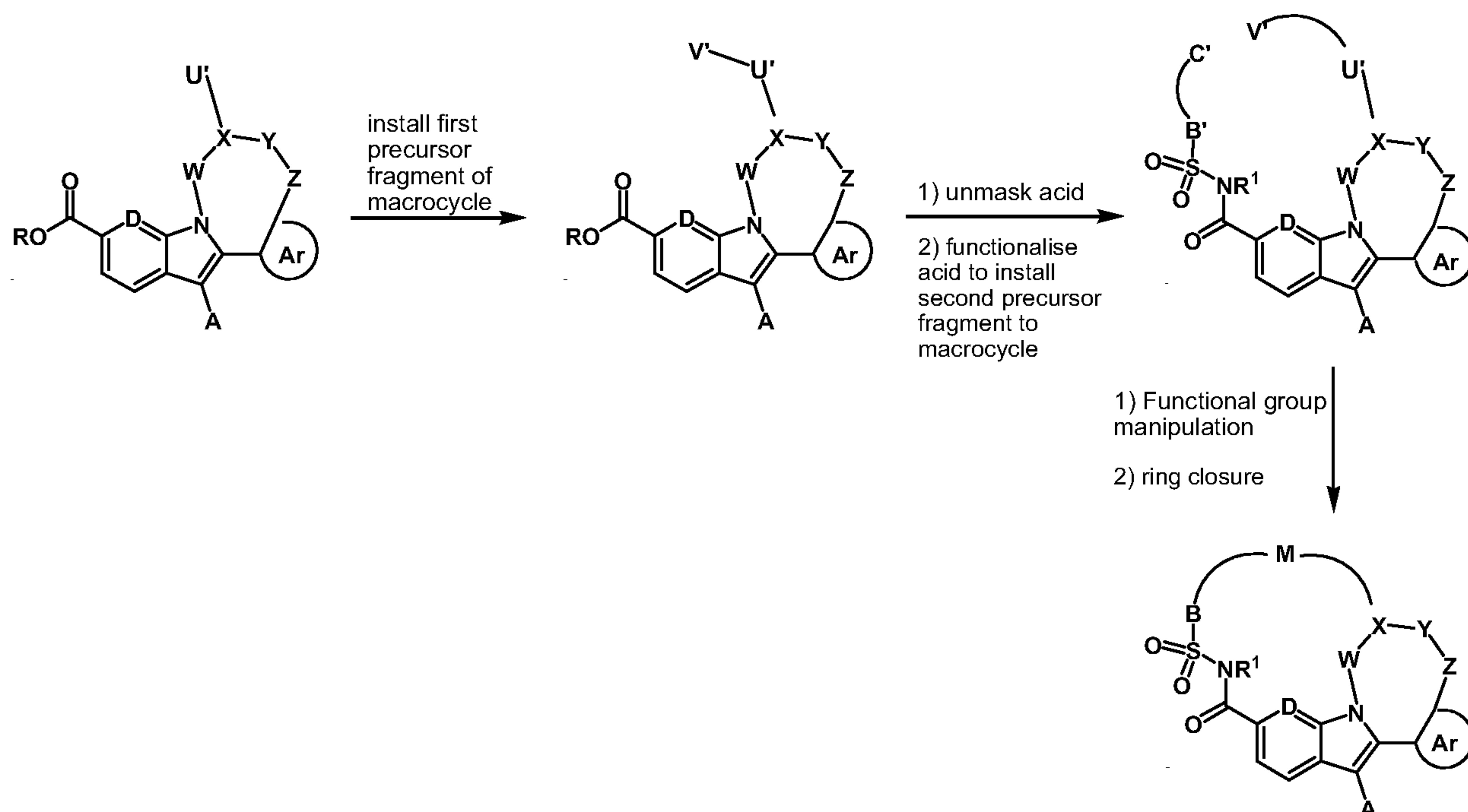
Compounds of formulae (II) and (III) are either known in the art or may be prepared by conventional methodology well known to one of ordinary skill in the art using, for instance, procedures described in the accompanying Descriptions and Examples, or by alternative procedures which will be readily apparent.

Compounds of formula (I) can be converted into other compounds of formula (I) using synthetic methodology well known in the art. For instance, the compound of formula (I) where M comprises an N-H group may be converted into the compound of formula (I) where M comprises an N-CH₃ group by methylation using formaldehyde followed by a mild reducing agent, such as sodium borohydride. By analogy, using similar conditions, the compound of formula (I) where M comprises an N-H group may be converted into the compound of formula (I) where M comprises an N-CH₂CH₃ or an N-CH(CH₃)₂ group by using acetaldehyde or acetone, respectively. Alternatively, alkylation of the N-H group may be carried out using a suitable alkyl halide and a base, such as potassium carbonate, in a suitable solvent, such as acetone, MeCN or DMF.

General Synthetic schemes

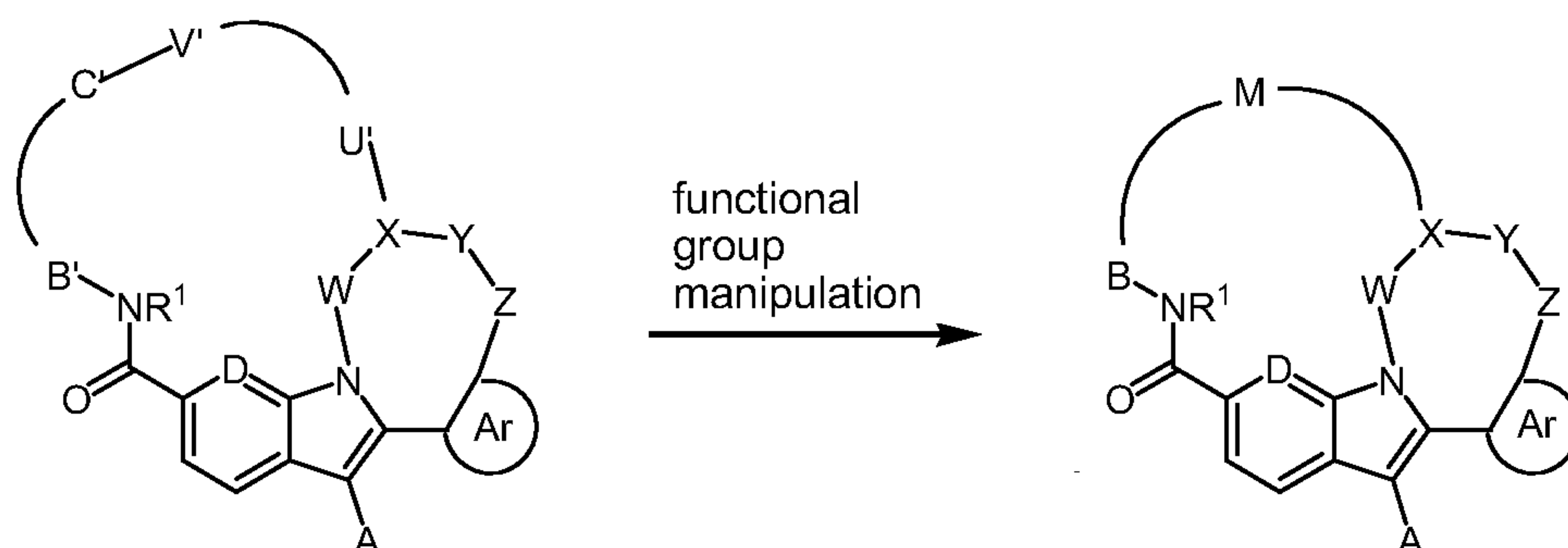
Three general strategies were employed for assembly of compounds from the macrocyclic class (**Methods A, B and C**); **Method B** can be regarded as an extension of **Method A**.

Method A



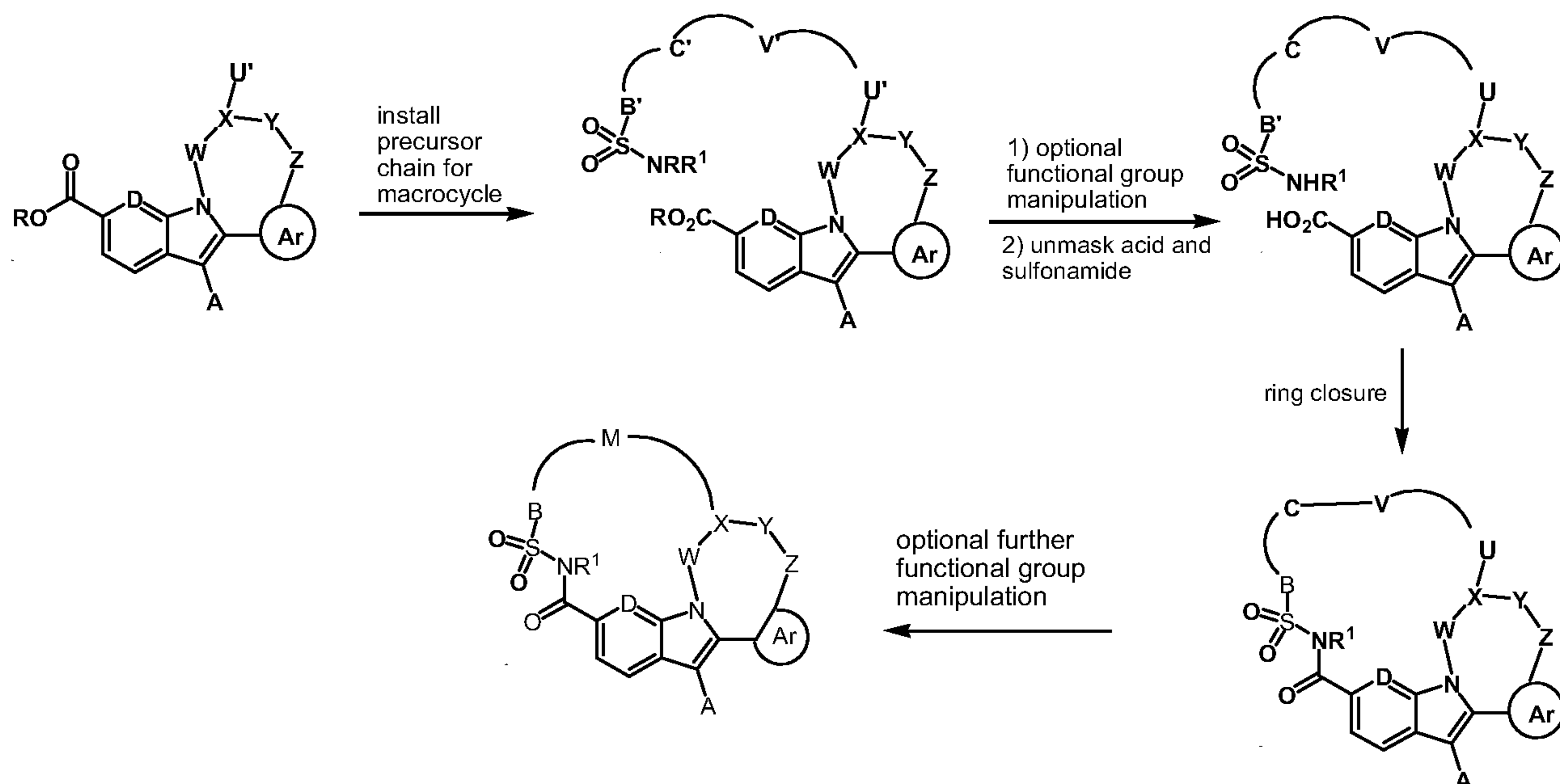
5 A suitably functionalised tether was assembled first (as described in published International patent applications WO2006/046030, WO2006/046039 and WO2007/054741). A precursor fragment to one section of the macrocycle was installed on the tether, with subsequent unmasking of the acid at C6 and functionalisation to introduce a precursor fragment to the remaining segment of the macrocycle. Functional group manipulation and macrocyclisation (*e.g.*, *via* amide bond formation, alkylation, reductive amination, metathesis *etc*) set up the macrocycle. Potentially, the bond formed in ring closure could be at almost any point around the macrocyclic linker (*e.g.*, forming the acylsulfonylurea bond could also be the ring closing step).

Method B



15 Functional groups on the macrocycle were manipulated post-closure, *e.g.*, *via* reductive amination, alkylation, amide reduction, amide formation *etc*. Potentially, sidechains can branch from any point around the macrocyclic linker.

Method C



A suitably functionalised tether was assembled first (as described in published International patent applications WO 2006/046030, WO 2006/046039 and WO 2007/054741). A precursor fragment to the macrocycle was installed on the tether (either step-wise or as a single transformation). Optionally, functionality on this precursor to the macrocycle could be modified prior to unmasking of the acid at C6 of the indole and, if appropriate the sulfonamide moiety, followed by macrocyclisation (*e.g.*, *via* amide bond formation) to set up the macrocycle.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 4th edition, 2007. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The present invention is illustrated further by the following non-limiting examples.

The compounds of the invention were tested for inhibitory activity against the HCV RNA dependent RNA polymerase (NS5B) in an enzyme inhibition assay as described in example i). The compounds generally have IC₅₀'s below 100 nM in this assay.

The potential for compounds of the invention to inhibit HCV replication may be demonstrated using a cell based sub-genomic replication assay as described in example ii).

Compound names in the examples were generated using software from ACDLabs (version 8.0).

i) In-vitro HCV NS5B Enzyme Inhibition Assay

Published International patent application WO 96/37619 describes the production of recombinant HCV RdRp from insect cells infected with recombinant baculovirus encoding the enzyme. The purified enzyme was shown to possess *in vitro* RNA polymerase activity using RNA as template. The reference describes a polymerisation assay using poly(A) and oligo(U) as a primer or an heteropolymeric template. Incorporation of tritiated UTP or NTPs is quantified by measuring acid-insoluble radioactivity. The present inventors have employed this assay to screen the various compounds described above as inhibitors of HCV RdRp.

Incorporation of radioactive UMP was measured as follows. The standard reaction (50 µl) was carried out in a buffer containing 20 mM tris/HCl pH 7.5, 5 mM MgCl₂, 1 mM DTT, 50 mM NaCl, 0.03% N-octylglucoside, 1 µCi [³H]-UTP (40 Ci/mmol, NEN), 10 µM UTP and 10 µg/ml poly(A) or 5µM NTPs and 5µg/ml heteropolymeric template. Oligo(U)₁₂ (1 µg/ml, Genset) was added as a primer in the assay working on Poly(A) template. The final NS5B enzyme concentration was 5 nM. The order of assembly was: 1) compound, 2) enzyme, 3) template/primer, 4) NTP. After 1 h incubation at 22 °C the reaction was stopped by adding 50 µl of 20% TCA and applying samples to DE81 filters. The filters were washed thoroughly with 5% TCA containing 1M Na₂HPO₄/NaH₂PO₄, pH 7.0, rinsed with water and then ethanol, air dried, and the filter-bound radioactivity was measured in the scintillation counter. Carrying out this reaction in the presence of various concentrations of each compound set out above allowed determination of IC₅₀ values by utilising the formula:

$$\% \text{ Residual activity} = 100 / (1 + [I] / IC_{50})^s$$

where [I] is the inhibitor concentration and “s” is the slope of the inhibition curve.

ii) Cell based HCV Replication Assay

Cell clones that stably maintain subgenomic HCV replicon were obtained by transfecting Huh-7 cells with an RNA replicon identical to I₃₇₇neo/NS3-3'/wt described by Lohmann *et al.* (1999) (EMBL-genbank No. AJ242652), followed by selection with neomycin sulfate (G418). Viral replication was monitored by measuring the expression of the NS3 protein by an ELISA assay performed directly on cells grown in 96 wells microtiter plates (Cell-ELISA) using the anti-NS3 monoclonal antibody 10E5/24 (as described in published International application WO 02/59321). Cells were seeded into 96 well plates at a density of 10⁴ cells per well in a final volume of 0.1 ml of DMEM/10% FCS. Two hours after plating, 50 µl of DMEM/10% FCS containing a 3x concentration of inhibitor were added, cells were incubated for 96 hours and then fixed for 10 minutes with ice-cold isopropanol. Each condition was tested in duplicate and average absorbance values were used for calculations. The cells were washed twice with PBS,

- 27 -

blocked with 5% non-fat dry milk in PBS + 0.1% Triton X100 + 0.02% SDS (PBSTS) and then incubated o/n at 4°C with the 10E5/24 mab diluted in Milk/PBSTS. After washing 5 times with PBSTS, the cells were incubated for 3 hours at room temperature with Fc specific anti-mouse IgG conjugated to alkaline phosphatase (Sigma), diluted in Milk/PBSTS. After washing again as
5 above, the reaction was developed with p-Nitrophenyl phosphate disodium substrate (Sigma) and the absorbance at 405/620 nm read at intervals. For calculations, we used data sets where samples incubated without inhibitors had absorbance values comprised between 1 and 1.5. The inhibitor concentration that reduced by 50% the expression of NS3 (IC₅₀) was calculated by fitting the data to the Hill equation,

$$\text{Fraction inhibition} = 1 - (A_i - b) / (A_0 - b) = [I]^n / ([I]^n + IC_{50})$$

where:

- A_i = absorbance value of HBI10 cells supplemented with the indicated inhibitor
15 concentration.
- A₀ = absorbance value of HBI10 cells incubated without inhibitor.
- b = absorbance value of Huh-7 cells plated at the same density in the same microtiter plates and incubated without inhibitor.
- n = Hill coefficient.

20 Representative data for compounds of this invention are reported in Tables A and 1- 5.

To determine cytotothe cellular toxicity of the compounds, a standard MTT assay as described by T. Mosmann (Rapid colorimetric assay for cellular growth and survival: application to
25 proliferation and cytotoxicity assays; J Immunol Methods. 1983, 65, 55-63) was used. The assay is based on the capacity of mitochondrial dehydrogenase enzymes in living cells to convert the yellow water-soluble substrate 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) into a dark blue formazan product, which is insoluble in water. The amount of formazan produced is directly proportional to the cell number in a range of cell line.

30 **iii) General Procedures**

All solvents were obtained from commercial sources (Fluka, puriss.) and were used without further purification. With the exception of routine deprotection and coupling steps, reactions were carried out under an atmosphere of nitrogen in oven dried (110 °C) glassware.
35 Organic extracts were dried over sodium sulfate, and were concentrated (after filtration of the drying agent) on rotary evaporators operating under reduced pressure. Flash chromatography was carried out on silica gel following published procedure (W.C. Still *et al.*, J. Org. Chem.

1978, 43, 2923) or on commercial flash chromatography systems (Biotage corporation and Jones Flashmaster II) utilising pre-packed columns.

Reagents were usually obtained directly from commercial suppliers (and used as supplied) but a limited number of compounds from in-house corporate collections were utilised.

5 In the latter case the reagents are readily accessible using routine synthetic steps that are either reported in the scientific literature or are known to those skilled in the art.

¹H NMR spectra were recorded on Bruker AM series spectrometers operating at (reported) frequencies between 300 and 600 MHz. Chemical shifts (δ) for signals corresponding to non-exchangeable protons (and exchangeable protons where visible) are recorded in parts per million (ppm) relative to tetramethylsilane and are measured using the residual solvent peak as
10 reference. Signals are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad, and combinations thereof); coupling constant(s) in hertz (Hz); number of protons. Mass spectral (MS) data were obtained on a Perkin Elmer API 100, or Waters MicroMass ZQ, operating in negative (ES⁻) or positive (ES⁺) ionization mode and results
15 are reported as the ratio of mass over charge (m/z) for the parent ion only. Preparative scale HPLC separations were carried out on a Waters Delta Prep 4000 separation module, equipped with a Waters 486 absorption detector or on an automated Waters Fraction Lynx or Gilson preparative system. In all cases compounds were eluted with linear gradients of water and MeCN both containing 0.1% TFA using flow rates between 15 and 40 mL/min.

20 The following abbreviations are used in the examples, the schemes and the tables:

Ac: acetyl; aq.: aqueous; Ar: aryl; atm: atmosphere; 9-BBN: 9-borabicyclo[3.3.1]nonane; cat.: catalytic; dioxan(e): 1,4-dioxane; dppf: (1,1'-bis(diphenylphosphino)ferrocene); DAST: diethylaminosulfur trifluoride; 1,2-DCE: 1,2-dichloroethane; DCM: dichloromethane; DIAD: diisopropylazodicarboxylate; DIC: 1,3-diisopropyl carbodiimide; DIPEA: diisopropylethyl
25 amine; DMAP: *N,N*-dimethylpyridin-4-amine; DME: dimethoxyethane; DMF: dimethylformamide; DMS: dimethylsulfide; DMSO: dimethylsulfoxide; DMP: Dess-Martin Periodinane; DPPA: diphenylphosphorylazide; EDC: 1-ethyl-(3-dimethylaminopropyl)carbodiimide HCl salt; eq: equivalent(s); Et₃N: triethylamine; EtOAc: ethyl acetate; Et₂O: diethyl ether; EtOH: ethanol; Et₃SiH: triethylsilane; FC: Flash
30 Chromatography; h: hour(s); HOAc: acetic acid; HATU: O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; HOBt: 1 hydroxybenzotriazole; Me: methyl; MeCN: acetonitrile; MeOH: methanol; min: minute(s); Ms: methanesulfonyl; MS: mass spectrum; NBS: *N*-bromo succinimide; PE: petroleum ether; Ph: phenyl; quant.: quantitative; RP-HPLC: reversed phase high-pressure liquid chromatography; RT: room temperature; sat.: saturated; sec:
35 second(s); SFC: Super-critical fluid chromatography; sat. aq.: saturated solution; TBAF: tetrabutyl ammonium fluoride; TBTU: O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate; TFA: trifluoroacetic acid; THF: tetrahydrofuran; THP: tetrahydropyranyl; TMS: trimethylsilyl; Ts: *para*-toluene sulfonyl.

Example 1: (7*R*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A1)

5 Step 1: *N*-(2,2-dimethoxyethyl)-*N*-methylsulfamide

Sulfamide (5 eq) was added to a solution of 2,2-dimethoxy-*N*-methylethanamine in dioxane (0.12 M). The reaction was stirred at reflux overnight. The solvent was removed *in vacuo*, the residue taken up in EtOAc and washed with H₂O, brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the crude material. DCM was added and a precipitated
10 formed, that was collected by filtration. Further trituration of the filtrate with DCM afforded clean product (67 %). ¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 2.67 (s, 3H), 2.98 (d, *J* 5.3, 2H), 3.28 (s, 6H), 4.48 (t, *J* 5.3, 1H), 6.7 (s, 2H).

Step 2: *tert*-butyl (2*R*)-2-({[(4-nitrophenyl)sulfonyl]oxy}methyl)aziridine-1-carboxylate

A solution of *tert*-butyl (2*R*)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)aziridine-1-carboxylate
15 (prepared following literature procedures: Travins, J.M.; Etzkorn, F.A. *Tetrahedron Lett.* **1998**, 39, 9389-9392) in THF/Et₂O (1/1) (0.17 M) was cooled in an ice bath and treated dropwise over 20 min with 1 M TBAF in THF (1.05 eq). The resulting solution was stirred in the ice bath for 30 min, before being quenched by the addition of sat. aq. NaHCO₃ and extracted into Et₂O/PE (4/1). The organic layers were collected, washed with brine, dried over Na₂SO₄, filtered and
20 concentrated *in vacuo*. The residue was taken up in dry DCM (0.17 M) and TEA (1.3 eq) introduced prior to cooling to 0 °C. DMAP (0.1 eq) and 4-nitrobenzenesulfonyl chloride (1.1 eq) were added and the resulting mixture left to stir at RT overnight. The reaction mixture was diluted with DCM and washed with sat. aq. NaHCO₃, water and brine before drying over Na₂SO₄, filtering and concentrating *in vacuo*. The crude was purified by FC (PE/EtOAc 8:2) to
25 afford the title compound as an off-white solid (57%). (ES⁺) *m/z* 359 (M+H)⁺.

Step 3: methyl (7*R*)-7-[(*tert*-butoxycarbonyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

A solution of methyl 3-cyclohexyl-2-(2-hydroxyphenyl)-1*H*-indole-6-carboxylate (prepared as described in published International patent application WO2006/046030) (0.15 M) in DMF was
30 treated with CsF (4 eq) in one portion; the resulting mixture was stirred for 20 min at RT then treated *via* dropping funnel over 30 min with a solution of *tert*-butyl (2*R*)-2-({[(4-nitrophenyl)sulfonyl]oxy}methyl)aziridine-1-carboxylate (1.3 eq) in DMF (0.5 M). The resulting solution was stirred at RT overnight. The reaction mixture was then placed into an ice bath and powdered KO^tBu (1.4 eq) added slowly to the reaction mixture. After 1.5 h, the
35 reaction was quenched with sat. aq. NH₄Cl and extracted into EtOAc. The combined organic layers were washed with water and brine, before being dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified by FC (PE/EtOAc 8:2) affording the product as an off-white foam (85%). (ES⁺) *m/z* 505 (M+H)⁺.

Step 4: methyl (7R)-7-amino-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

Methyl (7R)-7-[(*tert*-butoxycarbonyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.14 M) in DCM was treated with TFA (10 eq) and stirred at RT for 1h. The reaction was diluted with DCM and cautiously basified with aq. NaHCO₃, before separating the phases and extracting the aqueous with DCM. The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the product as an off-white foam (100 %) that was used without further purification. (ES⁺) *m/z* 405 (M+H)⁺; [α]_D²⁰ + 42.3 (c = 1.0, MeOH).

Step 5: methyl (7R)-14-cyclohexyl-7-(methylamino)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

A solution of methyl (7R)-7-amino-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.35 M) in THF was treated dropwise with 2,2,2-trifluoroethyl formate (1.2 eq) and stirred overnight at RT. The volatiles were removed *in vacuo* and the residue dissolved (0.11 M) in THF and treated dropwise with BH₃·DMS complex (2M in THF; 5 eq). The resulting solution was stirred at RT for 20 h. The reaction was quenched by the careful addition of HCl/MeOH (1.25 M) and the resulting solution refluxed for 2 h. The volatiles were then removed *in vacuo* and the residue partitioned between sat. aq. NaHCO₃ and EtOAc. The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude was purified by FC (EtOAc/PE 80:20 +1% NEt₃) to afford the product (79 %). (ES⁺) *m/z* 419 (M+H)⁺; [α]_D²⁰ + 47.4 (c = 0.46, CHCl₃).

Step 6: methyl (7R)-7-[(2-[(*tert*-butoxycarbonyl)amino]ethyl)(methylamino)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution of *tert*-butyl (2-oxoethyl)carbamate (1 eq; 0.38 M) in dry MeOH was added a mixture of methyl (7R)-14-cyclohexyl-7-(methylamino)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.14 M), acetic acid (2 eq) and sodium acetate (1 eq) in dry MeOH, and the mixture stirred at RT for 15 min. Then Pd/C (0.3 weight eq) was added as a slurry in MeOH under N₂. The atmosphere in the reaction vessel was charged with H₂ and the reaction stirred vigorously under a H₂ atmosphere (balloon) at 60 °C overnight. The reaction was allowed to cool to RT, flushed with N₂ and filtered through a plug of celite. The filtrate was concentrated *in vacuo* and the residue purified by FC (PE/EtOAc 2.5:1 to 1.5:1 gradient) to afford the title compound (82%). (ES⁺) *m/z* 562 (M+H)⁺; [α]_D²⁰ + 67.1 (c = 0.67, CHCl₃).

Step 7: (7R)-7-[(2-[(*tert*-butoxycarbonyl)amino]ethyl)(methylamino)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

2N NaOH (aq) (6 eq) was added to a solution of methyl (7R)-7-[(2-[(*tert*-butoxycarbonyl)amino]ethyl)(methylamino)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.02 M) in MeOH/THF (3/1) and the reaction stirred vigorously at 60 °C for 4 h. The reaction was allowed to cool to RT before reducing the volume

of MeOH/THF *in vacuo*. The residue was partitioned between 1N HCl (aq) and EtOAc, ensuring the aqueous phase was acidic. The aqueous was extracted a second time with EtOAc and the combined organics washed with water, brine before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The material was taken on without further purification. MS (ES⁺) *m/z* 548 (M+H)⁺.

Step 8: tert-butyl {2-[(7R)-14-cyclohexyl-11-[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}amino)carbonyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl}(methyl)amino]ethyl}carbamate

To a solution of (7R)-7-[2-[(tert-butoxycarbonyl)amino]ethyl}(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid (0.15 M) in DCM were added sequentially EDC (1.8 eq), N-(2,2-dimethoxyethyl)-N-methylsulfamide (1.8 eq) (prepared as described in Step 1) and DMAP (1.2 eq). The mixture was stirred at 40 °C for 1.5 hours. Further EDC (0.48 eq) and sulfamide (0.5 eq) were introduced and heating continued for 1 h. The reaction was left to cool with stirring overnight. The reaction was diluted with EtOAc and washed with 1N HCl (aq). The aqueous was extracted with EtOAc and the organics combined, washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to leave a brown gum. The residue was purified by RP-HPLC (Waters Xterra column; MeCN/H₂O/0.1 % TFA gradient). Fractions containing the pure compound were combined and lyophilized to afford the product as a white powder (44 %). MS (ES⁺) *m/z* 728 (M+H)⁺.

Step 9: (7R)-7-[(2-aminoethyl)(methyl)amino]-14-cyclohexyl-N-{[methyl(2-oxoethyl)amino]sulfonyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide

A solution of tert-butyl {2-[(7R)-14-cyclohexyl-11-[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}amino)carbonyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]-benzoxazocin-7-yl}(methyl)amino]ethyl}carbamate (0.03 M) in DCM was treated with TFA (100 eq) and water (180 eq) at RT and the resulting mixture stirred vigorously for 3 h at 40 °C. The volatiles were removed *in vacuo* and the residue diluted with Et₂O and re-evaporated to drive off excess TFA. The product was used in the subsequent step without further purification. MS (ES⁺) *m/z* 582 (M+H)⁺; 600 (M+H₂O+H)⁺.

Step 10: (7R)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

Catalytic HOAc was added to a solution of methyl (7R)-7-[(2-aminoethyl)(methyl)amino]-14-cyclohexyl-N-{[methyl(2-oxoethyl)amino]sulfonyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide (0.006 M) in MeOH at RT, followed by NaCNBH₃ (5 eq) and the reaction stirred for 30 mins. Additional NaCNBH₃ (5 eq) was introduced and the reaction stirred for 30 mins. Volatiles were removed *in vacuo* and the residue taken up in MeCN, filtered to remove insoluble material and concentrated *in vacuo*. The residue was purified by RP-HPLC (Waters Xterra column; MeCN/H₂O/0.1 % TFA gradient). Fractions

containing the pure compound were combined and lyophilized to afford the product as a white powder (15 %). ¹H NMR (500 MHz, DMSO-*d*₆ + TFA, 335 K) δ 1.14-1.22 (m, 1H), 1.31-1.40 (m, 2H), 1.53-1.57 (m, 1H), 1.68-1.75 (m, 2H), 1.91-2.07 (m, 4H), 2.39 (s, 3H), 2.63-2.68 (m, 1H), 2.97 (s, 3H), 3.04-3.45 (m, 7H), 3.47-3.49 (m, 1H), 3.98-4.15 (m, 2H), 4.16-4.18 (m, 1H), 4.45-4.59 (m, 1H), 4.61-4.64 (m, 1H), 7.31-7.44 (m, 4H), 7.55-7.58 (m, 1H), 7.92 (d, *J* 8.7, 1H), 8.03 (s, 1H); (ES⁺) *m/z* 566 (M+H)⁺. [α]_D²⁰ = + 73.2 (c = 0.7, DMSO).

Example 2: (7*R*)-14-cyclohexyl-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A2)

Formaldehyde (10 eq) (37 wt % aq solution) was added to a methanolic solution of (7*R*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (Example 1), followed by HOAc (cat.) and NaCNBH₃ (5 eq). After 30 min a further 5 eq NaCNBH₃ and HCHO (37% aqueous solution) were added. Volatiles were removed *in vacuo* and the residue treated with MeCN. The insoluble residue was filtered off and the resultant MeCN solution concentrated *in vacuo*. Purification was by automated RP-HPLC, eluting with MeCN/TFA buffered with 0.1 % TFA gradient. Fractions containing the product were combined and freeze dried to afford the product as a white powder (26 %). ¹H NMR (600 MHz, DMSO-*d*₆ + TFA, 300 K) δ 1.12-1.20 (m, 1H), 1.28-1.41 (m, 2H), 1.45-1.51 (m, 1H), 1.66-1.74 (m, 2H), 1.82-1.88 (m, 1H), 1.89-2.00 (m, 3H), 2.64-2.71 (m, 4H), 2.92 (s, 3H), 3.03 (s, 3H), 3.37-3.62 (m, 7H), 3.69-3.77 (m, 1H), 3.91-3.99 (m, 1H), 4.07-4.16 (m, 1H), 4.21-4.28 (m, 1H), 4.39-4.48 (m, 1H), 4.68-4.74 (m, 1H), 7.28-7.39 (m, 3H), 7.5 (d, *J* 8.3, 1H), 7.55-7.59 (m, 1H), 7.94 (d, *J* 8.3, 1H), 8.09 (s, 1H); (ES⁺) *m/z* 580 (M+H)⁺.

Example 3: (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A3)

Acetaldehyde (10 eq) was added to a methanolic solution of (7*R*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)-indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (Example 1), followed by HOAc (cat.) and NaCNBH₃ (5 eq). After 30 mins, volatiles were removed *in vacuo* and the residue treated with MeCN as described in Example 1. Purification was by automated RP-HPLC, eluting with MeCN/TFA buffered with 0.1 % TFA gradient. Fractions containing the product were combined and freeze dried to afford the product as a white powder (24 %). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.14-1.23 (m, 4H), 1.28-1.37 (m, 2H), 1.40-1.47 (m, 1H), 1.64-1.72 (m, 2H), 1.80-1.87 (m, 1H), 1.89-1.98 (m, 3H), 2.32 (s, 3H), 2.62-2.69 (m, 1H), 2.91-3.00 (m, 2H), 3.02 (s, 3H), 3.12-3.58 (m, 8H), 3.82-3.97 (m, 2H), 4.01-4.07 (m, 1H), 4.34-4.39 (m, 1H), 4.54-4.59 (m, 1H), 7.31-7.39 (m, 3H), 7.46 (d, *J* 8.8, 1H), 7.54-7.59 (m, 1H), 7.91 (d, *J* 8.8, 1H), 8.05 (s, 1H); (ES⁺) *m/z* 594 (M+H)⁺.

Example 4: (7*R*)-14-cyclohexyl-21-isopropyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A4)

Acetone (130 eq) was added to a methanolic solution of (7*R*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)-indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (Example 1), followed by HOAc (cat.) and NaCNBH₃ (40 eq). The reaction was warmed to 40 °C for 2 h before being left to stir overnight at RT. Volatiles were removed *in vacuo* and the residue treated with MeCN. Insolubles were filtered off and the resultant MeCN solution concentrated *in vacuo*. Purification was by automated RP-HPLC, eluting with MeCN/TFA buffered with 0.1 % TFA gradient. Fractions containing the product were combined and freeze dried to afford the product as a white powder (22 %). ¹H NMR (600 MHz, DMSO-*d*₆ + TFA, 320 K) δ 1.12-1.22 (m, 4H), 1.28-1.39 (m, 5H), 1.40-1.47 (m, 1H), 1.65-1.72 (m, 2H), 1.80-1.88 (m, 1H), 1.89-1.98 (m, 3H), 2.42 (s, 3H), 2.65-2.72 (m, 1H), 3.04 (s, 3H), 3.12-3.30 (m, 3H), 3.32-3.44 (m, 2H), 3.47-3.61 (m, 3H), 3.67-3.75 (m, 1H), 3.91-4.02 (m, 2H), 4.08-4.15 (m, 1H), 4.38-4.43 (m, 1H), 4.60-4.66 (m, 1H), 7.32-7.40 (m, 3H), 7.48 (d, *J* 8.4, 1H), 7.54-7.59 (m, 1H), 7.92 (d, *J* 8.4, 1H), 8.09 (s, 1H); (ES⁺) *m/z* 608 (M+H)⁺. [α]_D²⁰ = + 51.6 (c = 1.2, MeOH).

Example 5: (7*R*)-14-cyclohexyl-18-(cyclopropylmethyl)-21,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A5)

Step 1: *N*-(cyclopropylmethyl)-(2,2-dimethoxyethanamine)

A solution of cyclopropanecarboxaldehyde in MeOH (0.2 M) was treated with 2,2-dimethoxyethylamine (1.2 eq). The solution was cooled with an ice/water bath and treated portionwise with NaCNBH₃ (1.0 eq). The pH of the resulting solution was adjusted to 6 with AcOH, and the reaction left at RT for 24 h. The mixture was concentrated, diluted with EtOAc, washed with sat. aq. NaHCO₃, brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product (61 %). ¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 0.05-0.07 (m, 2H), 0.15-0.17 (m, 2H), 0.87-0.93 (m, 1H), 2.39-2.41 (m, 2H), 2.64-2.66 (m, 2H), 3.3 (s, 6H), 4.46 (t, *J* 3.0, 1H), 5.38 (m, 1H).

Step 2: *N*-(cyclopropylmethyl)-*N*-(2,2-dimethoxyethyl)sulfamide

Sulfamide (5 eq) was added to a solution of *N*-(cyclopropylmethyl)-(2,2-dimethoxyethanamine) in dioxane (0.12 M). The reaction was stirred at reflux overnight. The solvent was removed *in vacuo*, the residue taken up in EtOAc and washed with H₂O, brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the crude material. DCM was added and the resultant precipitate removed by filtration, while the filtrate was concentrated *in vacuo* to afford the product (68 %). ¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 0.15-0.19 (m, 2H), 0.44-0.47 (m, 2H), 1.03-1.05 (m, 1H), 2.95-2.98 (m, 2H), 3.17-3.19 (m, 2H), 3.28 (s, 6H), 4.51 (t, *J* 5.0, 1H), 6.63 (s, 2H).

Step 3: (7R)-14-cyclohexyl-18-(cyclopropylmethyl)-21,24-dimethyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

The synthesis to afford the title compound was directly analogous to Examples 1 and 2, using *N*-(cyclopropylmethyl)-*N*-(2,2-dimethoxyethyl)sulfamide in place of *N*-(2,2-dimethoxyethyl)-*N*-methylsulfamide. ¹H NMR (600 MHz, DMSO-*d*₆ + TFA, 300 K) δ 0.23-0.35 (m, 2H), 0.42-0.58 (m, 2H), 0.91-1.09 (m, 1H), 1.14-1.43 (m, 3H), 1.49-1.51 (m, 1H), 1.62-1.73 (m, 2H), 1.82-2.01 (m, 4H), 2.58-2.87 (m, 4H), 2.92 (s, 3H), 3.23-3.25 (m, 1H), 3.31-3.75 (m, 9H), 3.95-3.99 (m, 1H), 4.05-4.15 (m, 1H), 4.20-4.26 (m, 1H), 4.27-4.41 (m, 1H), 4.68-4.70 (m, 1H), 7.26-7.37 (m, 3H), 7.51 (d, *J* 8.4, 1H), 7.48-7.54 (m, 1H), 7.93 (d, *J* 8.4, 1H), 8.09 (s, 1H); (ES⁺) *m/z* 620 (M+H)⁺.

Example 6: (20R)-30-cyclohexyl-21-methyl-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide (A6)

Step 1: tert-butyl 4-(aminosulfonyl)piperazine-1-carboxylate

Sulfamide (5 eq) was added to a solution of *tert*-butyl piperazine-1-carboxylate in dioxane (0.12 M). The reaction was stirred at reflux overnight. The solvent was removed *in vacuo*, the residue taken up in EtOAc and washed with H₂O, brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the crude material. Purification was by automated FC (EtOAc:PE:Et₃N 40:60:0.02) to afford the title compound (70%). ¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.39 (s, 9H), 2.88-2.90 (m, 4H), 3.37-3.39 (m, 4H), 6.78 (s, 2H).

Step 2: methyl (7R)-7-[(2-chloroethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

HOAc (cat.) was added to a stirred mixture of methyl (7R)-14-cyclohexyl-7-(methylamino)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (prepared as described in Example 1, Step 5) (0.03 M) and chloroacetaldehyde (50 wt % in water; 1.5 eq) in MeOH. NaCNBH₃ (1.5 eq) was introduced and the reaction heated at 60 °C for 2 h. The reaction was allowed to cool to RT and partitioned between water and EtOAc. The organics were washed with saturated NaHCO₃ (aq), brine before being dried (Na₂SO₄) filtered and concentrated *in vacuo*. The material was taken on without further purification. (ES⁺) *m/z* 480 (M+H)⁺; 482 (M+H)⁺.

Step 3: (7R)-7-[(2-chloroethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

BBr₃ (1 M solution in DCM; 6 eq) was added to a solution of methyl (7R)-7-[(2-chloroethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.03 M) in DCM at 0 °C. Following complete addition, the cooling bath was removed and the reaction stirred at RT for 15 min. The reaction was then partitioned between 1N HCl (aq) and EtOAc. The organics were washed with brine, dried (Na₂SO₄), filtered and

concentrated *in vacuo*. The resultant carboxylic acid was taken on without further purification. (ES⁺) *m/z* 466 (M+H)⁺; 468 (M+H)⁺.

Step 4: tert-butyl 4-([(7R)-7-[(2-chloroethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-11-yl}carbonyl)amino]sulfonyl}piperazine-1-carboxylate

5 To a solution of (7R)-7-[(2-chloroethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid (0.15 M) in DCM were added sequentially EDC (1.5 eq), tert-butyl 4-(aminosulfonyl)piperazine-1-carboxylate (1.5 eq) (prepared as described in Step 1) and DMAP (3 eq). The mixture was stirred at 40 °C for 2 h. Further EDC (1.5 eq) and protected (aminosulfonyl)piperazine (1 eq) were introduced and heating continued
10 for 2 h. Additional EDC (0.5 eq) and protected (aminosulfonyl)piperazine (0.5 eq) were introduced and heating continued for 1 h. The reaction was allowed to cool before being partitioned between EtOAc and 1N HCl (aq). The aqueous was extracted with EtOAc and the organics combined, washed with saturated NaHCO₃ (aq), brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to leave a yellow gum. (ES⁺) *m/z* 713 (M+H)⁺; 715 (M+H)⁺.

15 Step 5: (7R)-7-[(2-chloroethyl)(methyl)amino]-14-cyclohexyl-N-(piperazin-1-ylsulfonyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide

TFA (100 eq) was added to a stirred solution of tert-butyl 4-([(7R)-7-[(2-chloroethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-11-yl}carbonyl)amino]sulfonyl}piperazine-1-carboxylate (0.12 M) in DCM. The reaction was
20 warmed at 40 °C for 1.5 h. The reaction was allowed to cool to RT and the volatiles were then removed *in vacuo*, diluting with Et₂O and re-concentrating to drive off excess TFA. The material was taken on without further purification. (ES⁺) *m/z* 613 (M+H)⁺; 615 (M+H)⁺

Step 6: (20R)-30-cyclohexyl-21-methyl-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide

DIPEA (20 eq) was added to a solution of (7R)-7-[(2-chloroethyl)(methyl)amino]-14-cyclohexyl-N-(piperazin-1-ylsulfonyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide (0.001 M) in MeCN and the mixture irradiated in a microwave (SmithCreator) at 150 °C for 5 mins. The volatiles were removed *in vacuo* and the residue purified by RP-HPLC,
30 eluting with MeCN/TFA buffered with 0.1 % TFA gradient. Fractions containing the product were combined and freeze dried to afford the product as a white powder (26 % overall for steps 2 through to 6). ¹H NMR (600 MHz, DMSO-*d*₆ + TFA, 330 K) δ 1.12-1.20 (m, 1H), 1.29-1.37 (m, 2H), 1.47-1.49 (m, 1H), 1.68-1.72 (m, 2H), 1.82-1.99 (m, 4H), 2.43 (s, 3H), 2.69-2.74 (m, 1H), 2.96-2.99 (m, 1H), 3.12-3.19 (m, 1H), 3.31-3.61 (m, 8H), 3.71-3.89 (m, 2H), 4.03-4.07 (m, 1H),
35 4.11-4.18 (m, 2H), 4.52-4.58 (m, 1H), 4.62-4.68 (m, 1H), 7.32-7.35 (m, 2H), 7.40-7.42 (m, 1H), 7.48 (d, *J* 8.4, 1H), 7.55-7.58 (m, 1H), 7.91 (d, *J* 8.4, 1H), 7.95 (s, 1H); (ES⁺) *m/z* 592 (M+H)⁺.

Example 7: (7S)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6H-7,11-(epoxyethanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A7)

Step 1 : N-benzyl-2-chloro-N-methylethanaminium chloride

5 2-[benzyl(methyl)amino]ethanol was added dropwise to an excess of SOCl₂ (50 eq) and the mixture heated at 35 °C for 16 h. Volatiles were removed *in vacuo* and the residual oil triturated with Et₂O to give the title compound as a white solid in quantitative yield. (ES⁺) *m/z* 184 (M+H)⁺; 186 (M+H)⁺.

Step 2: N-benzyl-2-{[(7S)-11-carboxy-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl]oxy}-N-methylethanaminium chloride

10 To a suspension of methyl (7S)-14-cyclohexyl-7-hydroxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (prepared as described in International patent application WO2006/046030) in toluene (0.05 M), were added 10 eq of 30% w/w aq. NaOH followed by 0.25 eq of NBu₄Br. After stirring for 30 min, 2.5 eq of N-benzyl-2-chloro-N-methylethanaminium chloride were added and the reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and the residue purified by RP-HPLC (Waters Xterra prep. C18 column, 5μm, 19x100 mm. Mobile phase: MeCN/H₂O buffered with 0.1% TFA). Fractions containing the pure compound were combined and freeze dried in the presence of HCl to afford the title compound (25%) as a white powder. (ES⁺) *m/z* 539 (M+H)⁺.

20 Step 3: (7S)-7-{2-[benzyl(methyl)amino]ethoxy}-14-cyclohexyl-N-{[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide

A solution (0.06 M) of N-benzyl-2-{[(7S)-11-carboxy-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl]oxy}-N-methylethanaminium chloride and DMAP (3 eq) in anhydrous DCM, was treated with EDC (1.5 eq) and N-(2,2-dimethoxyethyl)-N-methylsulfamide (prepared as described in Example 1, Step 1). The mixture was stirred at 40 °C for 14 h, and then diluted with EtOAc, washed with aqueous sat. aq. NaHCO₃ and brine. The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the title compound. The product was used in the next step without further purification. (ES⁺) *m/z* 719 (M+H)⁺.

30 Step 4: (7S)-14-cyclohexyl-N-{[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}-7-[2-(methylamino)ethoxy]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide

Pd/C (1 eq) was added to a solution of (7S)-7-{2-[benzyl(methyl)amino]ethoxy}-14-cyclohexyl-N-{[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide (0.06 M) in MeOH. The resulting mixture was stirred for 12 h under H₂ atmosphere. The mixture was filtered and then concentrated *in vacuo* to afford the title compound. The product was used in the next step without further purification. (ES⁺) *m/z* 629 (M+H)⁺.

Step 5: (7S)-14-cyclohexyl-7-[2-(methylamino)ethoxy]-N-{[methyl(2-oxoethyl)amino]sulfonyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide

A solution of (7S)-14-cyclohexyl-N-{[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}-7-[2-(methylamino)ethoxy]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide (0.06 M) in DCM was treated with an excess of TFA and H₂O (> 50 eq). The mixture was stirred at 40 °C for 30 min. All the volatiles were concentrated *in vacuo* to give the title compound, which was taken on without further purification. (ES⁺) *m/z* 583 (M+H)⁺.

Step 6: (7S)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6H-7,11-(epoxyethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

A solution (4 mM) of (7S)-14-cyclohexyl-7-[2-(methylamino)ethoxy]-N-{[methyl(2-oxoethyl)amino]sulfonyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide in MeOH was treated with NaBH₃CN (10 eq). The mixture was stirred at RT overnight, then quenched with few drops of aqueous sat. aq. NaHCO₃ and concentrated *in vacuo*. The crude was purified by automated RP-MS-HPLC (Waters Xterra prep. C18 column, 5µm, 19x100 mm. Mobile phase: MeCN/H₂O buffered with 0.1% TFA). Fractions containing the pure compound were combined and freeze dried to afford the title compound as a white powder (5 %; over steps 3-6). ¹H NMR (600 MHz, DMSO-*d*₆ + TFA, 335 K) δ 1.10 -1.40 (m, 4H), 1.50 -1.60 (m, 1H), 1.60 -1.70 (m, 2H), 1.80 - 1.90 (m, 1H), 1.90 - 2.0 (m, 2H), 2.60 -2.75 (m, 1H), 2.80 (s, 3H), 3.05 (s, 3H), 3.20 - 3.60 (m, 4H), 3.70 - 4.00 (m, 6H), 4.00 - 4.10 (m, 1H), 4.10 - 4.30 (m, 1H), 4.85 - 4.95 (m, 1H), 7.15 - 7.25 (m, 2H), 7.25 - 7.35 (m, 1H), 7.35 - 7.45 (m, 1H), 7.45 - 7.55 (m, 1H), 7.85 (d, *J* 8.4, 1H), 8.25 (s, 1H); (ES⁺) *m/z* 567 (M+H)⁺.

Example 8: (7R)-14-cyclohexyl-18,21,24-trimethyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A8)

Step 1: 4-bromo-3-hydroxyphenyl 4-methylbenzenesulfonate

K₂CO₃ (3 eq) was added to a stirred mixture of 4-bromoresorcinol (0.35 M) and TsCl (1.2 eq) in acetone and the mixture stirred at 50 °C for 18 h. Volatiles were removed *in vacuo* and the residue partitioned between 6 N HCl (aq) and EtOAc. The combined organic fractions were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound. The product was used in the next step without further purification. (ES⁺) *m/z* 343, 345 (M+H)⁺.

Step 2: 4-bromo-3-(methoxymethoxy)phenyl 4-methylbenzenesulfonate

A solution of 4-bromo-3-hydroxyphenyl 4-methylbenzenesulfonate in dry DMF (1.0 M) was treated with NaH (1.2 eq of a 60 % dispersion in mineral oil) and the mixture was stirred at RT for 30 min. Chloromethyl methyl ether (1.2 eq) was then added dropwise and the mixture was stirred at RT overnight. The mixture was diluted with EtOAc and the organic phase washed with 1 N HCl and brine before drying (Na₂SO₄), filtering and concentrating *in vacuo*. The crude was purified by FC (PE/EtOAc 1/9) to afford the title compound (77%). (ES⁺) *m/z* 387, 389 (M+H)⁺.

Step 3: (2-(methoxymethoxy)-4-{[(4-methylphenyl)sulfonyl]oxy}phenyl)boronic acid

To a solution (0.30 M) of 4-bromo-3-(methoxymethoxy)phenyl 4-methylbenzenesulfonate in a mixture (1:3) of THF/toluene, triisopropyl borate was added and then the mixture cooled to -78 °C. To the cold solution, n-BuLi (2.5 M in hexane; 1.5 eq) was added *via* syringe pump over 1.5 h. The mixture was stirred at -78 °C for a further 2 h and then left to warm to RT overnight.

The mixture was diluted with EtOAc and washed with 1 N HCl, extracting the aqueous fraction a further two times with EtOAc. The combined organics were washed with sat.aq. NaHCO₃ and brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product, that could be used directly as crude or purified by FC (PE/EtOAc 9/1) to afford the title compound (43 %). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 2.42 (s, 3H), 3.31 (s, 3H), 5.06 (s, 2H), 6.64 – 6.69 (m, 2H), 7.44 - 7.49 (m, 3H), 7.74 (d, *J* 8.3, 2H); (ES⁺) *m/z* 353 (M+H)⁺.

Step 4: methyl 3-cyclohexyl-2-(2-(methoxymethoxy)-4-{[(4-methylphenyl)sulfonyl]oxy}phenyl)-1H-indole-6-carboxylate

Methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (prepared as in International patent application WO 2004/087714), (2-(methoxymethoxy)-4-{[(4-methylphenyl)sulfonyl]oxy}phenyl)boronic acid (1 eq) and bis(triphenylphosphinepalladium(II) chloride (0.1 eq) were dissolved in dioxane (0.08M). The solution was degassed and flushed with argon. A 2M aqueous solution of Na₂CO₃ (1 eq) was added and the mixture was heated to 100 °C. After 3 h the temperature was raised to 110 °C. Heating was continued overnight. All volatiles were evaporated and the residual material was dissolved in EtOAc. The solution was washed with 1N aqueous HCl, sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The residual material was subjected to FC (PE:EtOAc, 8:2). After evaporation of the product fractions the product was obtained as a light orange amorphous solid (58%). (ES⁺) *m/z* 564 (M+H)⁺.

Step 5: methyl 3-cyclohexyl-2-[4-hydroxy-2-(methoxymethoxy)phenyl]-1H-indole-6-carboxylate

Methyl 3-cyclohexyl-2-(2-(methoxymethoxy)-4-{[(4-methylphenyl)sulfonyl]oxy}-phenyl)-1H-indole-6-carboxylate was suspended in MeOH (0.18 M) and NaOMe (5 eq) was added. The mixture was warmed in a closed vessel to 80 °C. After 4 h additional NaOMe (5 eq) was added. The mixture was warmed overnight. The mixture was cooled to RT and 1N aqueous HCl was added to the mixture. After dilution with H₂O the mixture was extracted with EtOAc. The organic phase was separated and washed with sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The residual material was filtered with PE:EtOAc (8:2) through a pad of silica gel. The product was obtained as a yellowish amorphous solid (49%). (ES⁺) *m/z* 410 (M+H)⁺.

Step 6: methyl 3-cyclohexyl-2-[2-(methoxymethoxy)-4-(pyridin-2-ylmethoxy)phenyl]-1H-indole-6-carboxylate

Methyl 3-cyclohexyl-2-[4-hydroxy-2-(methoxymethoxy)phenyl]-1H-indole-6-carboxylate was dissolved in DMF (0.17 M) and Cs₂CO₃ (1.05 eq) was added. The mixture was stirred for 20

min, then 2-bromomethylpyridine (1.05 eq) was added and the suspension was stirred at RT. After 4 h Cs₂CO₃ (0.3 eq) was added and the mixture was stirred overnight. Since the reaction was incomplete the mixture was warmed for 30 min to 35 °C. The mixture was diluted with EtOAc and extracted with 1N aqueous HCl, sat. aq. NaHCO₃ and brine. After drying over

5 Na₂SO₄ all volatiles were evaporated *in vacuo*. The product was obtained as a beige amorphous solid (89%). (ES⁺) *m/z* 501 (M+H)⁺.

Step 7: methyl 3-cyclohexyl-2-[2-hydroxy-4-(pyridin-2-ylmethoxy)phenyl]-1H-indole-6-carboxylate

10 Methyl 3-cyclohexyl-2-[2-(methoxymethoxy)-4-(pyridin-2-ylmethoxy)phenyl]-1H-indole-6-carboxylate was dissolved in MeOH (0.5 M). 3N HCl (2 eq) was added, followed by more MeOH. The mixture was warmed to 80 °C for 6 h. By this time a clear solution had formed. All volatiles were evaporated *in vacuo* and the residual material was dissolved in DCM. The solution was washed with sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo* leaving a beige amorphous solid (quant). (ES⁺) *m/z* 457 (M+H)⁺.

15 Step 8: methyl 3-cyclohexyl-2-[2-[(2S)-oxiran-2-ylmethoxy]-4-(pyridin-2-ylmethoxy)phenyl]-1H-indole-6-carboxylate

20 Methyl 3-cyclohexyl-2-[2-hydroxy-4-(pyridin-2-ylmethoxy)phenyl]-1H-indole-6-carboxylate was dissolved in DMF (0.1 M) and CsF (3 eq) was added. The resulting mixture was warmed to 30 °C. The fluorescent mixture was treated with (S)-(+)-glycidyl tosylate (1.2 eq) and stirred at 30 °C overnight. The mixture was diluted with EtOAc and extracted with H₂O, sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. A brownish sticky residue was obtained (99%). (ES⁺) *m/z* 513 (M+H)⁺.

Step 9: methyl (7S)-14-cyclohexyl-7-hydroxy-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

25 Methyl 3-cyclohexyl-2-[2-[(2S)-oxiran-2-ylmethoxy]-4-(pyridin-2-ylmethoxy)phenyl]-1H-indole-6-carboxylate was dissolved in DMF (0.1 M) and the solution was added slowly to a suspension of Cs₂CO₃ (0.5 eq) in DMF at 65 °C. After 1 h the mixture was diluted with Et₂O. The solution was extracted with H₂O, sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo* to leave an orange amorphous solid. The product was
30 purified by FC (PE:EtOAc, 1:1 + 1% NEt₃ to wash away remaining starting material, then EtOAc:MeOH, 9:1 + 1% NEt₃). The product was obtained as a yellowish amorphous solid (62%). (ES⁺) *m/z* 513 (M+H)⁺.

Step 10: methyl (7R)-7-azido-14-cyclohexyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

35 Methyl (7S)-14-cyclohexyl-7-hydroxy-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate was dissolved in THF (60 mM) and PPh₃ (1.2 eq) was added. The solution was cooled to 0 °C and treated with DIPEA (1 eq), followed by slow addition of DIAD (1.2 eq). The mixture was left stirring at this temperature for 5 min, then a

- 40 -

solution of DPPA in THF (1.2 eq) was added dropwise. After complete addition the mixture was stirred at 0 °C for further 30 min, then stirring was continued at RT. Since no reaction was observed after 1 h more PPh₃ in THF (1.2 eq), DIAD in THF (1.2 eq) and DPPA in THF (0.6 eq) were added at RT. The formation of a precipitate was observed. Stirring was continued for 1 h at RT after which time UPLC-MS indicated complete conversion. The mixture was used without further treatment in the next reaction (quant). (ES⁺) *m/z* 538 (M+H)⁺.

Step 11: methyl (7R)-7-amino-14-cyclohexyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

The reaction from the previous step was treated with a solution of PPh₃ in THF (1.3 eq). After 3 h H₂O was added. The mixture was warmed to 50 °C overnight. The mixture was diluted with EtOAc, then extracted with H₂O, sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo* to leave a yellowish oil. The material was dissolved in THF/MeOH (2:1). The mixture was diluted with water and 3N aqueous HCl was added. The resulting mixture was washed thoroughly with EtOAc. The combined organic phases were discarded. The aqueous phase was basified by addition of solid Na₂CO₃ to pH = 8. The resulting mixture was extracted twice with EtOAc. The combined organic phases were dried over Na₂SO₄ and evaporated *in vacuo*. The product was obtained as a yellowish amorphous solid (61%). (ES⁺) *m/z* 512 (M+H)⁺.

Step 12: methyl (7R)-7-(2-[(tert-butoxycarbonyl)(methyl)amino]ethyl)amino)-14-cyclohexyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

Methyl (7R)-7-amino-14-cyclohexyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate was dissolved in HC(OMe)₃ (50 eq) and a solution of *tert*-butyl methyl(2-oxoethyl)carbamate (1.6 eq, prepared according to *Tetrahedron* **2002**, 58, 1719-1737) in HC(OMe)₃ (50 eq) was added. The mixture was stirred overnight at RT to allow formation of the imine. All volatiles were evaporated and the residual material was dissolved in MeOH/HOAc (0.05 M). NaCNBH₃ (1 eq) was added and the mixture was stirred at RT for 1 h. Some formation of the *N*-formyl product was observed alongside formation of the desired product. The solution was used directly in the next step. (ES⁺) *m/z* 669 (M+H)⁺.

Step 13: methyl (7R)-7-[2-[(tert-butoxycarbonyl)(methyl)amino]ethyl](methyl)amino]-14-cyclohexyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To the solution of methyl (7R)-7-(2-[(tert-butoxycarbonyl)(methyl)amino]ethyl)amino)-14-cyclohexyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate in MeOH/HOAc containing NaCNBH₃ from the previous step was added a 37% solution of HCHO in water (1 eq) and stirring at RT was continued. After 1 h all volatiles were evaporated. The residual material was taken up with Et₂O and the resulting solution was washed with sat. aq. NaHCO₃ and with brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The yellow residue was subjected to FC (PE:EtOAc, 6:4 + 1% NEt₃). After evaporation

of the solvents the product was obtained as a colourless solid (44%). The material was used without further characterisation in the next reaction. (ES⁺) *m/z* 683 (M+H)⁺.

Step 14: (7R)-7-[{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}(methyl)amino]-14-cyclohexyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid

5 To the solution of methyl (7R)-7-[{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}(methyl)amino]-14-cyclohexyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate in dioxane (0.1 M) was added 2M KOH solution (3 eq). The mixture was warmed to 60 °C. After 4 days the mixture was neutralised by addition of 1N HCl and all volatiles were evaporated *in vacuo*. The residual material was dried *in vacuo* and
10 used without further purification. (ES⁺) *m/z* 669 (M+H)⁺.

Step 15: *tert*-butyl {2-[[[(7R)-14-cyclohexyl-11-[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}amino)carbonyl]-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocin-7-yl](methyl)amino]ethyl}methylcarbamate

15 (7R)-7-[{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}(methyl)amino]-14-cyclohexyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid, *N*-(2,2-dimethoxyethyl)-*N*-methylsulfamide (2 eq, see Example 1, Step 1) and DMAP (5 eq) were dissolved in DCM (24 mM) and EDC (3 eq) was added. The mixture was warmed to 40 °C. After 2 h the mixture was diluted with DCM and extracted twice with H₂O, sat. aq. NH₄Cl and brine. The organic phase was dried over Na₂SO₄ and evaporated *in vacuo*. The product was
20 obtained as a yellowish sticky solid and used without further purification (91%). (ES⁺) *m/z* 849 (M+H)⁺.

Step 16: (7R)-14-cyclohexyl-7-{methyl[2-(methylamino)ethyl]amino}-*N*-{[methyl(2-oxoethyl)amino]sulfonyl}-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxamide

25 *tert*-butyl {2-[[[(7R)-14-cyclohexyl-11-[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}amino)carbonyl]-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocin-7-yl](methyl)amino]ethyl}methylcarbamate was dissolved in DCM/H₂O/TFA (8:1:3, 15 mM). The mixture was warmed to 40 °C. After 30 min all volatiles were evaporated *in vacuo* and the residual material was coevaporated twice with toluene. The
30 remaining yellow oil was used in the next reaction without further purification.

Step 17: (7R)-14-cyclohexyl-18,21,24-trimethyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide

35 (7R)-14-cyclohexyl-7-{methyl[2-(methylamino)ethyl]amino}-*N*-{[methyl(2-oxoethyl)amino]sulfonyl}-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxamide was dissolved in MeOH (1.7 mM), NEt₃ (3.3 eq) and HOAc (6.6 eq) were added, followed by NaCNBH₃ (2 eq). After 1 h all volatiles were evaporated *in vacuo*. The material was dissolved in DMSO and purified by prep RP-HPLC.

- 42 -

After lyophilisation of the product fractions the product was obtained as a colourless amorphous material (27%, TFA-salt). ^1H NMR (400 MHz, DMSO- d_6 , 300 K, TFA-salt) δ 8.62 (d, 1H, J 4.52), 7.99 (s, 1H), 7.89 (d, 2H, 8.60), 7.60 (d, 1H, J 7.80), 7.44-7.38 (m, 2H), 7.28 (d, 1H, J 8.20), 7.03-7.01 (m, 2H), 5.30 (d, 1H, J 12.80), 5.25 (d, 1H, J 12.80), 4.55-4.51 (m, 1H), 4.34-4.32 (m, 1H), 4.10-4.05 (m, 1H), 3.98-3.85 (m, 2H), 3.51-3.45 (m, 2H), 3.33-3.10 (m, 5H), 3.00 (s, 3H), 2.99-2.90 (m, 1H), 2.83 (s, 3H), 2.66-2.62 (m, 1H), 2.34 (s, 3H), 1.92-1.67 (m, 6H), 1.45-1.13 (m, 4H); (ES $^+$) m/z 687 (M+H) $^+$.

Example 9: 13-cyclohexyl-5,17,20,23-tetramethyl-6,7-dihydro-5H-10,6-(methanoiminothioiminoethanoiminoethanoiminomethano)indolo[1,2- d][1,4]benzodiazepin-14-one 16,16-dioxide (A9)

Step 1: dimethyl 13-cyclohexyl-6,7-dihydro-5H-indolo[1,2- d][1,4]benzodiazepine-6,10-dicarboxylate

Methyl 2-bromo-3-cyclohexyl-indole-6-carboxylate (prepared as described in International patent application WO 2004/087714), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.4 eq) and Pd(PPh $_3$) $_2$ Cl $_2$ (0.1 eq) were dissolved in dioxane (0.08M) and 2M Na $_2$ CO $_3$ solution (1 eq) was added. The mixture was degassed and flushed with Ar. The mixture was heated to 100 °C under Ar atmosphere. After 6 h the mixture was cooled to RT and all volatiles were evaporated *in vacuo*. The residual material was dissolved in DCM and PE was added. The mixture was left stirring for 3 days. The resulting precipitate was filtered off and dissolved again in DCM. The product methyl-2-(2-aminophenyl)-3-cyclohexyl-1H-indole-6-carboxylate was precipitated from this solution with PE and obtained after filtration and drying *in vacuo* as a beige powder (68%). (ES $^+$) m/z 349 (M+H) $^+$.

The foregoing compound was dissolved in MeCN (0.07M) and Bu $_4$ NBr (0.3 eq) was added followed by K $_2$ CO $_3$ (6 eq). Ethyl α -chloroacrylate (1.7 eq) was added to the mixture which was then heated overnight to 60 °C. All volatiles were evaporated *in vacuo* and the residual material was mixed with EtOAc. The suspension was extracted with 10% citric acid, sat. aq. NaHCO $_3$ and brine. After drying over Na $_2$ SO $_4$ all volatiles were evaporated *in vacuo*. The residual material was subjected to purification by FC (PE, then PE:EtOAc, 9:1; then PE:EtOAc, 8:2). After evaporation of the solvents the product was obtained as a yellowish solid (84%). (ES $^+$) m/z 433 (M+H) $^+$.

Step 2: Dimethyl 13-cyclohexyl-5-methyl-6,7-dihydro-5H-indolo[1,2- d][1,4]benzodiazepine-6,10-dicarboxylate

Dimethyl 13-cyclohexyl-6,7-dihydro-5H-indolo[1,2- d][1,4]benzodiazepine-6,10-dicarboxylate was dissolved in anhydrous MeOH (0.05M) and HOAc was added. The mixture was treated with a 37% solution of HCHO in water (1.2 eq), then NaCNBH $_3$ (1.2 eq) was added. The solution was stirred for 2 h at RT. The product was isolated by FC (PE:EtOAc, 9:1, 0.5% NEt $_3$). After evaporation of the solvents a colourless solid was obtained (quant.). (ES $^+$) m/z 447 (M+H) $^+$.

- 43 -

Step 3: Methyl 13-cyclohexyl-6-(hydroxymethyl)-5-methyl-6,7-dihydro-5H-indolo[1,2-d][1,4]benzodiazepine-10-carboxylate

Dimethyl 13-cyclohexyl-5-methyl-6,7-dihydro-5H-indolo[1,2-d][1,4]benzodiazepine-6,10-dicarboxylate was dissolved in anhydrous THF (0.05M) and LiBH₄ (1 eq) was added. The mixture was stirred at RT. After 1 h only marginal conversion to the product was observed. BH₃·THF complex (1 eq) was added and the mixture was stirred at RT. After 2h a further equivalent of BH₃·THF complex was added and the mixture was stirred for 2 h. The mixture was quenched by addition of silica gel and all volatiles were evaporated *in vacuo*. The product was isolated by FC (PE:EtOAc, 8:2). After evaporation of the solvents the product was obtained as a colourless solid (80%). (ES⁺) *m/z* 419 (M+H)⁺.

Step 4: Methyl 13-cyclohexyl-6-formyl-5-methyl-6,7-dihydro-5H-indolo[1,2-d][1,4]benzodiazepine-10-carboxylate

DMSO (5 eq) was dissolved in DCM and the solution was cooled to -78 °C. At this temperature a 2M solution of oxalylchloride in DCM (2.5 eq) was added slowly and the mixture was stirred for 25 min at -78 °C. A solution of dimethyl 13-cyclohexyl-5-methyl-6,7-dihydro-5H-indolo[1,2-d][1,4]benzodiazepine-6,10-dicarboxylate (1 eq) in DCM (0.09M) was added slowly at -78 °C and stirring was continued for 25 min at this temperature. Then NEt₃ (8 eq) was added and the resulting slurry was placed into an ice bath at 0 °C. The mixture was left stirring for 90 min, then diluted with DCM and extracted with sat. aq. NH₄Cl, sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The product was obtained as a deep-yellow solid, which was filtered with DCM over a pad of silica. After evaporation of the solvent the product was obtained as a yellowish solid (quant.). (ES⁺) *m/z* 417 (M+H)⁺.

Step 5: 6-{[2-[(tert-butoxycarbonyl)(methyl)amino]ethyl](methyl)amino}methyl-13-cyclohexyl-5-methyl-6,7-dihydro-5H-indolo[1,2-d][1,4]benzodiazepine-10-carboxylic acid

Methyl 13-cyclohexyl-6-formyl-5-methyl-6,7-dihydro-5H-indolo[1,2-d][1,4]benzodiazepine-10-carboxylate was dissolved in MeOH (0.09M) and HOAc was added. *N,N'*-dimethylethylenediamine (4 eq) was added and the mixture was stirred for 5 min. NaCNBH₃ (1.5 eq) was added and the mixture was stirred overnight. All volatiles were then evaporated *in vacuo* and the residual material was dissolved in EtOAc. The solution was extracted with sat. aq. NH₄Cl, sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The crude residue of methyl 13-cyclohexyl-5-methyl-6-({methyl[2-(methylamino)ethyl]amino}methyl)-6,7-dihydro-5H-indolo[1,2-d][1,4]benzodiazepine-10-carboxylate was dissolved in dioxane (0.05M) and di-*tert*-butyl dicarbonate₂O (2 eq) was added. The mixture was stirred for 1 h. All volatiles were then evaporated *in vacuo* and the residual material was taken up in EtOAc. The solution was extracted with sat. aq. NH₄Cl, sat. aq. NaHCO₃ and with brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The residual material was filtered through a pad of silica gel (PE:EtOAc, 7:3). After evaporation of the solvents, the crude mixture of methyl 6-{[2-[(tert-butoxycarbonyl)(methyl)amino]ethyl]-

(methyl)amino]methyl}-13-cyclohexyl-5-methyl-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepine-10-carboxylate was dissolved in dioxane (0.05M) and 1M KOH solution (2 eq) was added. The mixture was warmed to 60 °C. After 12 h, EtOAc was added and the mixture was extracted with 10% aqueous citric acid solution and brine. After drying the organic phase over Na₂SO₄ all volatiles were evaporated *in vacuo*. The residual solid (6-{{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}-(methyl)amino]methyl}-13-cyclohexyl-5-methyl-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepine-10-carboxylic acid) was used without further purification in the next reaction (67% over 3 steps). (ES⁺) *m/z* 575 (M+H)⁺.

Step 6: 13-cyclohexyl-5-methyl-6-({methyl[2-(methylanino)ethyl]amino}methyl)-N-{[methyl(2-oxoethyl)amino]sulfonyl}-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepine-10-carboxamide 6-{{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}(methyl)amino]methyl}-13-cyclohexyl-5-methyl-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepine-10-carboxylic acid, *N*-(2,2-dimethoxyethyl)-*N*-methylsulfamide (2 eq, Example 1, Step 1) and DMAP (5 eq) were dissolved in DCM (0.06M) and EDC (3 eq) was added. The mixture was warmed to 40 °C. Within 5 min the clear yellow solution turned dark brown. The mixture was stirred overnight. After dilution with DCM the solution was extracted with 1N HCl, sat. aq. NaHCO₃ and brine. After drying the organic phase over Na₂SO₄ the solution was discoloured with activated charcoal. All volatiles were evaporated *in vacuo* leaving *tert*-butyl {2-[(13-cyclohexyl-10-[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl)-amino]carbonyl]-5-methyl-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepin-6-yl}methyl(methyl)amino]ethyl} methylcarbamate as a glassy brownish solid (MS (ES⁺) *m/z* 755 (m+H)⁺). The material was dissolved in DCM (0.03M) and water was added. To the biphasic system TFA was added and then the vigorously stirred mixture was warmed to 40 °C. After 2 h the acetal was completely cleaved, while some *N*-Boc-protected material was still around. More TFA was added until a monophasic system was obtained. Heating was continued for 3 h. Then all volatiles were evaporated *in vacuo* and the residual material was coevaporated three times with toluene. The residual sticky material was digested with Et₂O leaving a dark red powder. This material was used without further purification in the next reaction. (ES⁺) *m/z* 609 (M+H)⁺.

Step 7: 13-cyclohexyl-5,17,20,23-tetramethyl-6,7-dihydro-5*H*-10,6-(methanoiminothioimino ethanoiminoethanoiminomethano)indolo[1,2-*d*][1,4]benzodiazepin-14-one 16,16-dioxide 13-cyclohexyl-5-methyl-6-({methyl[2-(methylanino)ethyl]amino}methyl)-*N*-{[methyl(2-oxoethyl)amino]sulfonyl}-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepine-10-carboxamide was dissolved in MeOH (1.5mM), NEt₃ (3.3 eq) and HOAc (6.6 eq) were added, followed by NaCNBH₃ (2 eq). The solution was stirred at RT overnight. All volatiles were evaporated *in vacuo* and the residual material was dissolved in EtOAc. The solution was washed with 1N HCl, sat. aq. NH₄Cl, sat. aq. NaHCO₃ and brine. The organic phase was dried over Na₂SO₄ and evaporated *in vacuo*. The acidic aqueous phases were basified with sat. aq. NaHCO₃ and extracted with EtOAc. The organic phase was evaporated *in vacuo* and the residual material

unified with the previously obtained material. The material was dissolved in DMSO and purified by prep RP-HPLC. After lyophilisation of the product fractions the product was obtained as a yellowish amorphous material (11%). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K, TFA-salt) δ 8.20 (s, 1H), 7.91 (d, 1H, *J* 8.62), 7.53 (d, 1H, *J* 8.37), 7.45-7.42 (m, 1H), 7.28-7.25 (m, 2H), 7.16-7.12 (m, 1H), 4.73 (d, 1H, *J* 14.86), 3.96 (d, 1H, *J* 14.86), 3.87-3.67 (m, 1H), 3.56-3.19 (m, 5H), 3.04 (s, 3H), 3.02-2.98 (m, 1H), 2.92-2.67 (m, 9H), 2.45-2.39 (m, 2H), 2.05-1.86 (m, 6H), 1.72-1.62 (m, 2H), 1.55-1.14 (m, 6H); (ES⁺) *m/z* 593 (M+H)⁺.

Example 10: 13-cyclohexyl-3-methoxy-17,20-dimethyl-6,7-dihydro-5*H*-6,10-(ethanoiminoethanoiminiothioiminomethano)indolo[2,1-*a*][2]benzazepin-14-one 16,16-dioxide (A10)

Step 1: (2-bromo-5-methoxyphenyl)methanol

2-Bromo-5-methoxy benzoic acid (1 eq) was dissolved in anhydrous THF (0.55M solution) and BH₃·SMe₂ complex (2M in THF, 1 eq) was added dropwise to the solution. The mixture was stirred overnight, then HCl in MeOH was added and the mixture was warmed to 60 °C. All volatiles were evaporated and the residual material was dissolved in DCM. The solution was washed with 1N HCl and with brine, then dried over Na₂SO₄ and evaporated *in vacuo*. A colorless oil was obtained (94%), which was used without further characterization in the next reaction.

Step 2: [(2-bromo-5-methoxybenzyl)oxy](triisopropyl)silane

(2-Bromo-5-methoxyphenyl)methanol (1 eq) was dissolved in anhydrous DMF (1.1M solution) and imidazole (1.05 eq) was added. To the stirred solution triisopropylsilyl chloride (1.1 eq) was added and the resulting mixture was stirred at RT for 8 h. All volatiles were evaporated *in vacuo* and the residual material was filtered with PE / EtOAc (9:1) over a pad of silica gel. After evaporation *in vacuo* the product was obtained as a colorless oil (94%), which was used without further characterization in the next reaction.

Step 3: (4-methoxy-2-{[(triisopropylsilyl)oxy]methyl}phenyl)boronic acid

[(2-bromo-5-methoxybenzyl)oxy](triisopropyl)silane (1eq) was dissolved in anhydrous THF (0.43M solution) and the solution was cooled to -78 °C. A solution of *n*-BuLi (1.6M in hexanes, 1.05 eq) was added and the resulting mixture was stirred for 1 h at -78 °C. Then triisopropyl borate (50% in THF, 1.3 eq) was added dropwise and the mixture was allowed to warm to RT overnight. 1N HCl was added and the resulting mixture was stirred at RT for 30 min. THF was removed *in vacuo* and replaced with Et₂O. The organic phase was washed with water and with brine, then dried over Na₂SO₄ and evaporated *in vacuo*. The product was obtained as a colorless oil (64% yield, 65% pure) which was used without further purification in the next reaction.

Step 4: methyl 3-cyclohexyl-2-(4-methoxy-2-{[(triisopropylsilyl)oxy]methyl}phenyl)-1*H*-indole-6-carboxylate

Methyl-2-bromo-3-cyclohexyl-1*H*- indole-6-carboxylate (prepared as described in International patent application WO2004/087714 from commercially available methyl indole-6-carboxylate)

- 46 -

and (4-methoxy-2-{[(triisopropylsilyl)oxy]methyl}phenyl)boronic acid (1.1 eq) were dissolved in dioxane (0.125M solution) and 2M aq. Na₂CO₃ solution (3.3 eq) was added. The mixture was degassed and flushed with Argon. Then Pd(PPh₃)₂Cl₂ (0.1 eq) was added and the mixture was heated under argon atmosphere to 110 °C. After 5 h at this temperature all volatiles were evaporated *in vacuo* and the residual material was dissolved in EtOAc. The solution was extracted with water and with brine, then dried over Na₂SO₄ and evaporated *in vacuo*. The residual material was purified by FC (PE:EtOAc, 9:1). After evaporation of the solvents the product was obtained as an off-white foam (81%). The material was used without further characterization in the next reaction.

10 Step 5: methyl 1-allyl-3-cyclohexyl-2-(4-methoxy-2-{[(triisopropylsilyl)oxy]methyl}phenyl)-1H-indole-6-carboxylate

Methyl 3-cyclohexyl-2-(4-methoxy-2-{[(triisopropylsilyl)oxy]methyl}phenyl)-1H-indole-6-carboxylate (1 eq) was dissolved in DMF (0.34M solution) and the solution was degassed. NaH (60% dispersion in mineral oil; 1.1 eq) was added and the mixture was stirred for 5 min. Allyl bromide (1.2 eq) was added and stirring was continued for 5 h. All volatiles were evaporated *in vacuo* and the residual material was dissolved in Et₂O. The solution was washed with 0.5N HCl, saturated aq. NaHCO₃ solution and with brine. After drying the organic phase over Na₂SO₄ all volatiles were evaporated *in vacuo* and the residual material was purified by FC (PE:EtOAc, 10:1). After evaporation of the solvents the product was obtained as a colorless sticky solid (84%). The material was used without further characterization in the next reaction.

20 Step 6: methyl 1-allyl-3-cyclohexyl-2-[2-(hydroxymethyl)-4-methoxyphenyl]-1H-indole-6-carboxylate

Methyl 1-allyl-3-cyclohexyl-2-(4-methoxy-2-{[(triisopropylsilyl)oxy]methyl}phenyl)-1H-indole-6-carboxylate (1 eq) was dissolved in THF (0.28M solution) and a 1M solution of tetrabutylammonium fluoride in THF (1 eq) was added. The mixture was stirred at RT for 2 h, then all volatiles were evaporated *in vacuo* and the residual material was dissolved in Et₂O. The solution was washed with 1N HCl, saturated aq. NaHCO₃ solution and with brine. The organic phase was dried over Na₂SO₄ and evaporated *in vacuo*. The residual material was purified by FC (PE:EtOAc, 8:2). After evaporation of the solvents the product was obtained as colorless foam (88%). (ES⁺): 434.2 (M+H)⁺.

30 Step 7: methyl 1-allyl-3-cyclohexyl-2-(2-formyl-4-methoxyphenyl)-1H-indole-6-carboxylate

DMSO (5 eq) was dissolved in DCM and the solution was cooled to -78 °C. To the stirred solution oxalylchloride (2.5 eq) was added and the mixture was left stirring for 30 min. A solution of methyl 1-allyl-3-cyclohexyl-2-[2-(hydroxymethyl)-4-methoxyphenyl]-1H-indole-6-carboxylate (1 eq) in DCM (0.25M solution) was added and the mixture was stirred for 30 min at -78 °C. Et₃N (8 eq) was added and the mixture was allowed to warm to 0 °C. At this temperature stirring was continued for 2 h, and then stirring was continued at RT overnight. The mixture was diluted with DCM, and then washed with water, 1N HCl, saturated aq. NaHCO₃

solution and with brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The residual material was purified by FC (PE:EtOAc, 9:1). After evaporation of the solvents the product was obtained as a yellow foam (88%). (ES⁺): 432.1 (M+H)⁺.

Step 8: methyl rel-(3aS,14bS)-10-cyclohexyl-13-methoxy-1-methyl-1,2,3,3a,4,14b-

5 hexahydroindolo[2,1-a]pyrrolo[3,2-d][2]benzazepine-7-carboxylate

Methyl 1-allyl-3-cyclohexyl-2-(2-formyl-4-methoxyphenyl)-1*H*-indole-6-carboxylate (1 eq) was dissolved in toluene (0.05M solution) and sarcosine (1.1 eq) was added. After heating to 110 °C for 90 min 20 vol-% DMF were added and heating was continued for 2 h. After cooling to RT the mixture was diluted with EtOAc and the resulting solution was extracted with 1N HCl, sat.

10 aq. NaHCO₃ solution and with brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The residual material was purified by FC (PE:EtOAc, 8:2). The product was obtained as colorless foam (61%) which was used without further characterization in the next reaction.

Step 9: Methyl 13-cyclohexyl-3-methoxy-6-[2-(methylamino)ethyl]-6,7-dihydro-5*H*-indolo[2,1-a][2]benzazepine-10-carboxylate

15 To a 0.06 M solution of methyl 10-cyclohexyl-13-methoxy-1-methyl-1,2,3,3a,4,14b-hexahydroindolo[2,1-a]pyrrolo[3,2-d][2]benzazepine-7-carboxylate in EtOAc and MeOH 1:1, was added Pd/C (10 wt. %, 0.5 eq) and the mixture was stirred under hydrogen atmosphere for 18 h at RT. Since only traces of desired compound were detected the mixture was heated at 50 °C for 8 h. After filtration on a celite pad the solvent was removed *in vacuo* and the residual
20 material was used in the next step without further purification. MS (ES⁺) *m/z* 461 (M+H)⁺.

Step 10: Methyl 6-{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}-13-cyclohexyl-3-methoxy-6,7-dihydro-5*H*-indolo[2,1-a][2]benzazepine-10-carboxylate

Di-*tert*-butyl dicarbonates₂O (1.5 eq) and Et₃N (3 eq) were added to a 0.1 M solution of methyl 13-cyclohexyl-3-methoxy-6-[2-(methylamino)ethyl]-6,7-dihydro-5*H*-indolo[2,1-a][2]benzazepine-10-carboxylate in DCM and the mixture was stirred at RT for 1 h. All
25 volatiles were removed *in vacuo* and the residual material was dissolved in EtOAc. The resulting solution was washed with sat. aq. NaHCO₃ and brine. The organic phase was dried over Na₂SO₄ and evaporated *in vacuo*. The residual material was subjected to FC (PE:EtOAc 2:1). After evaporation of the solvent the product was obtained as white solid (45% yield, two
30 steps). (ES⁺) *m/z* 561 (M+H)⁺.

Step 11: 6-{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}-13-cyclohexyl-3-methoxy-6,7-dihydro-5*H*-indolo[2,1-a][2]benzazepine-10-carboxylic acid

To a 0.05M solution of methyl 6-{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}-13-cyclohexyl-3-methoxy-6,7-dihydro-5*H*-indolo[2,1-a][2]benzazepine-10-carboxylate in dioxane, 1M aqueous
35 KOH solution (10 eq) was added and the mixture was heated to 70 °C. After 2 h the mixture was neutralised with 1N HCl and then all volatiles were removed *in vacuo*. The residue was taken up with DCM and filtered to remove salts. The crude material was used without purification in the next step. (ES⁺) *m/z* 547 (M+H)⁺.

Step 12: *Tert-butyl (2-{13-cyclohexyl-10-[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}amino)carbonyl]-3-methoxy-6,7-dihydro-5H-indolo[2,1-a][2]benzazepin-6-yl}ethyl)methylcarbamate*

To a solution of 6-{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}-13-cyclohexyl-3-methoxy-6,7-dihydro-5H-indolo[2,1-a][2]benzazepine-10-carboxylic acid in DCM (0.07M), *N*-(2,2-dimethoxyethyl)-*N*-methylsulfamide (2 eq, Example 1, Step 1), EDC (3 eq) and DMAP (5 eq) were added. The mixture was stirred at 40 °C for 3 h, then diluted with EtOAc and washed with 1N HCl, 1N NaOH solution and brine. The organic phase was dried over Na₂SO₄ and evaporated *in vacuo* and the residual material was used in the next step without purification.

(ES⁺) *m/z* 727 (M+H)⁺.

Step 13: *13-cyclohexyl-3-methoxy-17,20-dimethyl-6,7-dihydro-5H-6,10-(ethanoiminoethanoiminothioiminomethano)indolo[2,1-a][2]benzazepin-14-one 16,16-dioxide*

To a 0.02 M solution of *tert*-butyl (2-{13-cyclohexyl-10-[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}amino)carbonyl]-3-methoxy-6,7-dihydro-5H-indolo[2,1-a][2]benzazepin-6-yl}ethyl)methylcarbamate in DCM:H₂O (99:1) TFA (170 eq) was added and the mixture was stirred at 40 °C for 1 h. All volatiles were removed *in vacuo* and the residual material was triturated with Et₂O. (ES⁺) *m/z* 581 (M+H)⁺. The crude material was then dissolved in MeOH (0.1M) and HOAc (5 eq) was added followed by Et₃N (3 eq) and NaCNBH₃ (2 eq). After stirring at RT for 2 h the volatiles were removed *in vacuo* and the product was isolated by mass-guided RP-HPLC. After lyophilisation a white solid was obtained (12% yield, 4 steps). ¹H NMR (400 MHz, DMSO-*d*₆, TFA-*d*, 300 K) δ 8.25 (s, 1H), 7.89 (d, 1H, *J* 8.4), 7.49 (d, 1H, *J* 8.26), 7.41 (d, 1H, *J* 8.26), 7.06-7.05 (m, 1H), 7.01-7.00 (m, 1H), 4.40 (d, 1H, *J* 15.54), 4.01-3.96 (m, 1H), 3.85 (s, 3H), 3.82-3.75 (m, 1H), 3.67-3.55 (m, 3H), 3.42-3.38 (m, 2H), 2.96 (s, 3H), 2.86-2.73 (m, 4H), 2.28-2.24 (m, 1H), 2.04 (s, 3H), 2.01-1.77 (m, 3H), 1.75-1.67 (m, 3H), 1.55-1.48 (m, 2H), 1.42-1.35 (m, 2H), 1.22-1.18 (m, 1H); MS (ES⁺): 565.5 (M+H)⁺. (ES⁺) *m/z* 565 (M+H)⁺.

Example 11: (7*R*)-14-cyclohexyl-3-fluoro-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A11)

Step 1: *methyl 3-cyclohexyl-2-(4-fluoro-2-hydroxyphenyl)-1H-indole-6-carboxylate*

The compound was prepared in analogy to Example 8, Step 4, substituting (2-(methoxymethoxy)-4-[(4-methylphenyl)sulfonyl]oxy}phenyl)boronic acid with (4-fluoro-2-hydroxyphenyl)boronic acid (97%). (ES⁺) *m/z* 368 (M+H)⁺.

Step 2: (7*R*)-14-cyclohexyl-3-fluoro-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-

(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide

The title compound was prepared using chemistry analogous to that described for Example 8, Steps 8-17, substituting methyl 3-cyclohexyl-2-[2-hydroxy-4-(pyridin-2-ylmethoxy)phenyl]-1*H*-

indole-6-carboxylate with methyl 3-cyclohexyl-2-(4-fluoro-2-hydroxyphenyl)-1*H*-indole-6-carboxylate ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.10-1.20 (m, 1H), 1.27-1.38 (m, 2H), 1.40-1.47 (m, 1H), 1.62-1.73 (m, 2H), 1.78-1.86 (m, 1H), 1.86-1.98 (m, 3H), 2.34 (s, 3H), 2.82 (s, 3H), 3.01 (s, 3H), 3.25-3.50 (m, 5H), 3.50-3.62 (m, 3H), 3.85-3.98 (m, 2H), 4.05-4.15 (m, 1H), 4.30-4.39 (m, 1H), 4.48-4.58 (m, 1H), 7.16-7.23 (m, 1H), 7.28 (br d, *J* 9.8, 1H), 7.37-7.47 (m, 3H), 7.91 (d, *J* 8.6, 1H), 8.00 (s, 1H), 11.69 (br s, 1H); (ES⁺) *m/z* 598 (M+H)⁺.

Example 12: (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-21-ethyl-3-fluoro-18-methyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)-indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A12)

Step 1: methyl (7*R*)-7-(benzylamino)-14-cyclohexyl-3-fluoro-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

Methyl (7*R*)-7-amino-14-cyclohexyl-3-fluoro-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (Example 11, Step 5) was dissolved in HC(OMe)₃ (50 eq) and a solution of benzaldehyde (1.1 eq) in HC(OMe)₃ (50 eq) was added. The mixture was stirred overnight at RT to allow formation of the imine. All volatiles were evaporated and the residual material was dissolved in MeOH/HOAc (0.05 M). NaCNBH₃ (1.1 eq) was added and the mixture was stirred at RT for 1 h. The solution was used directly in the next step. (ES⁺) *m/z* 513 (M+H)⁺.

Step 2: methyl (7*R*)-7-(benzyl{2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)-14-cyclohexyl-3-fluoro-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

To the solution of methyl (7*R*)-7-(benzylamino)-14-cyclohexyl-3-fluoro-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate in MeOH/HOAc containing NaCNBH₃ from the previous step was added *N*-Boc-2-aminoacetaldehyde (1.5 eq) and the solution was stirred at RT. After 1 h all volatiles were evaporated. The residual material was taken up with EtOAc and the resulting solution was washed with sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The yellow residue was subjected to FC (PE:EtOAc, 8:2 + 1% NEt₃). After evaporation of the solvents the product was obtained as a colourless solid (71%). (ES⁺) *m/z* 656 (M+H)⁺.

Step 3: (7*R*)-7-(benzyl{2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)-14-cyclohexyl-3-fluoro-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid

To a solution of methyl (7*R*)-7-(benzyl{2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)-14-cyclohexyl-3-fluoro-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate in dioxane (0.1 M) was added 2M KOH aqueous solution (3 eq). The mixture was warmed to 60 °C. After 2 h the mixture was neutralized by addition of 1N aqueous HCl and all volatiles were evaporated *in vacuo*. The residual material was taken up with EtOAc and water. The organic phase was separated and the aqueous layer was extracted with EtOAc. After drying the organic phases over Na₂SO₄ all volatiles were evaporated *in vacuo* (97%). (ES⁺) *m/z* 652 (M+H)⁺.

Step 4: tert-butyl [2-(benzyl{(7R)-14-cyclohexyl-11-[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}amino)carbonyl]-3-fluoro-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl}amino)ethyl]carbamate

The compound was prepared in analogy to Example 8, Step 15 (95%); (ES⁺) m/z 822 (M+H)⁺.

5 Step 5: (7R)-7-[(2-aminoethyl)(benzyl)amino]-14-cyclohexyl-3-fluoro-N-{[methyl(2-oxoethyl)amino]sulfonyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide

10 Tert-butyl [2-(benzyl{(7R)-14-cyclohexyl-11-[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}amino)carbonyl]-3-fluoro-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl}amino)ethyl]carbamate was dissolved in THF (50 mM) and 3M aqueous HCl (10 eq) was added. The solution was warmed to 60 °C and stirred for 2 h. The solution was then used directly in the next step. (ES⁺) m/z 676 (M+H)⁺.

Step 6: (7R)-24-benzyl-14-cyclohexyl-3-fluoro-18-methyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

15 The solution of (7R)-7-[(2-aminoethyl)(benzyl)amino]-14-cyclohexyl-3-fluoro-N-{[methyl(2-oxoethyl)amino]sulfonyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide in THF from the previous step was diluted with MeOH (10 mM) and pH was adjusted to 5 with 2M NaOH in MeOH. NaCNBH₃ (2 eq) was added in one portion and the resulting mixture was stirred at RT for 45 min. All volatiles were evaporated. The residual material was taken up with EtOAc and the resulting solution was washed with sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo* (94%). (ES⁺) m/z 660 (M+H)⁺.

Step 7: (7R)-24-benzyl-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

25 (7R)-24-benzyl-14-cyclohexyl-3-fluoro-18-methyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide was dissolved in MeOH/THF/HOAc (0.05 M) and acetaldehyde (5 eq) was added followed by NaCNBH₃ (2 eq). The resulting mixture was stirred at RT for 2 h then all volatiles were evaporated. The residual material was taken up with EtOAc and the resulting solution was washed with sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The yellow residue was subjected to FC (EtOAc:MeOH, 95:5 + 1% NEt₃). After evaporation of the solvents the product was obtained as a colourless solid (43%). (ES⁺) m/z 688 (M+H)⁺.

Step 8: (7R)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-7,8-dihydro-6H-7,11-

35 (epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

(7R)-24-benzyl-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one

17,17-dioxide was dissolved in MeOH (30 mM) and the solution treated with 1.25 M HCl in MeOH (3 eq). The resulting mixture was warmed to 40 °C and Pd/C (10% w/w, 1 eq) was added. The slurry was stirred under hydrogen atmosphere for 2 h then the catalyst was filtered off with Celite®. All volatiles were then evaporated *in vacuo*; the residue was partitioned
 5 between EtOAc and aq. sat. NaHCO₃ and the organic phase was collected. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo* (quant.). (ES⁺) m/z 598 (M+H)⁺.

Step 9: tert-butyl {2-[(7R)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-17,17-dioxido-15-oxo-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-24-yl]ethyl}methylcarbamate

10 The compound was prepared from (7R)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide in analogy to Step 7 substituting MeCHO with *tert*-butyl methyl(2-oxoethyl)carbamate (prepared according to *Tetrahedron* **2002**, 58, 1719-1737) (quant.). (ES⁺) m/z 755 (M+H)⁺.

15 Step 10: (7R)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-24-[2-(methylamino)ethyl]-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

Tert-butyl {2-[(7R)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-17,17-dioxido-15-oxo-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-

20 e][1,5]benzoxazocin-24-yl]ethyl}methylcarbamate was dissolved in a 3:1 mixture of DCM and TFA and the resulting solution was stirred at RT for 1 h then all volatiles were evaporated under reduced pressure (quant.). (ES⁺) m/z 655 (M+H)⁺.

Step 11: (7R)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-21-ethyl-3-fluoro-18-methyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-
 25 e][1,5]benzoxazocin-15-one 17,17-dioxide

The compound was prepared from (7R)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-24-[2-(methylamino)ethyl]-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide in analogy to Step 7 substituting MeCHO with HCHO (37% in water). The crude material was dissolved in DMSO and purified by prep

30 RP-HPLC. After lyophilisation of the product fractions the product was obtained as a colourless amorphous material (12%, TFA-salt). ¹H NMR (400 MHz, DMSO-*d*₆, 330 K) δ 1.13-1.22 (m, 1H), 1.22 (t, *J* 9.8, 3H), 1.29-1.37 (m, 2H), 1.40-1.47 (m, 1H), 1.62-1.73 (m, 2H), 1.80-1.89 (m, 1H), 1.90-1.98 (m, 3H), 2.62-2.83 (m, 4H), 2.84 (s, 6H), 2.96-3.46 (m, 7H), 3.07 (s, 3H), 3.46-3.61 (m, 3H), 3.85-4.04 (m, 4H), 4.15-4.24 (m, 1H), 4.55 (d, *J* 14.7, 1H), 7.09-7.21 (m, 2H),
 35 7.37-7.43 (m, 1H), 7.53 (d, *J* 8.4, 1H), 7.90 (d, *J* 8.4, 1H), 8.19 (s, 1H), 9.30 (br s, 1H); (ES⁺) m/z 669 (M+H)⁺.

Example 13: (+)-14-cyclohexyl-18,22-dimethyl-7,8-dihydro-6H-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A13)

Step 1: methyl 14-cyclohexyl-7-methylene-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

5 A solution of methyl 3-cyclohexyl-2-(2-hydroxyphenyl)-1H-indole-6-carboxylate (prepared as described in International patent application WO2006/046030) (0.12 M) in DMF was treated with KO^tBu (2.1 eq) in one portion; the resulting mixture was stirred for 30 min at RT then treated dropwise with 3-chloro-2-(chloromethyl)prop-1-ene (1.1 eq). The resulting solution was
10 stirred at RT overnight before being quenched by addition of HCl (1N) and extracted into EtOAc. The combined organic layers were washed with sat. aq. NaHCO₃ and brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude material was purified by FC (PE/EtOAc 85:15) affording the product as a yellow oil (97%). (ES⁺) *m/z* 402 (M+H)⁺.

Step 2: methyl (7R,S)-14-cyclohexyl-7-(hydroxymethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

15 A solution of methyl 14-cyclohexyl-7-methylene-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.14 M) in THF was cooled to 0 °C and treated with 0.5 M 9-BBN in THF (5 eq). The resulting solution was warmed to RT and stirred for 3 h before re-cooling to 0 °C. 1N NaOH (3 eq) and H₂O₂ (2 eq) were added and the solution warmed to RT for
20 2 h before diluting with EtOAc. The organic layers were washed with water then brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The material was taken on without further purification. (ES⁺) *m/z* 420 (M+H)⁺.

Step 3: methyl (7R,S)-14-cyclohexyl-7-({[(4-methylphenyl)sulfonyl]oxy}methyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

25 A solution of methyl 14-cyclohexyl-7(R,S)-(hydroxymethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.14 M) in DCM was treated with TsCl (3.5 eq) and pyridine (35 eq) and the resulting mixture was stirred overnight at RT. The reaction was quenched by addition of HCl (1N) and extracted into EtOAc. The combined organic layers were washed with sat. aq. NaHCO₃ and brine, before being dried (Na₂SO₄), filtered and concentrated
30 *in vacuo*. The crude material was purified by FC (PE/EtOAc 9:1) affording the product as a yellow oil (95%, over steps 2, 3). (ES⁺) *m/z* 574 (M+H)⁺.

Step 4: methyl 7(R,S)-(cyanomethyl)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

35 A solution of methyl 14-cyclohexyl-7(R,S)-({[(4-methylphenyl)sulfonyl]oxy}methyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.35 M) in DMF was treated with NaCN (1.2 eq) and the resulting mixture was stirred overnight at RT. The reaction was quenched by addition of sat. aq. NaHCO₃ and extracted into EtOAc. The combined organic layers were washed with brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo*.

The crude material was purified by FC (PE/EtOAc 9:1) affording the product as a yellow foam (90%). (ES⁺) *m/z* 429 (M+H)⁺.

Step 5: methyl 7(R, S)-(2-aminoethyl)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

- 5 Platinum(IV) oxide (0.5 eq) was added to a solution of methyl 7(R, S)-(cyanomethyl)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.20 M) in MeOH. The atmosphere in the reaction vessel was exchanged for H₂ and the reaction stirred vigorously at RT for 4 h. The reaction vessel was flushed with N₂ and the reaction mixture filtered through a plug of celite (washing well with MeOH and EtOAc). Volatiles were removed *in vacuo* to
10 afford the crude product which was purified by FC (EtOAc/MeOH/Et₃N 93:5:2) affording the product as a yellow oil (12%). (ES⁺) *m/z* 433 (M+H)⁺.

Step 6: methyl 7(R, S)-(2-{[N-(tert-butoxycarbonyl)-β-alanyl]amino}ethyl)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

- A solution of methyl 7(R, S)-(2-aminoethyl)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e]
15 [1,5]benzoxazocine-11-carboxylate (0.14 M) in DCM was treated with *N*-(tert-butoxycarbonyl)-β-alanine (2 eq) followed by HATU (1.3 eq) and DIPEA (2.5 eq) and the resulting mixture was stirred overnight at RT. The reaction was diluted with EtOAc and the combined organic layers were washed with sat. aq. NaHCO₃, HCl (1N) and brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The product was used directly in the next step without further
20 purification. (ES⁺) *m/z* 604 (M+H)⁺.

Step 7: methyl 7(R, S)-{2-[N-(tert-butoxycarbonyl)-N-methyl-β-alanyl](methylamino)ethyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

- A solution of methyl 7(R, S)-(2-{[N-(tert-butoxycarbonyl)-β-alanyl]amino}ethyl)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.18 M) in DMF
25 was treated with sodium hydride (2.4 eq) and the resulting solution stirred for 15 min at RT. Methyl iodide MeI (2.2 eq) was then added and the reaction stirred at RT for 90 min. The reaction was not complete so further NaH (60% dispersion in mineral oil; 2 eq) and MeI (1.5 eq) were added and stirring continued for 1 h. The reaction was diluted with EtOAc and the combined organic layers were washed twice with HCl (1N) and then brine, before being dried
30 (Na₂SO₄), filtered and concentrated *in vacuo*. The crude material was purified by FC (PE/EtOAc 8:2 to 6:4) affording the product as a yellow oil (49%, over steps 6, 7). (ES⁺) *m/z* 632 (M+H)⁺.

Step 8: methyl 14-cyclohexyl-7(R, S)-{2-[methyl(N-methyl-β-alanyl)amino]ethyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

- A solution of methyl 7(R, S)-{2-[N-(tert-butoxycarbonyl)-N-methyl-β-alanyl](methylamino)ethyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.09 M) in DCM was treated with TFA (20 eq) and the resulting mixture was stirred overnight at RT. The reaction was diluted with EtOAc and the combined organic layers were washed with sat. aq. NaHCO₃ then brine, before being dried (Na₂SO₄), filtered and

concentrated *in vacuo*. The product was used directly in the next step without further purification. (ES⁺) *m/z* 532 (M+H)⁺.

Step 9: methyl 14-cyclohexyl-7(R, S)-(2-{methyl[3-(methylamino)propyl]amino}ethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

- 5 A solution of methyl 14-cyclohexyl-7(R, S)-{2-[methyl(*N*-methyl-β-alanyl)amino]ethyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.02 M) in THF was treated dropwise with BH₃-DMS complex (2M in THF; 10 eq). The resulting solution was stirred at RT for 3 h. The reaction was quenched by the careful addition of HCl/MeOH (1.25 M) and the resulting solution refluxed for 2 h. The mixture was cooled before concentrating *in vacuo*. The
10 crude material was purified by FC (EtOAc/MeOH/Et₃N 90:8:2) affording the product as a yellow oil (48%, over steps 8, 9). (ES⁺) *m/z* 518 (M+H)⁺.

Step 10: methyl 14-cyclohexyl-7R-(2-{methyl[3-(methylamino)propyl]amino}ethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate and methyl 14-cyclohexyl-7S-(2-{methyl[3-(methylamino)propyl]amino}ethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-
15 carboxylate

- Methyl 14-cyclohexyl-7(R, S)-(2-{methyl[3-(methylamino)propyl]amino}ethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate was dissolved in MeOH and the enantiomers were separated by SFC chromatography (stationary phase: Chiralcel OD-H 250 x 10 mm; mobile phase: 25% EtOH containing 0.4% diethylamine/CO₂; flow rate 10 mL/min;
20 column pressure: 100 bar; column temperature: 35 °C; detection UV 254 nm). The enantiomeric excess of the two fractions thus obtained (compound recovery 60%) were determined by SFC analysis using the same conditions as described above: Isomer A (retention time 6.95 min, e.e. >98%) [α]_D²⁰ = - 30.9 (c = 0.14, MeOH); Isomer B (retention time 9.07 min, e.e. 98%) [α]_D²⁰ = + 21.0 (0.2, MeOH).

- 25 Step 11: methyl 7R or 7S-{2-[3-[[[tert-butoxycarbonyl]amino]sulfonyl}(methyl)amino]propyl}(methyl)amino]ethyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

- A solution of methyl 14-cyclohexyl-(7R or 7S)-(2-{methyl[3-(methylamino)propyl]amino}ethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (Isomer A from SFC separation) (0.09 M) in THF was treated with *N*-[1-[[[tert-butoxycarbonyl]amino]sulfonyl}pyridin-4(1*H*)-ylidene]-*N*-methylmethanaminium chloride (1.5
30 eq) (prepared following literature procedures: *Organic Letters* **2001**, 3, 2241) and stirred overnight at RT. The reaction was partitioned between HCl (1N) and EtOAc and the layers separated. The combined organics were washed with brine, dried (Na₂SO₄), filtered and
35 concentrated *in vacuo*. The crude material was purified by FC (EtOAc/PE 8:2) affording the product as a colourless oil (91%). (ES⁺) *m/z* 697 (M+H)⁺.

Step 12: 7R or 7S-{2-[{3-[[tert-butoxycarbonyl)amino]sulfonyl}(methyl)amino]propyl}(methyl)amino]ethyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

2N NaOH (aq) (10 eq) was added to a solution of methyl (7R or 7S)-{2-[{3-[[tert-butoxycarbonyl)amino]sulfonyl}(methyl)amino]propyl}(methyl)amino]ethyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.08 M) in MeOH and the reaction stirred at 60 °C for 2 h. The reaction was cooled to RT before diluting with EtOAc. The combined organic layers were washed with sat. aq. NH₄Cl and then brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The material was taken on without further purification. (ES⁺) *m/z* 683 (M+H)⁺.

Step 13: 7R or 7S-{2-[{3-[(aminosulfonyl)(methyl)amino]propyl}(methyl)amino]ethyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

A solution of (7R or 7S)-{2-[{3-[[tert-butoxycarbonyl)amino]sulfonyl}(methyl)amino]propyl}(methyl)amino]ethyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid (0.07 M) in DCM was treated with TFA (20 eq) and the resulting mixture was stirred overnight at RT. The reaction was not complete therefore further TFA (20 eq) was added and stirring continued for 3 h. The reaction was concentrated *in vacuo* and the residue evaporated 3 times from HCl/Et₂O. The product was used directly in the next step without further purification. (ES⁺) *m/z* 583 (M+H)⁺.

Step 14: 7R or 7S-14-cyclohexyl-18,22-dimethyl-7,8-dihydro-6H-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

A solution of (7R or 7S)-{2-[{3-[(aminosulfonyl)(methyl)amino]propyl}(methyl)amino]ethyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid (0.009 M) in DCM was treated with EDC (1.5 eq) and DMAP (5 eq) and the resulting mixture was stirred for 72 h at RT then 40 °C for 2 h before concentrating *in vacuo*. The residue was purified by RP-HPLC (Waters Xterra column; MeCN/H₂O/0.1% TFA gradient). Fractions containing the pure compound were combined and lyophilized in the presence of HCl to afford the product as a white powder (9%; over steps 12, 13, 14); This material was characterized as a 2:1* mixture of isomers (due to chiral nitrogen upon protonation) by ¹H NMR. ¹H NMR (400 MHz, DMSO-*d*₆ + TFA, 330 K) δ 1.19-1.33 (m, 5H), 1.46-1.72 (m, 4H), 1.82-2.04 (m, 4H), 2.10-2.15* and 2.27-2.34 (m, 2H), 2.63-2.72 (m, 1H), 2.77 and 2.81* (s, 3H), 3.03 and 3.07* (s, 3H), 3.13-3.18 (m, 1H), 3.23-3.35 (m, 1H), 3.55-4.08 (m, 7H), 4.38-4.41 and 4.67-4.71* (m, 1H), 7.14-7.24 (m, 1H), 7.27-7.40 (m, 2H), 7.42-7.51 (m, 1H), 7.53-7.60 (m, 1H), 7.86-7.93 (m, 1H), 8.04 and 8.47* (s, 1H); (ES⁺) *m/z* 565 (M+H)⁺; [α]_D²⁰ = + 22.0 (c = 0.1, MeOH).

Example 14: (-)-14-cyclohexyl-18,22-dimethyl-7,8-dihydro-6H-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A14)

The title compound was prepared using chemistry analogous to that described for Example 13, Steps 11-14, starting from methyl 14-cyclohexyl-(7*R* or 7*S*)-(2-{methyl[3-(methylamino)propyl]amino}ethyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (Isomer B from SFC separation) prepared as described in Example 13, Steps 1-10.

5 (ES⁺) *m/z* 565 (M+H)⁺; [α]_D²⁰ = - 21.0 (c = 0.1, MeOH).

Example 15: (7*S*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A15)

10 The title compound was prepared using chemistry analogous to that described for Example 1, Steps 1-10, starting from *tert*-butyl (2*S*)-2-([*tert*-butyl(dimethyl)silyl]oxy)methylaziridine-1-carboxylate (prepared in line with literature procedures: Travins, J.M.; Etzkorn, F.A.

Tetrahedron Lett. **1998**, 39, 9389-9392). (ES⁺) *m/z* 566 (M+H)⁺; [α]_D²⁰ = - 75.3 (0.1, DMSO).

Example 16: (7*R,S*)-14-[(1*R,2S*) or (1*S,2R*)-2-fluorocyclohexyl]-18,23-dimethyl-7,8-dihydro-6*H*-11,7-(methanoiminiothioiminobutanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A16)

Step 1: methyl (7*R,S*)-14-[(1*R,2S*) or (1*S,2R*)-2-fluorocyclohexyl]-7-([4-(methylphenyl)sulfonyl]oxy)methyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

20 The title compound was prepared using chemistry analogous to that described for Example 13, Steps 1-3, starting from methyl 3-[(1*R,2S*) or (1*S,2R*)-2-fluorocyclohexyl]-2-(2-hydroxyphenyl)-1*H*-indole-6-carboxylate (prepared as described in International patent application WO2007/054741) (23%). (ES⁺) *m/z* 592 (M+H)⁺.

Step 2: methyl (7*R,S*)-14-[(1*R,2S*) or (1*S,2R*)-2-fluorocyclohexyl]-7-[(methylamino)methyl]-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

25 Methyl (7*R,S*)-14-[(1*R,2S*) or (1*S,2R*)-2-fluorocyclohexyl]-7-([4-(methylphenyl)sulfonyl]oxy)methyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (0.5 M) in THF was treated with an equal volume of a 27% solution of MeNH₂ in MeOH (excess). The resulting mixture was stirred at 65 °C in a sealed tube overnight. The reaction mixture was concentrated and the residue was purified by FC (50 - 100% EtOAc in PE) to afford the title compound (72%). (ES⁺) *m/z* 451 (M+H)⁺.

Step 3: methyl (7*R,S*)-7-([4-[(*tert*-butoxycarbonyl)amino]butanoyl](methyl)amino)methyl)-14-[(1*R,2S*) or (1*S,2R*)-2-fluorocyclohexyl]-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

35 To a mixture of methyl (7*R,S*)-14-[(1*R,2S*) or (1*S,2R*)-2-fluorocyclohexyl]-7-[(methylamino)methyl]-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (0.05 M) and 4-[(*tert*-butoxycarbonyl)amino]butanoic acid (1.1 eq) in THF was added HATU (1.05 eq), and the resulting mixture was stirred overnight at RT. The reaction was quenched with water, extracted with EtOAc and the organic layer dried (Na₂SO₄), filtered and concentrated *in*

vacuo. The residue was purified by FC (25 - 50% EtOAc in PE) to afford the desired compound (44%). (ES⁺) *m/z* 636 (M+H)⁺.

Step 4: (7R,S)-7-{[4-[(*tert*-butoxycarbonyl)(methyl)amino]butanoyl}(methyl)amino]methyl}-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

To a suspension of NaH (60 % dispersion in mineral oil; 4.5 eq) in THF (0.3 M) was added a solution of methyl (7R,S)-7-{[4-[(*tert*-butoxycarbonyl)amino]butanoyl}(methyl)amino]methyl}-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate in THF (0.1 M). The mixture was stirred for 1 h at RT before introducing MeI (4.5 eq). The resulting mixture was stirred for 2 days. The reaction was quenched with H₂O and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was used directly in the next step. (ES⁺) *m/z* 636 (M+H)⁺.

Step 5: benzyl (7R,S)-7-{[4-[(*tert*-butoxycarbonyl)(methyl)amino]butanoyl}(methyl)amino]methyl}-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a mixture of (7R,S)-7-{[4-[(*tert*-butoxycarbonyl)(methyl)amino]butanoyl}(methyl)amino]methyl}-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid (0.02 M) and K₂CO₃ (4.5 eq) in acetone, was added benzyl bromide (4.5 eq). The resulting mixture was stirred for 3~4 h at RT before being quenched with water and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by FC (EtOAc/PE, 1:1) to afford the title compound (86% over steps 4 and 5). (ES⁺) *m/z* 726 (M+H)⁺.

Step 6: benzyl (7R,S)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7-({methyl[4-(methylamino)butanoyl]amino}methyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution of benzyl (7R,S)-7-{[4-[(*tert*-butoxycarbonyl)(methyl)amino]butanoyl}(methyl)amino]methyl}-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.02 M) in DCM was added TFA (> 350 eq). The resulting mixture was stirred for 1~2 h, then the volatiles were removed *in vacuo* and the residue partitioned between sat. aq. NaHCO₃ and EtOAc. The organics were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was used directly in the next step.

Step 7: benzyl (7R,S)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7-({methyl[4-(methylamino)butyl]amino}methyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

BH₃•Me₂S (2M in THF; 1.05 eq.) was added to a solution of benzyl (7*R*,*S*)-14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-7-({methyl[4-(methylamino)butanoyl]amino}methyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (0.013 M) in THF. The resulting mixture was stirred overnight at RT. After quenching the reaction with MeOH and dilute HCl, the mixture was basified with sat. aq. NaHCO₃ and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was used directly in the next step.

Step 8: benzyl (7*R*,*S*)-7-{{4-[[*tert*-

butoxycarbonyl)amino]sulfonyl}(methyl)amino]butyl}(methyl)amino]methyl}-14-[(1*R*,2*S*) or

(1*S*,2*R*)-2-fluorocyclohexyl]-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

(*tert*-butoxycarbonyl){[4-(dimethylamino)pyridinium-1-yl]sulfonyl}azanide (1.8 eq) (prepared

following literature procedures: *Organic Letters* **2001**, 3, 2241) was added to a solution of

benzyl (7*R*,*S*)-14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-7-({methyl[4-

(methylamino)butyl]amino}methyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-

carboxylate (0.013 M) in THF. The resulting mixture was stirred for 2~3 h at RT. The reaction mixture was concentrated *in vacuo*, and the residue was purified by FC (25 - 50% EtOAc/ PE) to afford the title compound (54 % over steps 6 - 8). (ES⁺) *m/z* 791 (M+H)⁺.

Step 9: (7*R*,*S*)-7-{{4-[[*tert*-

butoxycarbonyl)amino]sulfonyl}(methyl)amino]butyl}(methyl)amino]methyl}-14-[(1*R*,2*S*) or

(1*S*,2*R*)-2-fluorocyclohexyl]-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic

acid

Pd(OH)₂/C (0.25 wt eq) was added to benzyl (7*R*,*S*)-7-{{4-[[*tert*-

butoxycarbonyl)amino]sulfonyl}(methyl)amino]butyl}(methyl)amino]methyl}-14-[(1*R*,2*S*) or

(1*S*,2*R*)-2-fluorocyclohexyl]-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

(0.01 M) in THF. The resulting mixture was hydrogenated overnight at RT and atmospheric pressure. The catalyst was then filtered off and the filtrate concentrated *in vacuo* to give the title compound (98 %). (ES⁺) *m/z* 701 (M+H)⁺.

Step 10: (7*R*,*S*)-7-{{4-[(aminosulfonyl)(methyl)amino]butyl}(methyl)amino]methyl}-14-[(1*R*,2*S*)

or (1*S*,2*R*)-2-fluorocyclohexyl]-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic

acid

To a solution of (7*R*,*S*)-7-{{4-[[*tert*-

butoxycarbonyl)amino]sulfonyl}(methyl)amino]butyl}(methyl)amino]methyl}-14-[(1*R*,2*S*) or

(1*S*,2*R*)-2-fluorocyclohexyl]-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic

acid (0.01 M) in DCM was added TFA (> 600 eq). The resulting mixture was stirred for 1~2 h,

before removing the volatiles *in vacuo* to afford the product, which was used directly in the next step. (ES⁺) *m/z* 601 (M+H)⁺.

Step 11: (7R,S)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-18,23-dimethyl-7,8-dihydro-6H-11,7-(methanoiminothioiminobutanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

A mixture of (7R,S)-7-[[{4-[(aminosulfonyl)(methyl)amino]butyl}(methyl)amino]methyl]-14-
 5 [(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid (0.002 M), EDC (5.2 eq), DMAP (12.3 eq) and Et₃N (19.8 eq) in THF was stirred at RT for 2~3 days. The volatiles were evaporated *in vacuo* and the residue was purified by preparative HPLC (Sepax GP C18 30×150 mm; TFA: 0.1%; CH₃CN/H₂O: 45~80%). Fractions containing the pure compound were combined and lyophilized in the presence of HCl
 10 to afford the HCl salt of the title compound as a mixture of diastereoisomers (24%). ¹H NMR (600 MHz, DMSO-*d*₆, 320 K) δ 1.06-2.28 (m, 13H), 2.52-5.18 (m, 18H), 7.11-7.60 (m, 5H), 7.83-8.49 (m, 2H), 9.91-10.29 (m, 1H), 11.13-11.78 (m, 1H); (ES⁺) *m/z* 583 (M+H)⁺.

**Example 17: (20S)-31-cyclohexyl-10-methyl-19,22-dioxa-9-thia-1,8,10,13-tetraazahexacyclo[18.9.1.1^{2,6}.1^{3,29}.0^{13,17}.0^{23,28}]dotriaconta-2(32),3,5,23,25,27,29(31)-heptaen-
 15 7-one 9,9-dioxide (A17)**

Step 1: benzyl 1-benzylprolinate

Benzyl bromide (2 eq.) and K₂CO₃ (2.5 eq) were added to a solution (0.6 M) of DL-proline in DMF. The reaction was stirred at 100 °C overnight. The solution was allowed to cool to RT and then diluted with EtOAc and washed with 1 N HCl, brine, before being dried (Na₂SO₄), filtered
 20 and concentrated *in vacuo*. The crude material was purified by FC (PE/EtOAc 90:10) to afford the product (43%). (ES⁺) *m/z* 296 (M+H)⁺

Step 2: (1-benzylpyrrolidin-2-yl)methanol

A solution (0.06M) of benzyl 1-benzylprolinate in THF was cooled in an ice bath and treated with LiAlH₄ (3 eq). The resulting mixture was stirred at RT for 3 h, before being quenched by
 25 the addition of H₂O. The resulting mixture was stirred at RT for 30 min and then filtered through a pad of Solka-Floc and the filtrate concentrated *in vacuo*. The crude was purified by FC (PE/EtOAc 6:4 + 1% NEt₃) to afford the title compound as an off-white solid (62%). ¹H NMR (400 MHz, CDCl₃) δ 1.66-1.81 (m, 2H), 1.82-1.97 (m, 2H), 2.25-2.34 (m, 1H), 2.40-2.53 (m, 1H), 2.71-2.77 (m, 1H), 2.94-3.01 (m, 1H), 3.34-3.39 (m, 1H), 3.40-3.45 (m, 1H), 3.63-3.68 (m,
 30 1H), 3.95-3.99 (m, 1H), 7.26-7.30 (m, 5H).

Step 3: 1-benzyl-2-(chloromethyl)pyrrolidinium chloride

(1-benzylpyrrolidin-2-yl)methanol was slowly added to thionyl chloride (45 eq) and the resulting mixture was stirred for 15 h at 35 °C. All the volatiles were removed *in vacuo*. The yellow oil residue was treated with Et₂O and re-evaporated to drive off excess thionyl chloride. The crude
 35 material was then dried at the high vacuum pump for 2 h to afford the product (100%). ¹H NMR (400 MHz, CDCl₃) δ 1.85-2.01 (m, 1H), 2.15-2.32 (m, 3H), 2.85-3.05 (m, 1H), 3.43-3.54 (m, 1H), 3.65-3.79 (m, 1H), 3.92-4.02 (m, 2H), 4.20-4.22 (m, 1H), 4.41-4.43 (m, 1H), 7.44-7.62 (m, 5H).

- 60 -

Step 4: methyl (7S)-7-[(1-benzylpyrrolidin-2-yl)methoxy]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

Methyl (7S)-14-cyclohexyl-7-hydroxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate in toluene (0.17 M) was treated with 30% NaOH (aq) (10 eq) and
5 tetrabutylammonium bromide (0.25 eq). The solution was stirred at RT for 30 min, then 1-benzyl-2-(chloromethyl)pyrrolidinium chloride (2.5 eq) was added to the solution and the resulting mixture was stirred at 60 °C over night. Toluene was eliminated *in vacuo*; the residue was taken up in EtOAc and washed with 1 N HCl (aq), brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude material was purified by FC (PE/EtOAc 50:50 +
10 1% NEt₃) to afford the product (80%). (ES⁺) *m/z* 579 (M+H)⁺

Step 5: methyl (7S)-14-cyclohexyl-7-(pyrrolidin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution of methyl (7S)-7-[(1-benzylpyrrolidin-2-yl)methoxy]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.07 M) in EtOAc, was added an excess of
15 AcOH (>50 eq) and Pd(OH)₂/C. The atmosphere in the reaction flask was charged with H₂ and the reaction stirred vigorously under a H₂ atmosphere (balloon) at RT for 2 d. The mixture was filtered and the filtrate concentrated *in vacuo*. The crude was purified by FC (gradient from EtOAc/PE 6:4 +1% NEt₃ to EtOAc/PE 8:2 +1% NEt₃ + 5% MeOH) to afford the product (50%). (ES⁺) *m/z* 489 (M+H)⁺.

Step 6: methyl (7S)-7-[(1-{2-[(tert-butoxycarbonyl)(methyl)amino]ethyl}pyrrolidin-2-yl)methoxy]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution (0.02 M) of methyl (7S)-14-cyclohexyl-7-(pyrrolidin-2-ylmethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate in MeOH/THF (2/1), AcOH (cat.) was added followed by *tert*-butyl methyl(2-oxoethyl)carbamate (2 eq, prepared as described in
25 *Tetrahedron* **2002**, 58, 1719-1737). The reaction was stirred at RT for 30 min at which point NaCNBH₃ (2 eq) was added and the mixture was stirred at 40 °C for 1 h. Additional *tert*-butyl methyl(2-oxoethyl)carbamate (1 eq) and NaCNBH₃ (5 eq) were added and the reaction was stirred for further 30 min at 40 °C. The reaction was quenched by adding sat. aq. NaHCO₃. The aqueous phase was extracted with EtOAc and the combined organics washed with brine before
30 being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The product was used in the subsequent step without further purification. MS (ES⁺) *m/z* 646 (M+H)⁺

Step 7: methyl (7S)-14-cyclohexyl-7-({1-[2-(methylamino)ethyl]pyrrolidin-2-yl}methoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

A solution of methyl (7S)-7-[(1-{2-[(tert-butoxycarbonyl)(methyl)amino]ethyl}pyrrolidin-2-yl)methoxy]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate
35 (0.06 M) in DCM was treated with an excess of TFA (> 50eq). The mixture was stirred at RT for 2 h. Volatiles were removed *in vacuo* and the residue partitioned between EtOAc and sat. aq. NaHCO₃. The aqueous was extracted with EtOAc and the organics combined, washed with

brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product (82%). The material was taken on without further purification. MS (ES⁺) *m/z* 546 (M+H)⁺.

Step 8: methyl (7S)-7-[(1-{2-[(tert-

butoxycarbonyl)amino]sulfonyl}(methyl)amino]ethyl}pyrrolidin-2-yl)methoxy]-14-cyclohexyl-

5 7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution of methyl (7S)-14-cyclohexyl-7-[(1-{2-(methylamino)ethyl}pyrrolidin-2-yl)methoxy]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

(0.05 M) in THF was added (tert-butoxycarbonyl){[4-(dimethylamino)pyridinium-1-yl]sulfonyl}azanide (prepared following literature procedures: *Organic Letters* **2001**, 3, 2241)

10 (1.2 eq) and the resulting mixture was stirred for 2.5 h at RT. The solution was diluted in EtOAc and washed with 1 N HCl, brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude was purified by FC (EtOAc/PE 85:15 +1% NEt₃) to afford the product (14 %). MS (ES⁺) *m/z* 725 (M+H)⁺.

Step 9: (7S)-7-[(1-{2-[(tert-butoxycarbonyl)amino]sulfonyl}(methyl)amino]ethyl}pyrrolidin-2-

15 yl)methoxy]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

A solution of methyl (7S)-7-[(1-{2-[(tert-butoxycarbonyl)amino]sulfonyl}(methyl)amino]ethyl}pyrrolidin-2-yl)methoxy]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (7 mM) in MeOH was treated with 2 N NaOH (10eq). The mixture was stirred at 60 °C for 3 h. MeOH was eliminated *in vacuo*, the residue was dissolved in EtOAc and neutralized by adding 6 N HCl. The aqueous was extracted with EtOAc and the organics combined, washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product. The material was taken on without further purification. MS (ES⁺) *m/z* 711 (M+H)⁺.

Step 10: (7S)-7-[(1-{2-[(aminosulfonyl)(methyl)amino]ethyl}pyrrolidin-2-yl)methoxy]-14-

25 cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid
A solution of (7S)-7-[(1-{2-[(tert-butoxycarbonyl)amino]sulfonyl}(methyl)amino]ethyl}pyrrolidin-2-yl)methoxy]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid (7 mM) in DCM was treated with an excess of TFA (> 100eq). The mixture was stirred at RT for 3.5 h. Volatiles were removed *in vacuo*. The residue was dissolved in toluene and re-evaporated to drive off excess TFA. The material was taken on without further purification. MS (ES⁺) *m/z* 611 (M+H)⁺.

Step 11: (20S)-31-cyclohexyl-10-methyl-19,22-dioxa-9-thia-1,8,10,13-

tetraazahexacyclo[18.9.1.1^{2,6}.1^{3,29}.0^{13,17}.0^{23,28}]dotriaconta-2(32),3,5,23,25,27,29(31)-heptaen-7-one 9,9-dioxide

35 To a solution (7 mM) of (7S)-7-[(1-{2-[(aminosulfonyl)(methyl)amino]ethyl}pyrrolidin-2-yl)methoxy]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid in DCM, DMAP (5 eq) and EDC (2 eq) were added and the resulting mixture heated at 40 °C for 2 h and then at RT over night. Volatiles were eliminated *in vacuo* and the residue redissolved in

DMSO. Purification was by RP-HPLC (stationary phase: column Waters XTERRA prep. C18, 5µm, 19x100 mm) eluting with MeCN/TFA buffered with 0.1 % TFA gradient. Fractions containing the product were combined and freeze dried to afford the product as a white powder (34 %) as a mixture of isomers. ¹H NMR (600 MHz, DMSO-*d*₆ + TFA, 320 K) δ 1.15-2.02 (m, 14H), 2.68-2.70 (m, 1H), 2.94-3.08 (m, 3H), 3.14-4.11 (m, 11H), 4.32-4.61 (m, 2H), 4.81-4.90 (m, 1H), 7.16-7.39 (m, 2H), 7.40-7.49 (m, 1H), 7.50-7.57 (m, 2H), 7.85-7.94 (m, 1H), 8.13-8.43 (m, 1H); MS (ES⁺) *m/z* 593 (M+H)⁺.

Example 18: (18*R*)-29-cyclohexyl-10,17-dimethyl-20-oxa-9-thia-1,8,10,14,17-pentaazahexacyclo[16.9.1.1^{2,6}.1^{3,27}.1^{11,14}.0^{21,26}]hentriaconta-2(31),3,5,21,23,25,27(29)-heptaen-7-one 9,9-dioxide (A18)

Step 1: *tert*-butyl[1-(2-chloroethyl)pyrrolidin-3-yl]methylcarbamate

To a solution of *tert*-butyl methyl(pyrrolidin-3-yl)carbamate (1 eq) in MeOH chloroacetaldehyde (50% wt in H₂O) (2.4 eq) was added, the pH adjusted to 6 with HOAc and the solution left stirring for 1 h. NaCNBH₃ (1.5 eq) was then added and the solution left stirring for 3 h. The reaction was treated with sat. aq. NaHCO₃, diluted with DCM and washed with H₂O and brine, dried over Na₂SO₄ and evaporated *in vacuo* to obtain the title compound as yellow oil (98%). (ES⁺) *m/z* 263 (M+H)⁺.

Step 2: methyl (7*R*)-7-[(2-{3-[(*tert*-butoxycarbonyl)(methyl)amino]pyrrolidin-1-yl}ethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

A solution of methyl (7*R*)-14-cyclohexyl-7-(methylamino)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (1 eq) in MeCN was treated with *tert*-butyl[1-(2-chloroethyl)pyrrolidin-3-yl]methylcarbamate (2.4 eq) and NEt₃ (2 eq) and heated at 140 °C in a microwave oven. The solvent was removed *in vacuo* and the residue purified by FC (Biotage; DCM/MeOH) to get the title compound as a white powder (64%). (ES⁺) *m/z* 645 (M+H)⁺.

Step 3: methyl (7*R*)-14-cyclohexyl-7-(methyl{2-[3-(methylamino)pyrrolidin-1-yl]ethyl}amino)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

Methyl (7*R*)-7-[(2-{3-[(*tert*-butoxycarbonyl)(methyl)amino]pyrrolidin-1-yl}ethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate was dissolved in DCM and treated with TFA. The solution was stirred for 2 h at RT. The solvents were removed *in vacuo* to leave the product as pale yellow foam. (ES⁺) *m/z* 545 (M+H)⁺.

Step 4: methyl (7*R*)-7-[(2-{3-[[(*tert*-butoxycarbonyl)amino]sulfonyl}(methyl)amino]pyrrolidin-1-yl}ethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

Tert-BuOH/DCM (2M, 1.1 eq) was added to a stirred mixture of chlorosulfonyl isocyanate (1.1 eq) in dry DCM cooled to 0 °C. The mixture was left stirring at 0 °C for 90 min. A solution of methyl (7*R*)-14-cyclohexyl-7-(methyl{2-[3-(methylamino)pyrrolidin-1-yl]ethyl}amino)-7,8-

dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (1.0 eq) and NEt₃ (3.0 eq) in dry DCM was added and the mixture was stirred at 0 °C for 1h and at RT further 2 h. The residue obtained after evaporation of all volatiles was taken into EtOAc, diluted with HCl (1N), washed with brine, dried and concentrated *in vacuo* and the residue purified by FC (Biotage;

5 DCM/MeOH) to get the title compound as a white powder (52%). (ES⁺) *m/z* 724 (M+H)⁺.

Step 5: (7R)-7-[(2-{3-[[[(tert-butoxycarbonyl)amino]sulfonyl}(methyl)amino]pyrrolidin-1-yl}ethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

10 A solution of methyl (7R)-7-[(2-{3-[[[(tert-butoxycarbonyl)amino]sulfonyl}(methyl)amino]pyrrolidin-1-yl}ethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate in dioxane was treated with aqueous KOH (1M) (3eq) and heated at 70 °C for 1 h. The residue obtained after evaporation of all volatiles was taken into EtOAc, acidified with HCl (1N), and the organics washed with brine, dried and concentrated *in vacuo* to get the title compound as a white powder.
15 (ES⁺) *m/z* 710 (M+H)⁺.

Step 6: (7R)-7-[(2-{3-[(aminosulfonyl)(methyl)amino]pyrrolidin-1-yl}ethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

20 A solution of (7R)-7-[(2-{3-[[[(tert-butoxycarbonyl)amino]sulfonyl}(methyl)amino]pyrrolidin-1-yl}ethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid in DCM was treated with TFA and the solution was left stirring for 1 h. All volatiles were removed *in vacuo* to leave the product as pale yellow foam. (ES⁺) *m/z* 610 (M+H)⁺.

Step 7: (18R)-29-cyclohexyl-10,17-dimethyl-20-oxa-9-thia-1,8,10,14,17-pentaazahexacyclo[16.9.1.1^{2,6}.1^{3,27}.1^{11,14}.0^{21,26}]hentriaconta-2(31),3,5,21,23,25,27(29)-heptaen-7-one 9,9-dioxide

25 A solution of (7R)-7-[(2-{3-[(aminosulfonyl)(methyl)amino]pyrrolidin-1-yl}ethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid in DCM was treated with EDC (2 eq) and DMAP (3 eq) and the solution was left stirring for 1 h at 35 °C. The residue obtained after evaporation of all volatiles was purified by
30 automated RP-HPLC to obtain the title compound as bis TFA salt and as a mixture of two diastereoisomers (a/b) in a 1:1 ratio (55%). ¹H NMR (600 MHz, DMSO-*d*₆, 300 K, bis TFA-salt) δ 8.36-8.23 (bs, 1H-a), 7.94-7.83 (m, 1H-a, 1H-b), 7.82-7.74 (bs, 1H-b), 7.59-7.48 (m, 2H-a, 1H-b), 7.41-7.28 (m, 3H-a, 4H-b), 4.92-4.78 (m, 2H-a, 1H-b), 4.62-4.46 (m, 2H-b, 1H-a), 4.15-3.82 (m, 2H-a, 2H-b), 3.60-3.40 (m, 2H-a, 2H-b), 3.22-3.11 (m, 1H-a), 2.98 (s, 3H-a), 3.50-2.79 (m,
35 6H-a, 6H-b), 2.97-2.89 (m, 1H-b), 2.86 (s, 3H-b), 2.78-2.61 (m, 1H-a, 1H-b), 2.24 (s, 3H-a), 2.21 (s, 3H-b), 2.34-2.09 (m, 2H-a, 2H-b), 2.02-1.82 (m, 4H-a, 4H-b), 1.78-1.65 (m, 2H-a, 2H-b), 1.54-1.42 (m, 1H-a, 1H-b), 1.40-1.29 (m, 2H-a, 2H-b), 1.22-1.11 (m, 1H-a, 1H-b); (ES⁺) *m/z* 592 (M+H)⁺.

Example 19: (7R)-14-cyclohexyl-21-ethyl-4,18,24-trimethyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A19)

5 Step 1: 1-(methoxymethoxy)-2-methylbenzene

To a suspension of NaH (60% dispersion in mineral oil; 1.2 eq) in Et₂O/DMF (5:1, 0.2M) a solution of *o*-cresol in Et₂O (1 eq, 2M) was added dropwise over 15 min. A solution of MOMCl in Et₂O (1.1 eq, 2M) was added and the mixture was stirred for 30 min then poured into H₂O and extracted with Et₂O. The combined organic extracts were washed with 1N NaOH, H₂O and
10 brine, dried over Na₂SO₄, filtered and evaporated *in vacuo* to give the title compound. The product was used in the next step without further purification.

Step 2: [2-(methoxymethoxy)-3-methylphenyl]boronic acid

To a solution of 1-(methoxymethoxy)-2-methylbenzene in diethyl ether (0.3M) cooled at -60 °C *t*BuLi in pentane (1.7M, 1.4 eq) was added dropwise and the mixture was stirred for 1 h while
15 warming gradually to 0 °C then for further 2 h at 0 °C. The mixture was cooled to -78 °C and a solution of B(OMe)₃ in THF (3 eq, 3.0M) was added dropwise and the mixture was allowed to reach RT and stirred overnight. The mixture was cooled to 0 °C and 1N HCl was added, then the reaction mixture was stirred for 2 h. All volatiles were removed under reduced pressure and the residue was extracted with EtOAc. The combined extracts were washed with H₂O and brine,
20 dried over Na₂SO₄, filtered and evaporated *in vacuo* to give a yellow solid which was triturated with PE to give a white solid which was used in the next step without further purification.

Step 3: methyl 3-cyclohexyl-2-[2-(methoxymethoxy)-3-methylphenyl]-1H-indole-6-carboxylate

The compound was prepared in analogy to Example 8, Step 4, substituting (2-(methoxymethoxy)-4-{{[(4-methylphenyl)sulfonyl]oxy}phenyl}boronic acid with [2-(
25 (methoxymethoxy)-3-methylphenyl]boronic acid (83%). (ES⁺) *m/z* 408 (M+H)⁺.

Step 4: (7R)-14-cyclohexyl-4,18,24-trimethyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

The title compound was prepared using chemistry analogous to that described for Example 8,
30 Steps 7-17,. (ES⁺) *m/z* 580 (M+H)⁺

Step 5: (7R)-14-cyclohexyl-21-ethyl-4,18,24-trimethyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

Acetaldehyde (10 eq) was added to the reaction from the previous step followed by HOAc (cat.)
35 and NaCNBH₃ (5 eq). After 30 min, all volatiles were removed *in vacuo* and the residue taken in EtAOc and washed with sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ the crude was by purified by automated RP-HPLC, eluting with a MeCN/H₂O gradient (buffered with 0.1 %

TFA). Fractions containing the product were combined and lyophilised to afford the product as a white powder (25 % bis TFA salt).

¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.02-1.17 (m, 1H), 1.21 (t, *J* 6.7, 3H), 1.30-1.52 (m, 3H), 1.78-1.86 (m, 2H), 1.86-1.98 (m, 4H), 2.37 (s, 3H), 2.60 (s, 3H), 3.03 (s, 3H), 3.13-3.33 (m, 3H), 3.33-3.50 (m, 5H), 3.50-3.63 (m, 2H), 3.64-3.79 (m, 1H), 3.83-3.99 (m, 1H), 3.99-4.14 (m, 2H), 4.31-4.41 (m, 1H), 4.61 (d, *J* 14.8, 1H), 7.12-7.31 (m, 2H), 7.40-7.52 (m, 2H), 7.91 (d, *J* 8.5, 1H), 8.08 (s, 1H), 11.7 (br s, 1H); (ES⁺) *m/z* 608 (M+H)⁺.

Example 20: (7*R*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanooxyethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A20)

Step 1: methyl (7*R*)-7-[(2-[2-(benzyloxy)ethoxy]ethyl)(*tert*-butoxycarbonyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

[2-(benzyloxy)ethoxy]acetaldehyde was prepared by Swern oxidation of commercially available 2-[2-(benzyloxy)ethoxy]ethanol. A 0.15M solution of the foregoing aldehyde and methyl (7*R*)-7-amino-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (prepared as described in Example 1, Step 4) in CH(OMe)₃ was stirred overnight at RT; the residue obtained after removing volatiles *in vacuo* was dissolved in MeOH (0.15M solution), NaCNBH₃ (2.3 eq) was added and the mixture was left stirring for 4 h. All volatiles were evaporated and the residual material was dissolved in EtOAc and washed with sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*; FC (Biotage, PE/EtOAc 1:1 to 1:3 with 0.5% NEt₃) afforded 35% of methyl (7*R*)-7-[(2-[2-(benzyloxy)ethoxy]ethyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate.

A 1M solution of the latter in THF was treated with di-*tert*-butyl dicarbonate (1.5 eq) overnight at 40 °C; the residue obtained after evaporation was dissolved in EtOAc and washed with sat. aq. NaHCO₃ and brine, dried over Na₂SO₄ and concentrated; the crude (quantitative) was used without further purification.

Step 2: methyl (7*R*)-7-((*tert*-butoxycarbonyl){2-[2-(methylamino)ethoxy]ethyl}amino)-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

Methyl (7*R*)-7-[(2-[2-(benzyloxy)ethoxy]ethyl)(*tert*-butoxycarbonyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate was dissolved in MeOH/AcOH 10:1 (0.06M) and palladium on carbon (10%, 0.25 eq) was added. The mixture was degassed and hydrogen atmosphere was applied. The mixture was left stirring at RT. After 2 days all volatiles were evaporated *in vacuo* and the residue was filtered on celite using EtOAc and MeOH as solvents. After evaporation of the solvents *in vacuo* methyl (7*R*)-7-[(*tert*-butoxycarbonyl)[2-(2-hydroxyethoxy)ethyl]amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate was obtained. DMAP (0.2 eq) and MsCl (1.2 eq) was added to a 0.06M solution of previous crude and NEt₃ (1.5 eq) in dry DCM and the mixture was stirred at RT for 90 min.

After quenching with sat NaHCO₃ the mixture was extracted with DCM and the combined organic phases washed with 1N HCl and brine, dried and concentrated. A 0.07M solution of crude mesylate and NEt₃ (4 eq) was treated with 2M MeNH₂/THF (22 eq) at 80 °C overnight, evaporation gave a residue that was used as such. Yield 70% (three steps). (ES⁺) *m/z* 606

5 (M+H)⁺.

Step 3: methyl (7R)-7-[(tert-butoxycarbonyl)(2-{2-[(tert-butoxycarbonyl)amino]sulfonyl}(methyl)amino)ethoxy}ethyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

10 Chlorosulfonyl isocyanate (1.2 eq) was dissolved in dry DCM (0.2M) and 1.3 eq of a 2M solution of *t*-BuOH in ether was added at 0°C, after stirring for 1 h a 1M solution of methyl (7R)-7-[(tert-butoxycarbonyl){2-[2-(methylamino)ethoxy]ethyl}amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (1 eq) and NEt₃ (3 eq) in dry DCM was added dropwise, and stirring was continued for 30 min at 0 °C and then at RT for 2 h. All volatiles were evaporated *in vacuo* and the residue was taken in EtOAc, washed with 1N HCl and brine, dried and concentrated; the crude material was purified by FC (Biotage, gradient of PE/EtOAc 1:1 to 1:3) to afford 40% of the title compound. (ES⁺) *m/z* 785 (M+H)⁺.

15 Step 4: (7R)-14-cyclohexyl-18-methyl-7,8-dihydro-6H-7,11-(epiminoethanoxyethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

20 Methyl (7R)-7-[(tert-butoxycarbonyl)(2-{2-[(tert-butoxycarbonyl)amino]sulfonyl}(methyl)amino)ethoxy}ethyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate was dissolved in dioxane (0.07M) and 1M KOH solution (10 eq) was added. The mixture was left stirring at 75 °C for 3 h. After cooling to 0 °C the pH of the solution was adjusted with 1M HCl to pH 6 and all volatiles were removed *in vacuo*. The residue was extracted with EtOAc. The combined organic phases were washed with H₂O and brine and dried over Na₂SO₄. All volatiles were evaporated *in vacuo*. The residual material was dissolved in dry DCM, TFA (35 eq) was added and the mixture was left stirring at RT. After 2 h all volatiles were evaporated *in vacuo*. The residue (TFA salt of (7R)-7-[(2-{2-[(aminosulfonyl)(methyl)amino]ethoxy}ethyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid) was taken in dry DCM (0.07M), DMAP (3 eq) and EDC (2 eq) were added and the mixture was stirred at 40 °C for 1 h, some crystals of EDC were added and stirring was continued for 1 h. The residue obtained after evaporation was extracted with EtOAc. The combined organic phases were washed with sat. aq. NH₄Cl and brine, dried over Na₂SO₄ and concentrated to afford the title compound which was used without further purification. Yield: quantitative as crude. (ES⁺) *m/z* 553 (M+H)⁺.

30 Step 4: (7R)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6H-7,11-(epiminoethanoxyethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

NaCNBH₃ (2 eq) was added to a stirred solution (0.05M) of (7R)-14-cyclohexyl-18-methyl-7,8-dihydro-6H-7,11-(epiminoethanooxyethanoiminothioiminomethano)indolo[1,2-

e][1,5]benzoxazocin-15-one 17,17-dioxide, HCHO (3 eq) and AcOH (10 eq) in MeOH and the mixture was stirred at RT for 2 h. Evaporation gave a residue that was taken in DMSO and

5 purified by prep. RP-HPLC. After lyophilisation of the fractions the title compound was obtained as a white solid (35%). ¹H NMR (500 MHz, DMSO-*d*₆, 330 K, bis TFA-salt) δ 7.97 (b.s, 1H),

7.95 (d, 1H, *J* 8.4), 7.58 (t, 1H, *J* 7.7), 7.48 (b.d, 1H, *J* 8.4), 7.41 (d, 1H, *J* 6.3), 7.36-7.33 (m, 2H), 4.90 (d, 1H, *J* 15.2), 4.49 (b.s, 1H), 4.35 (dd, 1H, *J* 8.3, 12.3), 4.28 (b.s., 1H), 3.93-3.86 (m,

1H), 3.82-3.68 (m, 5H), 3.61-3.50 (m, 2H), 3.42-3.35 (m, 1H), 3.01 (s, 3H), 2.92 (s, 3H), 2.75-2.66 (m, 1H), 1.99-1.82 (m, 4H), 1.74-1.66 (m, 2H), 1.50 (b.d, 1H, *J* 11.8), 1.41-1.29 (m, 2H),

1.21-1.10 (m, 1H); (ES⁺) *m/z* 567 (M+H)⁺.

Example 21: (16S,18R)-29-cyclohexyl-10,17-dimethyl-20-oxa-9-thia-1,8,10,13,17-pentaazahexacyclo[16.9.1.1^{2,6}.1^{3,27}.1^{13,16}.0^{21,26}]hentriaconta-2(31),3,5,21,23,25,27(29)-heptaen-7-one 9,9-dioxide (A21)

15 Step 1: methyl (7R)-7-[[[(3S)-1-(tert-butoxycarbonyl)pyrrolidin-3-yl](methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

AcOH (4 eq) was added to a stirred mixture of *tert*-butyl 3-oxopyrrolidine-1-carboxylate (1.5 eq) and methyl (7R)-7-amino-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (1 eq, prepared as described in Example 1, Step 4) in dry DCE (1M); after 30 min

20 Na(OAc)₃BH (1.8 eq) was added and the mixture was stirred at RT for 4 h. Evaporation to dryness gave a residue that was taken in EtOAc, washed with sat. aq. NaHCO₃ and brine, dried and concentrated *in vacuo*. AcOH (4 eq) was added to a stirred mixture of foregoing crude (1 eq) and a 37% solution of HCHO in H₂O (2 eq) in dry MeOH (1M); NaCNBH₃ (1.6 eq) was added and the mixture was stirred at RT for 3 h. Evaporation to dryness gave a residue that was taken

25 in EtOAc, washed with sat. aq. NaHCO₃ and brine, then dried and concentrated *in vacuo*. The crude material was purified by FC (Biotage, PE:EtOAc:toluene, 4:3:3) to afford methyl (7R)-7-[[[(3S)-1-(tert-butoxycarbonyl)pyrrolidin-3-yl](methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (43%) and its diastereoisomer methyl (7R)-7-[[[(3R)-1-(tert-butoxycarbonyl)pyrrolidin-3-yl](methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (43%). (ES⁺) *m/z* 588 (M+H)⁺.

30 Step 2: tert-butyl (3S)-3-[[[(7R)-14-cyclohexyl-11-[[[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl]amino]carbonyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl](methyl)amino]pyrrolidine-1-carboxylate

1M KOH (3.5 eq) was added to a 0.3M solution of methyl (7R)-7-[[[(3S)-1-(tert-butoxycarbonyl)pyrrolidin-3-yl](methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (1 eq) in dioxane and the mixture was stirred at 75 °C for 12 h. The pH was adjusted at 0 °C by addition of 1N HCl (until pH=6), then all volatiles were evaporated, the solid residue was taken in CHCl₃ and salt was filtered off. The filtrate was

concentrated *in vacuo* to afford a residue that was taken in dry DCM (0.05M); DMAP (3.5 eq), EDC (1.5 eq) and *N*-(2,2-dimethoxyethyl)-*N*-methylsulfamide (1.5 eq; prepared as described in Example 1, step 1) were added and the mixture was stirred at 40 °C for 1 h. The residue obtained after evaporation was extracted with EtOAc. The combined organic phases were washed with 1M HCl, sat. aq. NaHCO₃ and brine, dried over Na₂SO₄ and concentrated to afford the title compound which was used without further purification. (ES⁺) *m/z* 754 (M+H)⁺.

Step 3: (16*S*,18*R*)-29-cyclohexyl-10,17-dimethyl-20-oxa-9-thia-1,8,10,13,17-pentaazahexacyclo[16.9.1.1^{2,6}.1^{3,27}.1^{13,16}.0^{21,26}]hentriaconta-2(31),3,5,21,23,25,27(29)-heptaen-7-one 9,9-dioxide

A 0.05M solution of *tert*-butyl (3*S*)-3-[(7*R*)-14-cyclohexyl-11-[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl]amino)carbonyl]-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocin-7-yl(methyl)amino]pyrrolidine-1-carboxylate in DCM/TFA 3:1 was stirred at RT for 1.5h. The residue obtained by evaporation was dissolved in MeOH, NEt₃ (5 eq) was added, followed by NaCNBH₃ (3 eq) and AcOH (10 eq) and the mixture was stirred for 4 h at RT.

The residue obtained after removing MeOH *in vacuo* was taken in sat. aq. NaHCO₃ and EtOAc and extracted with EtOAc; without further washings the organic phase was dried over Na₂SO₄ and concentrated, and the residue purified by RP-HPLC to afford after lyophilisation of the fractions the title compound as a white solid (6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.04 (s, 1H), 7.77 (d, 1H, *J* 8.4), 7.64 (d, 1H, *J* 8.4), 7.52 (t, 1H, *J* 7.6), 7.34-7.27 (m, 3H), 4.66 (d, 1H, *J* 15.6), 4.23 (dd, 1H, *J* 4.6, 11.2), 4.05 (b.t, 1H, *J* 11.2), 3.90-3.80 (m, 2H), 3.70-3.00 (m, 7H, partially obscured by water signal), 2.98-2.90 (m, 1H), 2.80-2.60 (m, 2H), 2.75 (s, 3H), 2.32-2.18 (m, 1H), 2.22 (s, 3H), 1.98-1.87 (m, 3H), 1.84-1.65 (m, 4H), 1.50-1.45 (m, 1H), 1.37-1.27 (m, 2H), 1.15-1.08 (m, 1H); (ES⁺) *m/z* 592 (M+H)⁺.

Example 22: (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-4-propyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A22)

Step 1: methyl 2-[2-(allyloxy)phenyl]-3-cyclohexyl-1*H*-indole-6-carboxylate

Methyl 3-cyclohexyl-2-(2-hydroxyphenyl)-1*H*-indole-6-carboxylate (prepared as described in published International patent application WO 2006/046030) was suspended in MeCN/DCM (1:1, 0.1M) and K₂CO₃ (1 eq) was added. To the stirred mixture allyl bromide (1.1 eq) was added and the mixture was warmed to 50 °C. After 4 h a further 0.5 eq of allyl bromide were added and heating was continued over night. The mixture was filtered and the filter cake was extracted with hot ethyl acetate. The combined filtrates were evaporated *in vacuo*. The residual material was dissolved in hot DCM and precipitated by addition of PE. The precipitate was collected and dried *in vacuo*. The product was obtained as a beige crystalline powder. (81%). (ES⁺) *m/z* 390 (M+H)⁺.

Step 2: methyl 2-(3-allyl-2-hydroxyphenyl)-3-cyclohexyl-1*H*-indole-6-carboxylate

Methyl 2-[2-(allyloxy)phenyl]-3-cyclohexyl-1H-indole-6-carboxylate was heated neat to 220 °C. The starting material liquified at about 190 °C and turned dark brown. After 1 h the starting material was consumed. The brown liquid solidified upon cooling to RT. The product was isolated by FC (biotage column, PE:EtOAc, 9:1). After evaporation of the solvents the product was obtained as a beige amorphous solid (80%). (ES⁺) *m/z* 390 (M+H)⁺.

Step 3: methyl 3-cyclohexyl-2-(2-hydroxy-3-propylphenyl)-1H-indole-6-carboxylate

Methyl 2-(3-allyl-2-hydroxyphenyl)-3-cyclohexyl-1H-indole-6-carboxylate was dissolved in EtOAc (0.08M). After adding Pd/C (10%) HOAc was added and the mixture was degassed and flushed with Ar. After degassing, H₂-atmosphere was applied and the mixture was left stirring at RT. After 30 min the reaction was complete and the catalyst was filtered off. After evaporation of the solvents the product was obtained as a yellowish solid (98%). (ES⁺) *m/z* 392 (M+H)⁺.

Step 4: (7R)-7-[(2-aminoethyl)(methyl)amino]-14-cyclohexyl-N-{[methyl(2-oxoethyl)amino]sulfonyl}-4-propyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide

The title compound was prepared using chemistry analagous to that described for Example 1, Steps 3-9. (ES⁺) *m/z* 624 (M+H)⁺.

Step 5: (7R)-14-cyclohexyl-21-ethyl-18,24-dimethyl-4-propyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

(7R)-7-[(2-aminoethyl)(methyl)amino]-14-cyclohexyl-N-{[methyl(2-oxoethyl)amino]sulfonyl}-4-propyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide was dissolved in MeOH (0.9 mM), NEt₃ and HOAc were added, followed by NaCNBH₃. After 30 min the ring-closed intermediate with [M+H]⁺ = 608 had formed and MeCHO was added. After one night all volatiles were evaporated *in vacuo* and the residual material was dissolved in MeCN. The product was isolated by mass-guided RP- HPLC. After lyophilisation a colourless powder was obtained (6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.09 (s, 1H), 7.91 (d, 1H, *J* 8.6), 7.47-7.45 (m, 2H), 7.30-7.27 (m, 1H), 7.21-7.19 (m, 1H), 4.62 (d, 1H, *J* 14.9), 4.41-4.36 (m, 1H), 3.98-3.84 (m, 3H), 3.58-3.13 (m, 8H), 3.04-2.98 (m, 4H), 2.67 (q, 3H, *J* 7.26), 2.63-2.56 (m, 1H), 2.34 (s, 3H), 1.95-1.65 (m, 10H), 1.48-1.09 (m, 8H), 0.98 (t, 3H, *J* 7.26); (ES⁺) *m/z* 636 (M+H)⁺.

Example 23: 31-cyclohexyl-8-oxa-24-thia-1,4,16,23,25-pentaazaheptacyclo[23.2.2.1^{4,6}.1^{6,16}.1^{15,18}.1^{17,21}.0^{9,14}]tritriaconta-9,11,13,15(31),17(30),18,20-heptaen-22-one 24,24-dioxide (A23)

Step 1: 5,5-bis(bromomethyl)-2,2-dimethyl-1,3-dioxane

TsOH monohydrate (0.1 eq) was added at 0 °C to a 0.2M solution of 2,2-bis(bromomethyl)propane-1,3-diol in acetone/2,2-dimethoxypropane (10:1) and the solution was stirred for 2 h at RT. Filtration over a pad of neutral alumina with EtOAc afforded the title compound as a white solid after evaporation of the solvent *in vacuo* (quant). ¹H NMR (300 MHz, CDCl₃, 300 K) δ 3.80 (s, 4H), 3.58 (s, 4H), 1.42 (s, 6H).

- 70 -

Step 2: methyl 14'-cyclohexyl-2,2-dimethylspiro[1,3-dioxane-5,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate

NaH (5 eq, 60% dispersion in mineral oil) was added to a degassed solution of methyl 3-cyclohexyl-2-(2-hydroxyphenyl)-1*H*-indole-6-carboxylate (prepared as described in published International patent application WO2006/046030) in DMF (0.2 M) and the solution was allowed to stir for 20 min at RT. The mixture was then placed in an oil bath preheated at 70 °C, a degassed solution of 5,5-bis(bromomethyl)-2,2-dimethyl-1,3-dioxane (1.5 eq) in dry DMF (0.4M) was added and the mixture was stirred for 1 h; additional electrophile (1.5 eq) was added and stirring was continued for 3 h at 70 °C. The reaction was quenched with sat. aq. NH₄Cl, acidified with 1N HCl and extracted with Et₂O; the organic layer was washed with H₂O and brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude was purified by FC (PE/EtOAc) to afford the title compound (50%) and recovered starting material (44%). (ES⁺) *m/z* 490 (M+H)⁺.

Step 3: Methyl 1-{2-[4-(aminosulfonyl)piperazin-1-yl]ethyl}-14'-cyclohexylspiro[azetidine-3,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate

Cat. TsOH monohydrate was added to a suspension of methyl 14'-cyclohexyl-2,2-dimethylspiro[1,3-dioxane-5,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate in MeOH/THF 1:2 (0.03 M), and the solution was stirred at RT for 3 h. Filtration on a pad of neutral alumina using EtOAc as eluent afforded after evaporation of the solvent *in vacuo* methyl 14-cyclohexyl-7,7-bis(hydroxymethyl)-7,8-dihydro-6*H*-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (quant). This material was dissolved in dry MeCN (0.2M) and DIPEA (4.0 eq) and trifluoromethane sulfonic anhydride (3.5 eq) was added at 0 °C. The mixture was stirred at 0 °C for 15 min, then more DIPEA (4 eq) was added at RT. *Tert*-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (2 eq) was added, and the mixture was stirred at 70 °C for 1 h. After removal of the solvent *in vacuo* EtOAc was added, the solution was washed with H₂O and brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude methyl 1-{2-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]ethyl}-14'-cyclohexylspiro[azetidine-3,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate was taken in DCM/TFA 3:1 (0.13M) and stirred at RT for 2 h. The mixture was evaporated to dryness and the residual material was dissolved in EtOAc. The solution was washed with sat. aq. NaHCO₃ and brine. The organic phase was dried over Na₂SO₄ and the solvent evaporated *in vacuo*. The residue was dissolved in dry dioxane (0.06M) and sulfamide (5 eq) was added. The mixture was stirred at reflux for 3 h, then overnight at RT. The residue obtained after evaporation was purified by FC (EtOAc/MeOH, 9:1) to afford the title compound in 40% yield. (ES⁺) *m/z* 622 (M+H)⁺.

Step 4: 31-cyclohexyl-8-oxa-24-thia-1,4,16,23,25-pentaazaheptacyclo[23.2.2.1^{4,6}.1^{6,16}.1^{15,18}.1^{17,21}.0^{9,14}]tritriaconta-9,11,13,15(31),17(30),18,20-heptaen-22-one 24,24-dioxide

0.1M aq KOH (3 eq) was added to a 0.1M solution of methyl 1-{2-[4-(aminosulfonyl)piperazin-1-yl]ethyl}-14'-cyclohexylspiro[azetidine-3,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate in dioxane and the mixture was stirred at 70 °C for 150 min. 1M HCl was added until pH=6, the compound was extracted with EtOAc, washed with brine, dried over Na₂SO₄ and concentrated.

5 The residue was dissolved in DCM (0.05M) and treated with DMAP (3 eq) and EDC (1.5 eq) for 90 min at 40 °C. The residue obtained after evaporation was purified by RP-HPLC to afford the title compound as bis-TFA salt (15%). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 8.17 (b.s, 1H), 7.89 (d, 1H, *J* 8.3), 7.46 (b.s, 2H), 7.24-7.16 (m, 3H), 5.15 (d, 1H, *J* 17.4), 4.16-4.05 (m, 2H), 4.05-3.78 (m, 2H), 3.78-3.15 (m, 6H), 3.15-2.40 (m, 10H, partially obscured by DMSO signal),
10 2.00-1.80 (m, 4H), 1.80-1.62 (m, 2H), 1.62-1.50 (m, 1H), 1.40-1.22 (m, 3H); (ES⁺) *m/z* 590 (M+H)⁺.

Example 24: (7*R*)-14-cyclohexyl-18,19,19,21,24-pentamethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A24)

15 Step 1: *tert*-butyl (2-hydroxy-1,1-dimethylethyl)methylcarbamate

A solution of *N*-(*tert*-butoxycarbonyl)-*N*,2-dimethylalanine in THF (0.17 M) was treated at RT with BH₃-DMS complex in THF (10 eq., 2M) and the mixture was stirred at 45 °C for 8 h. The reaction was carefully quenched with H₂O and the pH adjusted to 9 with 2M aq. Na₂CO₃. The mixture was then extracted with EtOAc and washed with brine. After drying over sodium
20 sulfate, the crude material was purified by FC (10-50 % EtOAc in PE) to afford the product. (ES⁺) *m/z* 204 (M+H)⁺.

Step 2: *tert*-butyl (1,1-dimethyl-2-oxoethyl)methylcarbamate

The foregoing compound was dissolved in DCM (0.1 M) and to the mixture was added DMP (1.5 eq,) in one portion. The mixture was stirred for 1 h, then it was diluted with Et₂O and treated
25 with sat. aq. NaHCO₃ containing Na₂S₂O₃. The mixture was stirred for 5 min, then Et₂O was added and the layers were separated. The organic phase was washed with sat. aq. NaHCO₃ and H₂O, dried over Na₂SO₄ and evaporated. The crude product was used without further purification. (ES⁺) *m/z* 202 (M+H)⁺.

30 Step 3: methyl (7*R*)-7-[(2-aminoethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

Methyl (7*R*)-7-[{2-[(*tert*-butoxycarbonyl)amino]ethyl}(methyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (Example 1, Step 6) was treated in analogy to Example 8, Step 11 (100%); (ES⁺) *m/z* 463 (M+H)⁺.

35 Step 4: methyl (7*R*)-7-[(2-[(2-[(*tert*-butoxycarbonyl)(methyl)amino]-2-methylpropyl)(methyl)amino]ethyl)(methyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

The foregoing compound and the compound from step 2 were reacted in analogy to Example 8, Step 12 and 13 to give the title compound; (ES⁺) *m/z* 662 (M+H)⁺.

Step 5: methyl (7R)-14-cyclohexyl-7-[methyl(2-{[2-methyl-2-(methylamino)propyl]amino}ethyl)amino]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

The material was prepared from the foregoing compound in analogy to Example 1, Step 4 (100%); (ES+) m/z 562 (M+H)⁺.

Step 6: methyl (7R)-7-[{2-[{2-[{(tert-butoxycarbonyl)amino}sulfonyl}(methyl)amino]-2-methylpropyl}(methyl)amino]ethyl}(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

Chlorosulfonylisocyanate (1 eq.) and *t*BuOH (1.3 eq.) were stirred at 0 °C in DCM (0.1 M) for 90 minutes. A solution of the compound from step 6 and NEt₃ (5 eq.) in DCM (0.04 M) was added and the resulting mixture was stirred at RT for 1 h. All volatiles were removed *in vacuo*. The crude material was purified by FC (2-10 % MeOH in EtOAc + 2% NEt₃) to afford the title compound (59%); (ES⁺) m/z 741 (M+H)⁺.

Step 7: (7R)-7-[{2-[{2-[{(tert-butoxycarbonyl)amino}sulfonyl}(methyl)amino]-2-methylpropyl}(methyl)amino]ethyl}(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

The foregoing compound was reacted in analogy to Example 10, Step 11 (71%); (ES+) m/z 727 (M+H)⁺.

Step 8: (7R)-7-[{2-[{2-[{(aminosulfonyl)(methyl)amino]-2-methylpropyl}(methyl)amino]ethyl}(methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

The material was prepared from the compound prepared in step 8 in analogy to Example 1, Step 4 (100%); (ES+) m/z 627 (M+H)⁺.

Step 9: (7R)-14-cyclohexyl-18,19,19,21,24-pentamethyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

The foregoing compound was reacted in analogy to Example 8, Step 14 (23%, TFA-salt); ¹H NMR (400 MHz, DMSO-*d*₆ + 2% TFA, 300 K) δ 1.07-1.20 (m, 1H), 1.26-1.36 (m, 3H), 1.39 (s, 3H), 1.43-1.52 (m, 1H), 1.57 (s, 3H), 1.64-1.77 (m, 2H), 1.80-1.88 (m, 1H), 1.89-2.02 (m, 3H), 2.73 (s, 3H), 2.93 (s, 3H), 3.08 (s, 3H), 3.33-3.44 (m, 1H), 3.51-3.65 (m, 3H), 3.65-3.81 (m, 2H), 3.89-4.00 (m, 1H), 4.04-4.17 (m, 1H), 4.27 (apparent t, *J* 11.0, 1H), 4.43-4.56 (m, 1H), 4.73 (d, *J* 15.2, 1H), 7.31-7.44 (m, 3H), 7.53 (d, *J* 8.4, 1H), 7.58 (apparent t, *J* 7.8, 1H), 7.95 (d, *J* 8.4, 1H), 8.09 (s, 1H), 11.7 (br s, 1H); (ES+) m/z 608 (M+H)⁺.

Example 25: (7R)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6H-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A25)

Step 1: (4S)-4-benzyl-3-pent-4-enoyl-1,3-oxazolidin-2-one

- 73 -

To a solution (0.49 M) of (4*S*)-4-benzyl-1,3-oxazolidinone in THF cooled to -78 °C was added dropwise *n*-BuLi in hexane (2.5 M, 1.1 eq). The resulting solution was stirred at -78 °C for 30 min, then a solution of 4-pentenoyl chloride in THF (4 M, 1.1 eq) was added dropwise. The resulting mixture was stirred at -78 °C for 20 min and then allowed to reach 0 °C, where it was stirred for another 40 min. The reaction was quenched by addition of sat. aq. NH₄Cl before partitioning between H₂O and EtOAc. The layers were separated and the aqueous phase re-extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with PE/EtOAc (10:1) to give the product as a colorless oil (72%). (ES⁺) *m/z* 260 (M+H)⁺.

10 Step 2: (4*S*)-4-benzyl-3-[2-(hydroxymethyl)pent-4-enoyl]-1,3-oxazolidin-2-one

The foregoing compound was dissolved in DCM (0.2 M) and cooled to 0 °C. TiCl₄ (1.1 eq) was added dropwise to the mixture, followed by Hünig's base (1.1 eq) and the resulting deep red mixture was stirred at 0 °C for 40 min. *s*-Trioxane (1.1 eq) was added to the reaction mixture in one portion, followed by dropwise addition of TiCl₄ (1.1 eq). The reaction mixture was stirred for 3 h at 0 °C and then quenched by dropwise addition of sat. aq. NH₄Cl. The mixture was stirred for 30 min, poured into H₂O and extracted with DCM. The combined organic extracts were washed once with sat. aq. NH₄Cl, dried with Na₂SO₄, filtered and concentrated *in vacuo*. The resulting orange oil was used without further purification. (ES⁺) *m/z* 290 (M+H)⁺.

20 Step 3: (4*S*)-4-benzyl-3-[(2*R*)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pent-4-enoyl]-1,3-oxazolidin-2-one

The foregoing compound was dissolved in DCM (0.2 M) and at RT treated with DMAP (0.1 eq), NEt₃ (1.5 eq) and *tert*-butyldimethylchlorosilane (1.2 eq). The mixture was stirred at RT °C for 18 h, then ethyl acetate was added and the resulting mixture was washed with HCl (1N), sat. aq. NaHCO₃, water and brine. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with PE/EtOAc (20:1) to give the product as a colorless oil (73% over two steps). (ES⁺) *m/z* 404 (M+H)⁺; [α]_D²⁰: +32.9° (c = 1.3, CHCl₃).

Step 4: (2*S*)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pent-4-en-1-ol

The foregoing compound was dissolved in Et₂O (0.19 M) and cooled to = °C. Solid LiBH₄ (1.2 eq) was added in one portion followed by the dropwise addition of methanol (1.2 eq). The resulting mixture was stirred for 40 min at 0 °C, then for 90 min at RT. The mixture was then cooled to 0 °C and sat. aq. NaHCO₃ was carefully added over 30 min. The biphasic mixture was stirred vigorously for 1 h at 0 °C and then poured into H₂O. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with PE/EtOAc (12:1) to give the product as a colorless oil (80%). (ES⁺) *m/z* 231 (M+H)⁺; [α]_D²⁰: -4.1° (c = 1.4, CHCl₃).

Step 5: (2*R*)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pent-4-en-1-yl methanesulfonate

The foregoing compound was dissolved in DCM (0.5 M), *N,N*-diisopropylethylamine (2 eq) was added and the mixture was cooled to 0 °C. MsCl (1.2 eq) was added dropwise and the mixture was stirred for 1h at RT. The reaction mixture was then diluted with EtOAc and washed with HCl (1N), sat. aq. NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was used without further purification (98%). (ES⁺) *m/z* 309 (M+H)⁺.

Step 6: methyl 2-(2-{{[(2*S*)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pent-4-en-1-yl]oxy}phenyl)-3-cyclohexyl-1*H*-indole-6-carboxylate

A solution of methyl 3-cyclohexyl-2-(2-hydroxy-phenyl)-1*H*-indole-6-carboxylate (prepared as described in published International patent application WO2006/046030) in DMA (0.1 M) was treated with Cs₂CO₃ (1.2 eq) at and heated to 60 °C. The mesylate from prepared in the foregoing step was added in as a DMA solution (0.5 M) over 30 min and the resulting mixture was heated to 65-70 °C and left for 15h. After cooling to RT the solution was diluted with EtOAc and washed with H₂O (3x) and brine. The organic layer was dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by FC eluting with PE/EtOAc (20:1) to give the product as a colorless solid (79%). (ES⁺) *m/z* 562 (M+H)⁺.

Step 7: methyl 3-cyclohexyl-2-(2-{{[(2*R*)-2-(hydroxymethyl)pent-4-en-1-yl]oxy}phenyl)-1*H*-indole-6-carboxylate

A solution of the foregoing compound in THF (0.1 M) was treated with TBAF (1.0 eq, 1.0 M in THF) at RT and stirred for 20 min. Most of the THF was removed *in vacuo*, and the residue was diluted with EtOAc. After washing with HCl (1N), water and brine, the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with PE/EtOAc (8:1 to 5:1) to give the product as a yellowish foam (93%). (ES⁺) *m/z* 448 (M+H)⁺; [α]_D²⁰ : +13.4° (c = 0.93, CHCl₃).

Step 8 : methyl (7*R*)-7-allyl-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

The foregoing compound was converted to its mesylate as described in step 5 and the crude product was dissolved in DMA (0.3 M) and added dropwise over 40 minutes to a suspension of Cs₂CO₃ (2 eq) in DMA (final concentration 0.080 M) heated at 65 °C. After completion of the addition the mixture was stirred at that temperature for another 1.5 h, then cooled to RT, diluted with EtOAc and washed with H₂O (4x) and brine (2x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with PE/EtOAc to give the product as a colorless foam (86%). (ES⁺) *m/z* 430 (M+H)⁺; [α]_D²⁰ : +68.6° (c = 0.7, CHCl₃).

Step 9 : methyl (7*R*)-14-cyclohexyl-7-(3-hydroxypropyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

A solution of the foregoing compound in THF (1.0 M) was added to a solution of 9-BBN in THF (0.5 M, 2.5 eq) cooled to 0 °C. The resulting mixture was stirred for 24 h at RT, and was then

- 75 -

cooled to 0 °C. Sodium hydroxide (1 M, 5 eq) was added, followed by dropwise addition of hydrogen peroxide (35%, 5 eq). The resulting mixture was stirred for 15 min at 0 °C and then for further 30 min at RT. Water was added and the mixture was extracted several times with EtOAc and DCM. The combined organic extracts were dried over Na₂SO₄, filtered and

5 concentrated *in vacuo*. The residue was purified by FC eluting with PE/EtOAc (9:1 to 2:1, containing 2% MeOH) to give the product as a colorless solid (75%). (ES⁺) *m/z* 448 (M+H)⁺.

Step 10: methyl (7R)-7-{3-[{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}{(methyl)amino]propyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

10 The foregoing compound was dissolved in DCM (0.12 M) and oxidized to the corresponding aldehyde using DMP (1.5 eq). After stirring for 1 h at RT, the reaction was diluted with EtOAc and washed with a mixture of sat. aq. NaHCO₃ and sat. aq. Na₂S₂O₃ (1:1, v/v, 2x), water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude aldehyde was dissolved in 1,2-DCE (0.12 M) at RT. To the resulting solution *tert*-butyl

15 methyl[2-(methylamino)ethyl]carbamate (prepared as described in European patent application 1998/296811 from commercially available *N,N'*-dimethylethylenediamine) was added (1.5 eq), followed by sodium triacetoxyborohydride (1.4 eq). After 1.5 h sodium hydroxide (1 M, 2 eq) was added and the mixture stirred vigorously for 10 min). After dilution with EtOAc, the organic phase was washed with water and brine. The organic layer was dried over Na₂SO₄, filtered and

20 concentrated *in vacuo*. The residue was purified by FC eluting with PE/EtOAc (1:1, containing 0.5% NEt₃ and 0.5% MeOH) to give the product as a sticky foam (69%). (ES⁺) *m/z* 618 (M+H)⁺.

Step 11: methyl (7R)-7-{3-[{2-[(*tert*-butoxycarbonyl)amino]-sulfonyl}{(methyl)amino]ethyl}{(methyl)amino]propyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

25 The foregoing compound was dissolved in DCM (0.08 M) and TFA was added (165 eq). After stirring for 30 min at RT, the reaction mixture was evaporated to dryness, taken into EtOAc and washed with sat. aq. NaHCO₃. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude amine was dissolved in THF (0.2 M) and (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (1.2 eq) (prepared

30 following literature procedure: Winum, J.-Y. *et al Org. Lett.* **2001**, 3, 2241-2243) was added. The resulting mixture was heated to 40 °C for 18 h, cooled to RT, diluted with EtOAc and washed with HCl(1 N), sat. aq. NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the product as a yellow oil (91%), which was used without further purification. (ES⁺) *m/z* 697 (M+H)⁺.

35 Step 12: (7R)-7-{3-[{2-[(*tert*-butoxycarbonyl)amino]sulfonyl}{(methyl)amino]ethyl}{(methyl)amino]propyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

- 76 -

The foregoing compound was dissolved in dioxane (0.07 M) and KOH (1 M, 10 eq) was added. The mixture was heated to 65 °C for 3.5 h, then cooled to RT and diluted with EtOAc. HCl (1 N) was added until the aq. phase had a pH of about 2. The aq. phase was separated, extracted with EtOAc and the combined extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the product as a clear oil (99%), which was used without further purification. (ES⁺) *m/z* 683 (M+H)⁺.

Step 13: (7R)-7-{3-[2-[(aminosulfonyl)(methyl)amino]ethyl}(methyl)amino]propyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

The foregoing compound in DCM (0.03 M) was treated with TFA (52 eq) and the mixture was heated to 50 °C. After 20 min all the stirred volatiles were removed *in vacuo* and the residue partitioned between water and EtOAc. The organic layers was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the product as a yellow solid (73%) which was used without further purification. (ES⁺) *m/z* 583 (M+H)⁺.

Step 14: (7R)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6H-7,11-

(propanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

The title compound was prepared in analogy to Example 18, Step 7 from the foregoing compound using EDC (3 eq) and DMAP ((5 eq) and heating the mixture to 40 °C for 15 h). The residue obtained after evaporation of all volatiles was purified by automated RP-HPLC to obtain the title compound as its TFA salt (23%) and as a mixture of two atropisomers (8:1). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K, data for major atropisomer) δ 0.97-1.08 (m, 1H), 1.10-1.21 (m, 1H), 1.25-1.53 (m, 4H), 1.63-1.75 (m, 2H), 1.78-2.05 (m, 6H), 2.60-2.72 (m, 1H), 2.74-2.80 (m, 1H), 2.85 (bs, 3H), 3.08 (s, 3H), 3.1-3.49 (m, 5H, partially covered by water), 3.54-3.70 (m, 2H), 3.78-3.98 (m, 2H), 4.38 (d, *J* 14.5, 1H), 4.44 (bs, 1H), 7.29-7.40 (m, 3H), 7.47 (d, *J* 7.9 Hz, 1H), 7.58 (app. t, *J* 7.9 Hz, 1H), 7.91 (d, *J* 8.5, 1H); 8.02 (s, 1H), 9.89 (bs, 1H), 11.9 (bs, 1H); MS (ES⁺) *m/z* 565 (M+H)⁺; [α]_D²⁰ : +22° (c = 0.28, CH₃CN).

Example 26: (7R)-14-cyclohexyl-21-ethyl-18,24-dimethyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A26)

Step 1: methyl 3-cyclohexyl-2-(3-formyl-2-methoxyphenyl)-1H-indole-6-carboxylate

Methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (prepared as in International patent application WO 2004/087714), (3-formyl-2-methoxyphenyl) boronic acid (1.5 eq) and Pd(PPh₃)₂Cl₂ (0.1 eq) were dissolved in dioxane (0.08M). The solution was degassed and flushed with Ar. 2M Na₂CO₃ solution (1 eq) was added and the mixture was heated to 110 °C for 2 h. All volatiles were evaporated *in vacuo* and the residual material was dissolved in EtOAc, filtered over Celite and evaporated *in vacuo*. The residual material was filtered over a plug of silica gel eluting with (PE/EtOAc 1:1). After evaporation of the fractions containing product and trituration with Et₂O methyl 3-cyclohexyl-2-(3-formyl-2-methoxyphenyl)-1H-indole-6-

- 77 -

carboxylate was obtained as off-white solid (77%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.16-1.39 (m, 3H), 1.51-1.97 (m, 7H), 2.59-2.67 (m, 1H), 3.47 (s, 3H), 3.85 (s, 3H), 7.40-7.45 (m, 1H), 7.61 (d, *J* 8.4, 1H), 7.68 (d, *J* 7.4, 1H), 7.85 (d, *J* 8.4, 2H), 8.00 (s, 1H), 10.39 (s, 1H), 11.55 (s, 1H); (ES⁺) *m/z* 392 (M+H)⁺.

5 Step 2: methyl 3-cyclohexyl-2-(3-formyl-2-hydroxyphenyl)-1H-indole-6-carboxylate

The foregoing compound e was dissolved in dry DCM (0.1M) and treated dropwise with BBr₃ (1 M in DCM, 2 eq). After stirring for 1 h at RT, an excess of MeOH was added dropwise and stirring continued for 20 min. The volatiles were evaporated and the mixture partitioned between EtOAc and 1N HCl. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Methyl 3-cyclohexyl-2-(3-formyl-2-hydroxyphenyl)-1H-indole-6-carboxylate (75%) was obtained pure after trituration with Et₂O. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.10-1.33 (m, 3H), 1.64-1.88 (m, 7H), 2.54-2.61 (m, 1H), 3.85 (s, 3H), 7.19-7.24 (m, 1H), 7.57-7.64 (m, 2H), 7.81 (d, *J* 8.5, 1H), 7.89 (dd, *J* 8.5, 1.1 1H), 7.96 (d, *J* 1.1, 1H), 10.14 (s, 1H), 11.16 (s, 1H), 11.41 (s, 1H); (ES⁺) *m/z* 378 (M+H)⁺.

15 Step 3: methyl 3-cyclohexyl-2-[2-hydroxy-3-(piperidin-1-ylmethyl)phenyl]-1H-indole-6-carboxylate

A suspension of the foregoing compound and NaBH(OAc)₃ in 1,2-DCE was stirred overnight at RT. After addition of sat. aq. NaHCO₃ the mixture was extracted into EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the title compound which was used without further purification. (ES⁺) *m/z* 447 (M+H)⁺.

20 Step 4: (7R)-14-cyclohexyl-21-ethyl-18,24-dimethyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

The compound was prepared in analogy to Example 1, Steps 3 – 10 and Example 3 from the product of step 3 above. The compound was used without further purification after those steps in parallel to Example 1 steps 3, 7 and 9. *Tert*-butyl (2-oxoethyl)carbamate and *N*-(2,2-dimethoxyethyl)-*N*-methylsulfamide were used as reactants in steps parallel to Example 1 steps 6 and 8 The steps parallel to Example 1 steps 9 and 10 and Example 3 were a one pot procedure. The compound was prepared in one pot following the procedures described in Example 1, Steps 9 and 10 and in Example 3. Purification of the one pot procedure was done by automated RP-HPLC, eluting with MeCN/H₂O buffered with 0.1% TFA gradient. Fractions containing the product were combined and freeze dried to afford the product as a white powder (2%). The (ES⁺) *m/z* (M+H)⁺ of the products of the steps parallel to Example 1 steps 3 to 8 was 602, 502, 516, 659, 645 and 826 respectively. Data for product last step 691 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.08-1.99 (m, 19H), 2.50-2.75 (m, 8H, partially obscured by DMSO signal), 2.89-3.61 (m, 17H), 3.85-4.54 (m, 3H), 7.36-7.52 (m, 2H), 7.55-7.79 (m, 2H), 7.91 (d, *J* 8.7, 1H), 8.12 (s, 1H) 9.30 (bs, 1H); (ES⁺) *m/z* 691 (M+H)⁺.

Example 27: (7R)-14-cyclohexyl-4-methoxy-18,24-dimethyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A27)

Step 1: methyl 3-cyclohexyl-2-(2-hydroxy-3-methoxyphenyl)-1H-indole-6-carboxylate

5 The compound was prepared in analogy to Example 8, Step 4, from (2-hydroxy-3-methoxyphenyl)boronic acid. 99% after FC (PE:EtOAc, 4:1 to 1:1). (ES⁺) *m/z* 380 (M+H)⁺.

Step 2: tert-butyl {2-[(7R)-14-cyclohexyl-11-[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}amino)carbonyl]-4-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl}(methyl)amino]ethyl}carbamate

10 The compound was prepared in analogy to Example 8, Steps 8- 15 from the product of step 1 above. The yield of the products of Example 8 steps 9, 11, 12 and 13, 14 and 15 was 100%, 41%, (extracted with EtOAc at acidic pH and precipitated pure from the organic layer), 75%; (purified by FC, PE:EtOAc 2:1 to 1:1 + 0.2% NEt₃), 74% and 100% as crude respectively. The (ES⁺) *m/z* (M+H)⁺ of the products of the steps parallel with Example 8 steps 8-15 was 436, 436, 461, 435, 15 592, 578, 758 and 612 respectively. The product of the steps parallel to Example 8 steps 12 and 13 was produced using *tert*-butyl (2-oxoethyl)carbamate instead of *tert*-butyl methyl(2-oxoethyl)carbamate.

Step 9: (7R)-7-[(2-aminoethyl)(methyl)amino]-14-cyclohexyl-4-methoxy-N-{[methyl(2-oxoethyl)amino]sulfonyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide

20 TFA (22 eq) was added to a 0.15M solution of the foregoing crude material in dry DCM and the mixture was stirred at RT for 1.5 h. Evaporation gave a residue that was used as such; (ES⁺) *m/z* 612 (M+H)⁺.

Step 10: (7R)-14-cyclohexyl-4-methoxy-18,24-dimethyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

25 The compound was prepared in analogy to Example 8, Step 17 (16%). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.08-1.20 (m, 1H), 1.27-1.40 (m, 2H), 1.40-1.49 (m, 1H), 1.65-1.74 (m, 2H), 1.78-1.99 (m, 4H), 2.41 (s, 3H), 2.69 (br s, 1H), 2.98 (s, 3H), 3.25-3.45 (m, 8H), 3.91 (s, 3H), 3.96-4.15 (m, 3H), 4.51 (d, *J* 11.2, 1H), 4.64 (d, *J* 14.4, 1H), 6.94 (br d, *J* 6.0, 1H), 7.27- 30 7.32 (m, 2H), 7.44 (d, *J* 8.0, 1H), 7.91 (d, *J* 8.0, 1H), 8.01 (s, 1H); (ES⁺) *m/z* 596 (M+H)⁺.

Example 28: (7R)-14-cyclohexyl-21-ethyl-4-methoxy-18,24-dimethyl-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A28)

Prepared in analogy to Example 3 from the compound obtained in Example 27, Step 10 (35%).

35 ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.08-1.20 (m, 1H), 1.20-1.26 (m, 3H), 1.28-1.39 (m, 2H), 1.39-1.47 (m, 1H), 1.64-1.75 (m, 2H), 1.70-2.00 (m, 4H), 2.58 (s, 3H), 2.62-2.72 (m, 1H), 3.22 (s, 3H), 3.15-3.61 (m, 9H), 3.70-3.78 (m, 1H), 3.92 (s, 3H), 3.90-4.02 (m, 1H), 4.02-4.12

- 79 -

(m, 2H), 4.44-4.48 (m, 1H), 4.69 (d, *J* 15.6, 1H), 6.95 (br d, *J* 6.8, 1H), 7.27-7.34 (m, 2H), 7.49 (d, *J* 8.5, 1H), 7.93 (d, *J* 8.5, 1H), 8.06 (s, 1H); (ES⁺) *m/z* 624 (M+H)⁺.

Example 29: (7*R*)-14-cyclohexyl-4-methoxy-18,24-dimethyl-21-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-7,8-dihydro-6*H*-7,11-

5 **(epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A29)**

Prepared in analogy to Example 3 from the compound obtained in Example 27, Step 10 and substituting acetaldehyde with 1-methyl-1*H*-pyrazole-4-carbaldehyde (35%). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 1.06-1.20 (m, 1H), 1.27-1.38 (m, 2H), 1.38-1.46 (m, 1H), 1.64-1.74 (m, 2H), 1.80-1.98 (m, 4H), 2.54 (s, 3H), 2.64-2.73 (m, 1H), 3.03 (s, 3H), 3.21-3.48 (m, 6H), 3.63-3.78 (m, 2H), 3.85 (s, 3H), 3.91 (s, 3H), 3.92-4.07 (m, 3H), 4.21 (br d, *J* 14.4, 1H), 4.33 (br d, *J* 14.4, 1H), 4.39-4.43 (m, 1H), 4.68 (d, *J* 14.8, 1H), 6.95 (d, *J* 6.8, 1H), 7.26-7.34 (m, 2H), 7.48 (d, *J* 8.2, 1H), 7.61 (s, 1H), 7.89 (s, 1H), 7.92 (d, *J* 8.2, 1H), 8.04 (s, 1H); (ES⁺) *m/z* 690 (M+H)⁺.

15 **Example 30: 2-[(7*R*)-14-cyclohexyl-18,21-dimethyl-17,17-dioxido-15-oxo-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-24-yl]-*N*-methylacetamide (A30)**

Step 1: (7*R*)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6*H*-7,11-

20 (epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide

The title compound was prepared in analogy to Example 12, Steps 1-8 from methyl (7*R*)-7-amino-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate. (The ES⁺) *m/z* (M+H)⁺ of the products of the steps parallel to Example 8 steps 1-8 was 495, 638, 624, 804, 658, 642, 656 and 566 respectively. The yield of the product of the step parallel to Example 8 step 7 was 40%.

Step 9: [(7*R*)-14-cyclohexyl-18,21-dimethyl-17,17-dioxido-15-oxo-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-24-yl]acetic acid

30 A solution of the foregoing compound in MeOH (0.1 M) was treated with HOAc until pH was 5. NaCNBH₃ (2 eq) was added in one portion and the resulting mixture was stirred at RT for 90 min. All volatiles were evaporated *in vacuo*. The residual material was taken up with EtOAc and the resulting solution was washed with sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The crude material was used without further purification. (ES⁺) *m/z* 624 (M+H)⁺.

35 Step 10: 2-[(7*R*)-14-cyclohexyl-18,21-dimethyl-17,17-dioxido-15-oxo-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-24-yl]-*N*-methylacetamide

The foregoing compound was dissolved in DCM/DMA (2:1, 0.1 M) and to the resulting solution DMAP (5 eq) and EDC (1.5 eq) were added. The mixture was stirred for 5 min then MeNH₂·HCl (2 eq) was added and stirring continued for 16 h. All volatiles were removed *in vacuo* and the residue was dissolved in DMSO and purified by mass-guided prep RP-HPLC. After

5 lyophilisation the product was obtained as a colourless amorphous material (16%, TFA-salt). ¹H NMR (400 MHz, DMSO-*d*₆ + 3% TFA, 330 K) δ 1.09-1.22 (m, 1H), 1.29-1.42 (m, 2H), 1.45-1.55 (m, 1H), 1.64-1.77 (m, 2H), 1.81-1.87 (m, 1H), 1.88-2.00 (m, 3H), 2.67 (s, 3H), 2.71 (m, 1H), 2.87 (s, 3H), 3.06 (s, 3H), 3.07-3.14 (m, 2H), 3.15-3.25 (m, 2H), 3.30 (s, 2H), 3.35-3.44 (m, 1H), 3.46-3.55 (m, 2H), 3.59-3.70 (m, 1H), 3.92 (br d, *J* 10.0 Hz, 1H), 3.93-4.03 (m, 2H), 4.47 (d, 10 *J* 14.8 Hz, 1H), 4.49-4.58 (m, 1H), 7.30-7.41 (m, 3H), 7.46 (d, *J* 8.0 Hz, 1H), 7.56 (br t, *J* 7.4 Hz, 1H), 7.83 (br s, 1H), 7.90 (d, *J* 8.4 Hz, 1H), 8.06 (s, 1H); MS (ES⁺) *m/z* 637 (M+H)⁺.

Example 31: (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-18,21,21-trimethyl-7,8-dihydro-6*H*-7,11-(epiminopentanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocine-15-one 17,17-dioxide (A31)

15 Step 1: 3,3-dimethylpent-4-enal

The compound was prepared by Swern oxidation of 3,3-dimethylpent-4-en-1-ol as described in *Tetrahedron Lett* **2004**, 45 (14), 2939-2942 (95%).

Step 2: methyl (7*R*)-7-[(tert-butoxycarbonyl)(3,3-dimethylpent-4-en-1-yl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

20 The compound was prepared in analogy to Example 20, Step 1 substituting [2-(benzyloxy)ethoxy]acetaldehyde with 3,3-dimethylpent-4-enal, and purified by FC (PE/EtOAc 9:1 to 5:1). Yield 100%. (ES⁺) *m/z* 601 (M+H)⁺.

Step 3: methyl (7*R*)-7-[(tert-butoxycarbonyl)(5-hydroxy-3,3-dimethylpentyl)amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

25 BH₃·DMS (3.4 eq) was added at 0 °C to a 1M solution of the foregoing compound in dry THF and the mixture was stirred at RT for 2 h. After cooling to 0 °C H₂O was carefully added followed by sodium perborate tetrahydrate (10 eq) and the mixture was stirred at RT for 3 h. After diluting with H₂O the reaction was extracted with EtOAc, washed with brine, dried and concentrated. The crude material was purified by FC (PE/EtOAc 2:1) to afford the title 30 compound (72%). (ES⁺) *m/z* 619 (M+H)⁺.

Step 4: methyl (7*R*)-7-[(tert-butoxycarbonyl)[3,3-dimethyl-5-(methylamino)pentyl]amino]-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

35 DMAP (0.1 eq) and MsCl (1.5 eq) was added to a 0.05M solution of the foregoing compound and NEt₃ (3 eq) in dry MeCN and the mixture was stirred at RT for 3 h. This solution was treated with additional NEt₃ (3 eq) and 2M MeNH₂/THF (22 eq) at 85 °C overnight, evaporation gave a residue that was taken in EtOAc and washed with sat. aq. NaHCO₃ and brine, dried and concentrated (97%). (ES⁺) *m/z* 632 (M+H)⁺.

Step 5: methyl (7R)-7-((tert-butoxycarbonyl){5-[{(tert-butoxycarbonyl)amino)sulfonyl}(methyl)amino]-3,3-dimethylpentyl}amino)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

Prepared in analogy to Example 20, Step 3. (94% as crude). (ES⁺) *m/z* 833 (M+Na)⁺.

5 Step 6: (7R)-7-({5-[(aminosulfonyl)(methyl)amino]-3,3-dimethylpentyl}amino)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

1M aq. KOH was added to a 0.2M solution of the previous crude in dry dioxane and the mixture was stirred at 75 °C overnight. After adding 1N HCl the reaction mixture was extracted with EtOAc and washed with brine, dried and concentrated. The residue was dissolved in dry DCM (0.2M) and treated with TFA (20 eq) at RT for 2 h, then all volatiles were removed *in vacuo* to give a residue that was used as such (95%). (ES⁺) *m/z* 597 (M+H)⁺.

Step 7: (7R)-7-{{5-[(aminosulfonyl)(methyl)amino]-3,3-dimethylpentyl}[2-(dimethylamino)ethyl]amino}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

15 NaCNBH₃ (2 eq) was added to a stirred mixture of the previous crude, Et₃N (5 eq) and *tert*-butyl (2-oxoethyl)carbamate (1.5 eq) in MeOH (0.08M); AcOH (11 eq) was added and the mixture was stirred at RT for 3 h. MeOH was evaporated, H₂O added and extracted with EtOAc, the organic phase was washed once with a small amount of brine, dried and concentrated, and this crude was taken in dry DCM (0.2M) and treated with TFA (20 eq) at RT for 2 h. Evaporation to dryness gave a residue that was taken in MeOH (0.1M); NEt₃ (6 eq), 37% aq. solution of HCHO (7 eq) and NaCNBH₃ (4 eq) were added, then AcOH (10 eq) was added and the mixture was stirred at RT for 3 h. All volatiles were evaporated *in vacuo*, H₂O and EtOAc were added. The phases were separated and the organic phase was washed once with a small amount of brine, dried and concentrated. The crude material was used as such (74%); (ES⁺) *m/z* 668 (M+H)⁺.

25 Step 8: (7R)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-18,21,21-trimethyl-7,8-dihydro-6H-7,11-(epiminopentanoiminomethano)indolo[1,2-e][1,5]benzoxazocine-15-one 17,17-dioxide

EDC (2 eq) was added to a stirred mixture of previous crude and DMAP (4 eq) in dry DMF (0.04M) and the mixture was stirred at 65 °C for 90 min. DMF was partially evaporated, the residue taken in DMSO and purified by automated RP-HPLC to give the title compound (7%).

30 ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 0.88 (s, 3H), 0.93 (s, 3H), 1.10-1.20 (m, 1H), 1.21-1.39 (m, 4H), 1.42-1.63 (m, 2H), 1.64-1.76 (m, 2H), 1.80-2.00 (m, 4H), 2.14-2.25 (m, 1H), 2.50-2.87 (m, 5H, partially under DMSO signal), 2.83 (s, 6H), 3.01 (s, 3H), 3.05-3.13 (m, 1H), 3.13-3.25 (m, 2H), 3.26-3.38 (m, 1H), 3.47-3.59 (m, 1H), 3.86-3.97 (m, 1H), 3.97-4.08 (m, 1H), 4.21-4.30 (m, 1H), 4.60 (d, *J* 14.7, 1H), 7.28-7.38 (m, 3H), 7.47 (d, *J* 8.3, 1H), 7.54-7.58 (m, 1H), 7.90 (d, *J* 8.3, 1H), 8.08 (s, 1H), 11.66 (br s, 1H); (ES⁺) *m/z* 650 (M+H)⁺.

Example 32: (7R)-14-cyclohexyl-18,21,24-trimethyl-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A32)

Step 1: 2-(benzyloxy)-6-bromophenol

- 5 *Tert.*-butyl amine (2 eq) was dissolved in toluene (1M) and the solution was cooled to -30 °C. Br₂ (1 eq) was added dropwise maintaining the temperature. The mixture was left stirring for 30 min, then it was cooled to -78 °C. A solution of 2-benzyloxyphenol (1 eq) in DCM (6M) was added dropwise. The mixture was allowed to reach RT over the course of 3 h. The mixture was diluted with Et₂O and H₂O was added. The mixture was washed with 1N HCl, sat. aq. Na₂S₂O₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The residue was
10 purified by FC (PE:EtOAc, 9:1). The colourless oil was used without further characterization in the next reaction. (ES⁻) *m/z* 277, 279 (M-H)⁻.

Step 2: methyl 3-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-6-carboxylate

- 15 Methyl 2-bromo-3-cyclohexyl indole-6-carboxylate (prepared as described in International patent application WO 2004/087714) was dissolved in dioxane (0.4M) and to the solution were added NEt₃ (4 eq), Pd(OAc)₂ (0.05 eq) and 2-(dicyclohexyl)phosphino biphenyl (0.19 eq). Pinacolborane (3 eq) was added dropwise and the mixture was heated at 80 °C for 1 h. The mixture was cooled to RT and then quenched with sat. aq. NH₄Cl. The mixture was extracted
20 with Et₂O. The combined organic phases were washed with brine and dried over Na₂SO₄. All volatiles were evaporated *in vacuo*. The residual material was purified by FC (PE:EtOAc, 9:1). After evaporation of the product fractions a yellowish solid was obtained. This material was dissolved in DCM and PE was added to induce crystallisation. The product was obtained as a beige crystalline powder (44%). (ES⁺) *m/z* 384 (M+H)⁺.

25 Step 3: methyl 2-[3-(benzyloxy)-2-hydroxyphenyl]-3-cyclohexyl-1H-indole-6-carboxylate

- The foregoing compound and 2-(benzyloxy)-6-bromophenol (1.5 eq) were dissolved in dioxane (0.11M). The solution was degassed and Pd(PPh₃)₂Cl₂ (0.1 eq) was added followed by 2M Na₂CO₃ solution (6 eq). The mixture was warmed under Ar atmosphere to 100 °C. After 1 h all volatiles were evaporated *in vacuo* and the residual material was dissolved in EtOAc. The
30 resulting mixture was washed with 1N HCl, sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The residual material was purified by FC (PE:EtOAc, 9:1). After evaporation of the solvents a colourless foam was obtained (45%). (ES⁺) *m/z* 456 (M+H)⁺.

35 Step 4: methyl (7R)-4-(benzyloxy)-14-cyclohexyl-7-(methylamino)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

The compound was prepared in analogy to Example 1, Steps 3-5, from the product of step 3 above. The yield of the products of the steps parallel to Example 1 steps 3 and 5 was 76% and

60% respectively. The (ES⁺) *m/z* (M+H)⁺ of the products of the steps parallel to Example 1 steps 3-5 was 611, 511 and 525 respectively.

Step 5: methyl (7R)-4-(benzyloxy)-7-[[2-[(tert-butoxycarbonyl)amino]ethyl](methyl)amino]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

- 5 To a solution of the foregoing compound in MeOH was added HOAc (2 eq), followed by N-Boc-aminoacetaldehyde (1.2 eq). The mixture was left stirring for 15 min, then NaBH(OAc)₃ (1.5 eq) was added and the resulting solution was left stirring at RT over night. A precipitate was observed. The mixture was diluted with DCM and the resulting solution was extracted with sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The residual material was purified by FC (PE:EtOAc, 8:2). After evaporation of the solvents the product was obtained as a yellowish amorphous solid (78%). (ES⁺) *m/z* 668 (M+H)⁺.

Step 6: methyl (7R)-7-[[2-[(tert-butoxycarbonyl)amino]ethyl](methyl)amino]-14-cyclohexyl-4-hydroxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

- 15 To a solution of the foregoing compound in EtOAc/HOAc was added Pd/C (10%). After degassing, H₂ atmosphere was applied and the mixture was left stirring at RT for one night. The mixture was flushed with Ar and filtered. The filter cake was washed with EtOAc and the combined filtrates were evaporated *in vacuo*. The residual material was used without further characterisation in the next reaction (quant).

Step 7: methyl (7R)-7-[[2-[(tert-butoxycarbonyl)amino]ethyl](methyl)amino]-14-cyclohexyl-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

- 20 The foregoing compound was dissolved in DMF (0.05M) and NaH (2.2 eq) was added. After stirring for 5 min RT 3-(2-chloroethyl)pyrrolidine hydrochloride (1.1 eq) was added and the mixture was warmed to 50 °C over night. The reaction was quenched by addition of sat. aq. NH₄Cl. The product was extracted with DCM. The combined organic phases were washed with brine. After drying over Na₂SO₄ all volatiles were evaporated *in vacuo*. The residual material was purified by FC (PE:EtOAc, 6:4 + 1% MeOH + 1% NEt₃). After evaporation of the solvents the product was obtained as a colourless amorphous solid. (50%). (ES⁺) *m/z* 675 (M+H)⁺.

Step 8: (7R)-7-[(2-aminoethyl)(methyl)amino]-14-cyclohexyl-N-[[methyl(2-oxoethyl)amino]sulfonyl]-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide

- 30 The compound was prepared in analogy to Example 1, Steps 7-9, from the product of step 7 above (quant.). The yield of the product of the step parallel to Example 1 step 8 was 79%. The (ES⁺) *m/z* (M+H)⁺ of the products of the steps parallel to Example 1 steps 7 and 8 was 661 and 841 respectively. The product of the step parallel to Example 1 step 9 was used without characterization in the next reaction.

Step 9: (7R)-14-cyclohexyl-18,21,24-trimethyl-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6H-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

- 84 -

The compound was prepared in analogy to Example 22, Step 11, from (7*R*)-7-[(2-aminoethyl)(methyl)amino]-14-cyclohexyl-N- {[methyl(2-oxoethyl)amino]sulfonyl}-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxamide and using a 37% solution of formaldehyde in H₂O instead of acetaldehyde (11%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.04 (s, 1H), 7.93 (d, 1H, *J* 8.4), 7.48-7.46 (d, 1H, *J* 8.4), 7.36-7.31 (m, 2H), 7.03-6.98 (m, 2H), 4.60 (d, 1H, *J* 15.6), 4.44-4.33 (m, 3H), 4.00-3.90 (m, 3H), 3.71-3.69 (m, 4H), 3.41-3.31 (m, 2H), 3.25-3.15 (m, 3H), 3.04 (s, 3H), 2.86-2.83 (m, 3H), 2.67-2.65 (m, 1H), 2.32 (s, 3H), 2.07-1.89 (m, 10H), 1.73-1.65 (m, 2H), 1.43-1.31 (m, 4H), 1.14-1.10 (m, 2H); (ES⁺) *m/z* 693 (M+H)⁺.

Example 33: (7*R*)-14-cyclohexyl-4-methoxy-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A33)

Step 1: methyl 4-azidobutanoate

To a solution of methyl-4-bromobutyrate in DMSO (0.6 M) was added with stirring NaN₃ (1.5 eq). The suspension was heated (45-50 °C, oil bath) with stirring for 5 h. After cooling, H₂O was added and the mixture extracted with Et₂O. The organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo* and the crude oil used without further purification (99%).

Step 2: 4-azidobutanoic acid

Methyl 4-azidobutanoate was suspended in 1N NaOH (1.2 eq) and the minimum of MeOH was added to make the reaction mixture homogenous. After 1 h at RT temperature, MeOH was removed *in vacuo*. The aqueous solution was extracted with Et₂O and acidified to pH = 0 with concentrated HCl. The acids were then extracted with ether and the organic phases dried over Na₂SO₄. The crude oil obtained was used without further purification (quant.).

Step 3: (4*S*)-3-(4-azidobutanoyl)-4-benzyl-1,3-oxazolidin-2-one

NEt₃ was added to a stirred mixture of 4-azidobutanoic acid in THF (0.3 M) cooled to -78 °C and stirring was continued at this temperature for 10 min. Pivaloyl chloride (1.3 eq) was added dropwise. The resulting mixture was warmed to 0 °C and stirred for 1 h before re-cooling to -78°C. In a separate flask, (4*S*)-4-benzyl-1,3-oxazolidin-2-one was dissolved in THF (0.8 M) and cooled to -78°C before dropwise addition of N-BuLi (1.6M, 1.35 eq.) over 10 min. The mixture was stirred at -78 °C for 1 h and then transferred into the -78°C solution of mixed anhydride using a syringe. The reaction was stirred at -78 °C for 1 h, then at RT for a further 1h. The reaction was quenched by addition of sat. aq. NH₄Cl before partitioning between H₂O and EtOAc. The layers were separated and the aqueous phase re-extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with 10 to 30% EtOAc/PE to give the product as a colorless oil (74%). (ES⁺) *m/z* 289 (M+H)⁺.

Step 4: (4S)-3-[(2R)-4-azido-2-(hydroxymethyl)butanoyl]-4-benzyl-1,3-oxazolidin-2-one

The foregoing compound was dissolved in DCM (0.1 M) and cooled to -10 °C. TiCl₄ (1.1 eq) was added dropwise to the mixture, such that the internal temperature did not rise above 0 °C. The mixture was stirred an additional 30 min and then Hünig's base (1.15 equiv.) was added dropwise, such that the internal temperature did not rise above 0 °C. The deep red solution was stirred an additional 45 min at -10 °C. *s*-Trioxane (1.2 eq) was added to the reaction mixture in one portion, followed by dropwise addition of TiCl₄ (1.1 eq). The reaction mixture was stirred for 2 h at -10 °C and then quenched by dropwise addition of sat. aq. NaHCO₃. The mixture was stirred for 30 min, poured into H₂O and extracted with DCM. The combined organic extracts were washed once with sat. aq. NH₄Cl, dried with Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with 30 to 70% EtOAc/PE to give the product as a colorless oil (61%). (ES⁺) *m/z* 319 (M+H)⁺; [α]_D²⁰: +42.9° (*c* 1, CHCl₃).

Step 5: (4S)-3-[(2R)-4-azido-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)butanoyl]-4-benzyl-1,3-oxazolidin-2-one

The foregoing compound was dissolved in DCM (0.17 M) and treated with DMAP (0.1 eq) and NEt₃ (1.8 eq). The solution was cooled to 0 °C and *tert*-butyldimethylchlorosilane (1.5 eq) was added in one portion. The mixture was stirred at 0 °C for 30 min, warmed to RT and stirred for an additional 18 h. The reaction mixture was poured into sat. aq. NaHCO₃ and extracted with DCM. The combined organic extracts were dried with Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with 10 to 20 % EtOAc/PE to give the product as a colorless oil (90%). (ES⁺) *m/z* 433 (M+H)⁺; [α]_D²⁰: +30.2° (*c* 1, CHCl₃).

Step 6: (2S)-4-azido-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)butan-1-ol

The foregoing compound was dissolved in Et₂O (0.17 M), treated with MeOH (1.1 eq) and cooled to 0 °C. LiBH₄ (1.1 eq) was added in one portion and the mixture was stirred for 30 min at 0 °C. The mixture was warmed to RT and stirred for 1 h. The mixture was then cooled to 0 °C and sat. aq. NaHCO₃ was carefully added over 30 min. The biphasic mixture was stirred vigorously for 1 h at 0 °C and then poured into H₂O. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried with Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with 10 to 20% EtOAc/PE to give the product as a colorless oil (60%). (ES⁺) *m/z* 260 (M+H)⁺; [α]_D²⁰: -1.5° (*c* 1, CHCl₃).

Step 7: (2R)-4-azido-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)butyl methanesulfonate

The foregoing compound was dissolved in DCM (0.13 M), *N,N*-diisopropylethylamine (2 eq) was added and the mixture was cooled to 0 °C. MsCl (1.1 eq) was added dropwise and the mixture was stirred for 15 min at 0 °C, then warmed to RT and stirred for an additional 15 min. The reaction mixture was then poured into 1N HCl and extracted with DCM. The combined organic extracts were washed once with sat. aq. NaHCO₃ and brine, dried with Na₂SO₄, filtered and concentrated *in vacuo*. The residue was used without further purification (95%).

Step 8: methyl 2-(2-{{[(2S)-4-azido-2-{{[tert-butyl(dimethyl)silyl]oxy}methyl}butyl]oxy}-3-methoxyphenyl)-3-cyclohexyl-1H-indole-6-carboxylate

A solution of methyl 3-cyclohexyl-2-(2-hydroxy-3-methoxyphenyl)-1H-indole-6-carboxylate (Example 27, Step 1) in DMA (0.1 M) was treated with Cs₂CO₃ (1.0 eq) at 60 °C and stirred for 5 30 min. (2R)-4-azido-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)butyl methanesulfonate was added in one portion and the mixture was stirred for 18 h at 60 °C. After cooling the solution was diluted with EtOAc and washed with H₂O (x3) and brine. The organic layer was dried with Na₂SO₄, filtered and evaporated to dryness. The residue was purified by FC eluting with 10 to 30% EtOAc/PE to give the product as a colorless solid (69%). (ES⁺) *m/z* 621 (M+H)⁺; [α]_D²⁰ : 10 +1.2° (*c* 1, CHCl₃).

Step 9: methyl 2-(2-{{[(2R)-4-azido-2-(hydroxymethyl)butyl]oxy}-3-methoxyphenyl)-3-cyclohexyl-1H-indole-6-carboxylate

A solution of the foregoing compound in THF (0.1 M) was treated with TBAF (1.1 eq, 1.0 M in THF) at RT and stirred for 1 h. Reaction mixture was poured into 1N HCl and extracted with 15 DCM. The combined organic extracts were washed once with sat. aq. NaHCO₃ and brine, dried with Na₂SO₄, filtered and concentrated *in vacuo*. The residue was used without further purification (quant.). (ES⁺) *m/z* 507 (M+H)⁺;

Step 10 : methyl 2-{2-[(2S)-4-azido-2-{{[(methylsulfonyl)oxy]methyl}butyl]oxy]-3-methoxyphenyl}-3-cyclohexyl-1H-indole-6-carboxylate

20 The title compound was prepared in analogy to Step 7 from methyl 2-(2-{{[(2R)-4-azido-2-(hydroxymethyl)butyl]oxy}-3-methoxyphenyl)-3-cyclohexyl-1H-indole-6-carboxylate. The residue was used without further purification (99%). (ES⁺) *m/z* 585 (M+H)⁺.

Step 11 : methyl (7R)-7-(2-azidoethyl)-14-cyclohexyl-4-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

25 A solution of the foregoing compound in DMA (0.5 M) was added dropwise over 30 minutes to a suspension of Cs₂CO₃ in DMA (final concentration 0.050 M) heated at 60 °C. 30 minutes after completion of the addition mixture was cooled to RT, diluted with EtOAc and washed with H₂O (x2) and brine (x2). The combined organic extracts were dried with Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with 20 to 35% EtOAc/PE to give 30 the product as a colorless solid (67%). (ES⁺) *m/z* 489 (M+H)⁺; [α]_D²⁰ : +34.6° (*c* 1, CHCl₃).

Step 12 : methyl (7R)-7-(2-aminoethyl)-14-cyclohexyl-4-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

The foregoing compound was dissolved in EtOAc/MeOH (1:1, 0.15 M). Pd/C (10% w/w, 0.1 eq.) was added and the mixture was stirred at RT under H₂ atmosphere overnight then filtered on 35 a short pad of Celite® washing with MeOH. The residue was used without further purification (94%). (ES⁺) *m/z* 463 (M+H)⁺.

Step 13 : methyl (7R)-14-cyclohexyl-4-methoxy-7-[2-(methylamino)ethyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

- 87 -

The title compound was prepared in analogy to Example 1, Step 5 from methyl (7R)-7-(2-aminoethyl)-14-cyclohexyl-4-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate. The crude product was used without further purification (99%). (ES⁺) *m/z* 477 (M+H)⁺.

5 Step 14 : methyl (7R)-7-{2-[[N-(tert-butoxycarbonyl)-N-methyl-β-alanyl](methyl)amino]ethyl}-14-cyclohexyl-4-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

The title compound was prepared in analogy to Example 13, Step 6 from methyl (7R)-14-cyclohexyl-4-methoxy-7-[2-(methylamino)ethyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate and *N*-(tert-butoxycarbonyl)-*N*-methyl-β-alanine

10 The crude product was purified by FC eluting with 50 to 75% EtOAc/PE to give the product as a colorless solid (63%). (ES⁺) *m/z* 662 (M+H)⁺.

Step 15 : methyl (7R)-14-cyclohexyl-4-methoxy-7-(2-{methyl[3-(methylamino)propyl]amino}ethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

15 The title compound was prepared in analogy to Example 13, Step 9 from methyl (7R)-7-{2-[[*N*-(tert-butoxycarbonyl)-*N*-methyl-β-alanyl](methyl)amino]ethyl}-14-cyclohexyl-4-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate. The crude product was used without further purification (quant.). (ES⁺) *m/z* 549 (M+H)⁺.

20 Step 16: (7R)-14-cyclohexyl-4-methoxy-18,22-dimethyl-7,8-dihydro-6H-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

The title compound was prepared in analogy to Example 18, Steps 4-7 from the product of step 15 above. The crude product was used without further purification after the steps parallel to Example 18 steps 4-6. The yield of the products of the steps parallel to Example 18 steps 4 and 5 was 96% and 86% respectively. The (ES⁺) *m/z* (M+H)⁺ of the products of the steps parallel to Example 18 steps 4-6 was 728, 714 and 614 respectively.

25 The residue obtained after evaporation of all volatiles of the product produced after the last step was purified by automated RP-HPLC to obtain the title compound as bis TFA salt and as a mixture of two atropisomers (20%). Data for product of last step, ¹H NMR (400 MHz, DMSO-*d*₆ + 3% TFA, 300 K, data for major atropisomer) δ 1.05-1.21 (m, 1H), 1.25-1.38 (m, 2H), 1.39-1.47 (m, 1H), 1.56-1.77 (m, 4H), 1.79-1.86 (m, 1H), 1.87-2.00 (m, 3H), 2.01-2.13 (m, 1H), 2.20-2.33 (m, 1H), 2.60-2.72 (m, 1H), 2.74-2.80 (m, 1H), 2.81 (br s, 3H), 3.02 (s, 3H), 3.05-3.14 (m, 2H), 3.19-3.37 (m, 2H), 3.53-3.65 (m, 2H), 3.68-3.82 (m, 2H), 3.89 (s, 3H), 4.35 (d, *J* 14.8 Hz, 1H), 4.52 (m, 1H), 6.93 (d, *J* 7.6 Hz, 1H), 7.19-7.31 (m, 2H), 7.48 (d, *J* 8.6 Hz, 1H), 7.90 (d, *J* 8.6 Hz, 1H), 8.05 (br s, 1H); MS (ES⁺) *m/z* 596 (M+H)⁺.

Example 34: 30-cyclohexyl-18-oxa-2-thia-1,3,10,24-tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide (A34)

Step 1: methyl 14-cyclohexyl-7-formyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

5 A solution (0.03 M) of methyl 14-cyclohexyl-7-(hydroxymethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (prepared as described in example 13, steps 1-2) in DCM was added to a solution of DMP (0.04 M; 1.25 eq) in DCM at RT. The reaction was then left to stir at RT for 1 h. The mixture was diluted with EtOAc and washed with a 1:1 mixture of sat. aq. NaHCO₃ and sodium thiosulfate (aq) (3x) before washing with brine, drying (Na₂SO₄), filtering and concentrating *in vacuo* to afford the product as a tinted glass (98 %). The material was taken on without further purification. (ES⁺) *m/z* 418 (M+H)⁺; 436 (M+H₂O+H)⁺.

10 Step 2: methyl 7-[3-tert-butoxy-3-oxoprop-1-en-1-yl]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

(*tert*-butoxycarbonylmethylene)triphenylphosphorane (1.12 eq) was added directly to methyl 14-cyclohexyl-7-formyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.02 M) in THF and the mixture stirred at RT overnight. The volatiles were removed *in vacuo*. The residue was partitioned between EtOAc and 1N HCl (aq). The organics were washed with 1N HCl (aq), sat. aq. NaHCO₃, brine and then dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10 % EtOAc/PE) to afford the product (93 %) as a mixture of double bond geometric isomers. (ES⁺) *m/z* 516 (M+H)⁺; 538 (M+Na)⁺.

20 Step 3: methyl 7-(3-tert-butoxy-3-oxopropyl)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

Cobalt chloride hexahydrate (cat.; 0.12 eq) was added to a solution of methyl 7-[3-*tert*-butoxy-3-oxoprop-1-en-1-yl]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate in MeOH (0.02 M). Once the cobalt chloride was in solution, NaBH₄ (5.4 eq) was introduced. Vigorous effervescence was noted, along with a darkening of the solution to grey/black. After circa 5 min, effervescence had subsided and the dark colour in the reaction began to dissipate with the reaction returning to yellow within 10 min. The reaction mixture was partitioned between EtOAc and 1N HCl (aq). The organics were washed with sat. aq. NaHCO₃, water and brine before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The product was taken on without further purification (97 %). (ES⁺) *m/z* 518 (M+H)⁺; 540 (M+Na)⁺.

30 Step 4: 3-[14-cyclohexyl-11-(methoxycarbonyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl]propanoic acid

TFA (> 150 eq) and a few drops of water were added to a stirred solution of methyl 7-(3-*tert*-butoxy-3-oxopropyl)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.03 M) in DCM at RT. The reaction was heated at 60 °C (oil bath temp) for 1 h. Further TFA was introduced (circa 60 eq) and heating continued for 2 h. Volatiles were removed *in vacuo*. The residue was taken up in EtOAc and washed with 1N HCl (aq), brine before being dried (Na₂SO₄) filtered and concentrated *in vacuo*. Residual *tert*-BuOH was

removed by sonication in Et₂O/PE to afford the product (45 %). (ES⁺) *m/z* 462 (M+H)⁺; 484 (M+Na)⁺.

Step 5: methyl 7-{3-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]-3-oxopropyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

- 5 HATU (1.1 eq) was added to a stirred mixture of *tert*-butyl piperazine-1-carboxylate (1.1 eq), DIPEA (2.5 eq) and 3-[14-cyclohexyl-11-(methoxycarbonyl)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocin-7-yl]propanoic acid (0.03 M) in DMF under N₂ at RT. The reaction was warmed at 50 °C for 10 min. The reaction was allowed to cool to RT before being partitioned between EtOAc and 1N HCl (aq). The organics were washed with 1N HCl (aq), sat. aq.
- 10 NaHCO₃, water and brine before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The material was taken on without further purification (88 %). (ES⁺) *m/z* 630 (M+H)⁺; 652 (M+Na)⁺.

Step 6: methyl 14-cyclohexyl-7-(3-oxo-3-piperazin-1-ylpropyl)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

- 15 Methyl 7-{3-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]-3-oxopropyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (0.04 M) in DCM was treated with TFA (170 eq) and stirred at RT overnight. The volatiles were then removed *in vacuo* and the residue partitioned between sat. aq. NaHCO₃ and EtOAc. The combined organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product as an off-white foam (100 %) that was used without further purification. (ES⁺) *m/z* 530 (M+H)⁺.

- 20 Step 7: methyl 14-cyclohexyl-7-(3-piperazin-1-ylpropyl)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

- A solution of methyl 14-cyclohexyl-7-(3-oxo-3-piperazin-1-ylpropyl)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (0.08 M) in THF was treated dropwise with BH₃·DMS complex (2M in THF; 10 eq). The resulting solution was stirred at RT for 2.5 h. The
- 25 reaction was quenched by the careful addition of HCl/MeOH (1.25 M) and the resulting solution refluxed for 2 h. The volatiles were then removed *in vacuo* and the residue partitioned between sat. aq. NaHCO₃ and EtOAc. The combined organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product as a yellow foam (100 %) that was used without further purification. (ES⁺) *m/z* 516 (M+H)⁺.

- 30 Step 8: methyl 7-[3-(4-{[(*tert*-butoxycarbonyl)(methyl)amino]sulfonyl}piperazin-1-yl)propyl]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

- To a solution of methyl 14-cyclohexyl-7-(3-piperazin-1-ylpropyl)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (0.11 M) in dry THF was added (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4H)-yl]sulfonyl}azanide (1 eq) (prepared following literature
- 35 procedure: Winum, J.-Y. *et al Org. Lett.* **2001**, 3, 2241-2243) and the mixture stirred at 40 °C for 2 h. The reaction was allowed to cool to RT before diluting with EtOAc. The combined organics were washed with 1N HCl (aq), sat. aq. NaHCO₃ then brine, dried (Na₂SO₄), filtered and

- 90 -

concentrated *in vacuo* to afford the product as a yellow foam (58 %) that was used without further purification. (ES⁺) *m/z* 695 (M+H)⁺.

Step 9: 7-[3-(4-{[(*tert*-butoxycarbonyl)(methyl)amino]sulfonyl}piperazin-1-yl)propyl]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

5 2N NaOH (aq) (30 eq) was added to a solution of methyl 7-[3-(4-{[(*tert*-butoxycarbonyl)(methyl)amino]sulfonyl}piperazin-1-yl)propyl]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.06 M) in MeOH and the reaction stirred at 70 °C for 3 h. The reaction was allowed to cool to RT before reducing the volume of MeOH *in vacuo*. The residue was partitioned between 1N HCl (aq) and EtOAc, ensuring the aqueous
10 phase was acidic. The aqueous was extracted a second time with EtOAc and the combined organics washed with brine before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The material was taken on without further purification. (ES⁺) *m/z* 681 (M+H)⁺.

Step 10: 7-{3-[4-(aminosulfonyl)piperazin-1-yl]propyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

15 7-[3-(4-{[(*tert*-butoxycarbonyl)(methyl)amino]sulfonyl}piperazin-1-yl)propyl]-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid (0.07 M) in DCM was treated with TFA (200 eq) and stirred at RT for 1 h. The volatiles were then removed *in vacuo* and the residue partitioned between 1N HCl (aq) and EtOAc. The combined organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was treated
20 with 2M HCl in Et₂O to afford the product as a beige solid (65 %) that was used without further purification. (ES⁺) *m/z* 581 (M+H)⁺.

Step 11: 30-cyclohexyl-18-oxa-2-thia-1,3,10,24-tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide

25 To a solution of 7-{3-[4-(aminosulfonyl)piperazin-1-yl]propyl}-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid (0.04 M) in DCM were added EDC (1.5 eq) and DMAP (3 eq). The mixture was stirred at 50 °C for 2 h before cooling to RT and evaporating all volatiles *in vacuo*. The residue was purified by RP-HPLC (Waters Sunfire column; MeCN/H₂O/0.1 % TFA gradient). Fractions containing the pure compound were
30 combined and lyophilized to afford the product as a white powder (19 %). ¹H NMR (400 MHz, DMSO-*d*₆ + TFA, 335 K) δ 1.16-1.23 (m, 2H), 1.31-1.39 (m, 2H), 1.47-1.50 (m, 1H), 1.69-1.73 (m, 2H), 1.83-2.19 (m, 7H), 2.64-2.66 (m, 1H), 3.29-3.36 (m, 4H), 3.49-3.74 (m, 7H), 3.89-3.93 (m, 2H), 4.28-4.39 (m, 1H), 4.40-4.44 (m, 1H), 7.28-7.32 (m, 2H), 7.35-7.37 (m, 1H), 7.45-7.47 (m, 1H), 7.52-7.56 (m, 1H), 7.90-7.92 (m, 2H); (ES⁺) *m/z* 563 (M+H)⁺.

35 **Example 35: (-)-14-cyclohexyl-3-methoxy-18,22-dimethyl-7,8-dihydro-6H-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A35)**

- 91 -

Step 1: 2-[4-methoxy-2-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Boron pinacolate (3.5 eq), Et₃N (4 eq), Pd(OAc)₂ (0.05 eq) and 2-(dicyclohexylphosphino)biphenyl (0.19 eq) were added to a solution of 1-bromo-4-methoxy-2-(methoxymethoxy)benzene (prepared as described in *JACS*, **2007**, 129, 6716-6717) in toluene (0.2 M). The reaction was heated to 80 °C for 1.5 h. The mixture was cooled, diluted with EtOAc, washed with 1 N HCl (aq), brine, dried (Na₂SO₄), filtered and the solvent was removed *in vacuo* to give the product, which was taken on without further purification (quant.). (ES⁺) *m/z* 295 (M+H)⁺.

Step 2: methyl 3-cyclohexyl-2-[4-methoxy-2-(methoxymethoxy)phenyl]-1H-indole-6-carboxylate

A mixture of methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (prepared as described in International patent application WO2004087714, from commercially available methyl indole-6-carboxylate), 2-[4-methoxy-2-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2 eq) and 2 M Na₂CO₃ (aq) (6 eq) in dioxane (0.15 M) was prepared. Then the mixture was degassed with nitrogen and bis(triphenylphosphine)palladium (II) chloride (0.2 eq) was added. The resulting mixture was immersed in a pre-heated oil bath at 110 °C for 2 h. The mixture was cooled, diluted with EtOAc, washed with 1 N HCl (aq), brine, dried (Na₂SO₄), filtered and the solvent removed *in vacuo*. The crude was purified by automated FC (PE/EtOAc 9:1) to afford the product (93 %). (ES⁺) *m/z* 424 (M+H)⁺.

Step 3: methyl 3-cyclohexyl-2-(2-hydroxy-4-methoxyphenyl)-1H-indole-6-carboxylate

3 M HCl (aq) (4 eq) was added to a stirred mixture of methyl 3-cyclohexyl-2-[4-methoxy-2-(methoxymethoxy)phenyl]-1H-indole-6-carboxylate in MeOH (0.05 M) and the mixture was stirred at 80 °C for 2h. The mixture was cooled, solvents were concentrated *in vacuo* and the residue diluted with EtOAc, washed with sat. aq. NaHCO₃, brine, dried (Na₂SO₄), filtered and the solvent was removed *in vacuo* to afford the title compound (95 %). (ES⁺) *m/z* 380 (M+H)⁺.

Step 4: methyl 14-cyclohexyl-7-(hydroxymethyl)-3-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

The title compound was prepared starting from methyl 3-cyclohexyl-2-(2-hydroxy-4-methoxyphenyl)-1H-indole-6-carboxylate using the same methodology described for example 13 (steps 1-2) (41 %). (ES⁺) *m/z* 450 (M+H)⁺.

Step 5: (+)- and (-)- methyl 14-cyclohexyl-7-(hydroxymethyl)-3-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

The enantiomers of methyl 14-cyclohexyl-7-(hydroxymethyl)-3-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate were separated *via* chiral SFC (Chiralpak IA column, modifier 25% (MeOH; 0.2% Et₂NH), pressure 100 bar, temperature 35 °C) to afford the first eluting ([α]_D²⁰ - 24 (c = 1, MeOH)) and second eluting ([α]_D²⁰ + 26 (c = 1, MeOH)) isomers. (ES⁺) *m/z* 450 (M+H)⁺.

Step 6: (-)-14-cyclohexyl-3-methoxy-18,22-dimethyl-7,8-dihydro-6H-7,11-(ethanoimino)propanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

The title compound was prepared starting from (+)-methyl 14-cyclohexyl-7-(hydroxymethyl)-3-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (second eluting isomer from SFC) using the same methodology described for example 13 (steps 3-9 and 11-14). Purification was by automated RP-HPLC, eluting with a MeCN/H₂O (buffered with 0.1% TFA) gradient. Fractions containing the pure compound were combined and lyophilized to afford the product as a white powder (26 %). ¹H NMR (600 MHz, Py-*d*₅, 320 K) δ 1.12-1.26 (m, 3H), 1.35-1.41 (m, 3H), 1.69-1.70 (m, 2H), 1.75-1.77 (m, 1H), 1.86-1.88 (m, 1H), 2.05-2.27 (m, 10H), 2.56-2.62 (m, 2H), 2.99-3.03 (m, 1H), 3.34 (s, 3H), 3.56-3.68 (m, 4H), 3.90 (s, 3H), 4.13-4.15 (m, 1H), 4.19-4.21 (m, 1H), 6.93-6.97 (m, 2H), 7.40 (d, *J* 8.4, 1H), 7.92-7.93 (m, 1H), 8.09 (d, *J* 8.4, 1H), 8.21 (s, 1H). (ES⁺) *m/z* 595 (M+H)⁺; [α]_D²⁰ -47 (c = 0.1, MeOH).

Example 36: (+)-14-cyclohexyl-3-methoxy-18,21-dimethyl-7,8-dihydro-6H-7,11-(propanoimino)ethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A36)

Step 1: 3-[14-cyclohexyl-3-methoxy-11-(methoxycarbonyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl]propanoic acid

The title compound was prepared starting from methyl 14-cyclohexyl-7-(hydroxymethyl)-3-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (prepared as described in example 35, steps 1-4) using the same methodology described for example 34 (steps 1-4). (ES⁺) *m/z* 492 (M+H)⁺.

Step 2: methyl 7-{3-[2-[(tert-butoxycarbonyl)(methyl)amino]ethyl}{(methyl)amino]-3-oxopropyl}-14-cyclohexyl-3-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

The title compound was prepared starting from 3-[14-cyclohexyl-3-methoxy-11-(methoxycarbonyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl]propanoic acid applying the same methodology described for example 34 (step 5), using *tert*-butyl methyl[2-(methylamino)ethyl]carbamate (prepared as described in European patent application 1998/296811 from commercially available *N,N'*-dimethylethylenediamine) instead of *tert*-butyl piperazine-1-carboxylate. The product was taken on without further purification. (ES⁺) *m/z* 662 (M+H)⁺.

Step 3: (+)-14-cyclohexyl-3-methoxy-18,21-dimethyl-7,8-dihydro-6H-7,11-(propanoimino)ethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

The title compound was prepared starting from methyl 7-{3-[2-[(tert-butoxycarbonyl)(methyl)amino]ethyl}{(methyl)amino]-3-oxopropyl}-14-cyclohexyl-3-methoxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate, using the same methodology

described for example 34 (steps 6-11). The product was purified by RP-HPLC (Waters Sunfire column C18 OBD 10 μ M; 19x250 mm MeCN/H₂O/0.1 % TFA gradient). Fractions containing the pure product were combined and lyophilized to afford the racemic mixture (8 %); The racemic mixture was separated *via* chiral SFC (Chiralpak AS-H column, modifier 40% (*i*PrOH; 0.4% Et₂NH), pressure 100 bar, temperature 35 °C) to afford the first eluting ($[\alpha]_{D^{20}} +18.0$ (c = 0.1, MeOH)) and second eluting ($[\alpha]_{D^{20}} -18.0$ (c = 0.1, MeOH)) isomers. ¹H NMR (600 MHzcryo, DMSO-*d*₆ + TFA, 300 K) δ 0.92-1.16 (m, 1H), 1.25-1.49 (m, 4H), 1.65-1.77 (m, 3H), 1.78-1.98 (m, 7H), 2.61-2.67 (m, 1H), 2.87 (s, 3H), 3.09 (s, 3H), 3.16-3.28 (m, 2H), 3.31-3.37 (m, 1H), 3.54-3.62 (m, 2H), 3.64-3.69 (m, 1H), 3.78-95 (m, 5H), 4.28-4.42 (m, 2H), 6.87-6.91 (m, 2H), 7.23-7.24 (m, 1H), 7.41-7.49 (m, 1H), 7.61 (d, *J* 8.2, 1H), 8.08 (s, 1H). (ES⁺) *m/z* 595 (M+H)⁺.

Example 37: (-)-14-cyclohexyl-3-methoxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A37)

Step 1: (-)-14-cyclohexyl-3-methoxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide

The title compound was prepared as for example 36, and is the second eluting isomer from chiral SFC (Chiralpak AS-H column, modifier 40% (*i*PrOH; 0.4% Et₂NH), pressure 100 bar, temperature 35 °C). ($[\alpha]_{D^{20}} -18.0$ (c = 0.1, MeOH)). (ES⁺) *m/z* 595 (M+H)⁺.

Example 38: 14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-3-methoxy-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide (A38)

Step 1: methyl 14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-7-(hydroxymethyl)-3-methoxy-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

The title compound was prepared starting from (-)-methyl 2-bromo-3-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-1*H*-indole-6-carboxylate (isomer A - prepared as described in International patent application WO2007054741) using the same methodology described for example 35 (steps 1-4).

Step 2: 14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-3-methoxy-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide

The title compound was prepared starting from methyl 14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-7-(hydroxymethyl)-3-methoxy-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate using the same methodology described for example 13 (steps 3-9 and 11-14). The residue was purified by RP-HPLC (Sepax GP C18 30x100 mm; gradient 40-75 % CH₃CN in H₂O; solvents buffered with 0.1 % TFA). Fractions containing the pure compound were combined and lyophilized in the presence of HCl to afford the HCl salt of

- 94 -

the title compound as a mixture of diastereoisomers (5 % overall). ¹H NMR (300 MHz, CD₃CN, 300 K) δ 1.11-2.40 (m, 13H), 2.62-3.38 (m, 11H), 3.61-4.09 (m, 7H), 4.36-4.68 (m, 2H), 4.88-5.32 (m, 1H), 6.64-7.18 (m, 2H), 7.34-7.62 (m, 2H), 7.69-8.21 (m, 2H); (ES⁺) *m/z* 613 (M+H)⁺.

5 **Example 39: (7*R* or 7*S*)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(methanooxyethanoiminoethanoiminioiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocine-15-one 17,17-dioxide (A39)**

Step 1: (+)- and (-)- methyl 14-cyclohexyl-7-(hydroxymethyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

10 The enantiomers of methyl 14-cyclohexyl-7-(hydroxymethyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (prepared as described in example 13, steps 1-2) were separated *via* chiral SFC (Chiralpak AD column, modifier 40% MeOH, pressure 100 bar, temperature 35 °C) to afford the first eluting ([α]_D²⁰ - 43.5 (c = 1, MeOH)) and second eluting ([α]_D²⁰ + 43.6 (c = 1, MeOH)) isomers. (ES⁺) *m/z* 420 (M+H)⁺.

15 Step 2 : *N*-benzyl-2-chloro-*N*-methylethanaminium chloride

2-[benzyl(methyl)amino]ethanol was added dropwise to an excess of SOCl₂ (50 eq) and the mixture was heated at 35 °C for 16 h). Excess SOCl₂ was removed *in vacuo* and the residual oil triturated with Et₂O to give the title compound as a white solid in quantitative yield. (ES⁺) *m/z* 184 (M+H)⁺.

20 Step 3: (7*R* or 7*S*)-7-({2-[benzyl(methyl)amino]ethoxy}methyl)-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid

A solution of (+)-methyl 14-cyclohexyl-7-(hydroxymethyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (second eluting isomer) in toluene (0.04 M) was treated with 30 % w/v NaOH (10 eq) and tetrabutylammonium bromide (0.25 eq) followed by *N*-benzyl-25 2-chloro-*N*-methylethanaminium chloride (2.5 eq). The resulting solution was stirred at 65 °C for 18 h. Toluene was removed *in vacuo*, the residue was taken up in EtOAc and washed with 1N HCl (aq) and brine before drying (Na₂SO₄), filtering and concentrating *in vacuo* to afford the product as an oil that was used without further purification. (ES⁺) *m/z* 553 (M+H)⁺.

30 Step 4: (7*R* or 7*S*)-7-({2-[benzyl(methyl)amino]ethoxy}methyl)-14-cyclohexyl-*N*-{[(2,2-dimethoxyethyl)(methyl)amino]sulfonyl}-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxamide

- 95 -

A solution of (7R or 7S)-7-({2-[benzyl(methyl)amino]ethoxy}methyl)-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid in dry DCM (0.06 M) was treated with DMAP (3 eq), EDC (1.5 eq) and N-(2,2-dimethoxyethyl)-N-methylsulfamide (prepared as described in example 1 step 1). The mixture was stirred at 40 °C for 2 h, and then
5 diluted with EtOAc, washed with 1N HCl (aq), sat. aq. NaHCO₃ and brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the title compound. The crude material was used in the next step without further purification. (ES⁺) *m/z* 733 (M+H)⁺.

Step 5: (7R or 7S)-14-cyclohexyl-N-{{(2,2-dimethoxyethyl)(methyl)amino}sulfonyl}-7-{{2-(methylamino)ethoxy}methyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide

10 A solution of (7R or 7S)-7-({2-[benzyl(methyl)amino]ethoxy}methyl)-14-cyclohexyl-N-{{(2,2-dimethoxyethyl)(methyl)amino}sulfonyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide in MeOH (0.06 M) was treated with AcOH (1 eq) and Pd/C (2 eq). The resulting mixture was stirred for 12 h under an H₂ atmosphere. The mixture was filtered and then concentrated *in vacuo* to afford the title compound. The crude material was used in the next step
15 without further purification. (ES⁺) *m/z* 643 (M+H)⁺.

Step 6: (7R or 7S)-14-cyclohexyl-7-{{2-(methylamino)ethoxy}methyl}-N-{{methyl(2-oxoethyl)amino}sulfonyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxamide

A solution of (7R or 7S)-14-cyclohexyl-N-{{(2,2-dimethoxyethyl)(methyl)amino}sulfonyl}-7-{{2-(methylamino)ethoxy}methyl}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-
20 carboxamide (0.05 M) in DCM was treated with an excess of TFA and H₂O (> 50 eq of each). The mixture was stirred at 40 °C for 40 min. The solution was allowed to cool to RT and used in the next step. (ES⁺) *m/z* 597 (M+H)⁺.

Step 7: (7R or 7S)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6H-7,11-(methanooxyethanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one
25 17,17-dioxide

DCM solution coming from previous step was diluted with anhydrous MeOH (to give a final substrate concentration of 0.01M) and the pH adjusted with Et₃N to pH 5-6. NaBH₃CN (10 eq) was introduced and the mixture was stirred at RT for 1 h, then quenched with few drops of sat. aq. NaHCO₃ and concentrated *in vacuo*. Purification was by automated RP-HPLC, eluting with a
30 MeCN/H₂O (buffered with 0.1 % TFA) gradient. Fractions containing the product were combined and freeze dried to afford the product as a white powder (7 %, over preceding 5 steps).
¹H NMR (600 MHz, DMSO-*d*₆ + TFA, 300 K) δ 1.12-1.20 (m, 1H), 1.26-1.39 (m, 2H), 1.44-1.55 (m, 1H), 1.63-1.74 (m, 2H), 1.79-1.86 (m, 1H), 1.88-2.00 (m, 3H), 2.30-2.40 (m, 1H), 2.65-2.75 (m, 1H), 2.90 (s, 3H), 3.06 (s, 3H), 3.20-3.30 (m, 1H), 3.37-3.43 (m, 1H), 3.44-3.53 (m,
35 3H), 3.54-3.65 (m, 2H), 3.66-3.95 (m, 5H), 4.40-4.48 (m, 1H), 4.55-4.65 (m, 1H), 7.20-7.27 (m, 1H), 7.29-7.34 (m, 1H), 7.36-7.43 (m, 2H), 7.52-7.58 (m, 1H), , 7.88 (d, *J* 8.4, 1H), 8.08 (s, 1H); (ES⁺) *m/z* 581 (M+H)⁺; [α]_D²⁰ + 11 (c = 0.1, MeOH).

Example 40: (7R)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-18,21-dimethyl-7,8-dihydro-6H-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide (A40)

Step 1: (2S)-5-azido-2-([tert-butyl(dimethyl)silyl]oxy)methylpentan-1-ol

5 The title compound was prepared from methyl 5-bromopentanoate, in analogous fashion to that described for methyl 4-bromobutanoate in example 33, steps 1-6. Purification by flash chromatography (9:1 to 7:3 PE:EtOAc) afforded the product as a colourless oil (38 %). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.28-1.33 (m, 2H), 1.48-1.53 (m, 1H), 1.53-1.61 (m, 2H), 3.28-3.31 (m, 2H), 3.32-3.36 (m, 2H), 3.50 (dd, *J* 10.0, 5.6, 1H), 3.57 (dd, *J* 10.0, 5.6, 1H), 4.34-4.36 (m, 1H); [α]_D²⁰ = - 6.5 (c = 2.2, CHCl₃).

Step 2: (2R)-5-azido-2-([tert-butyl(dimethyl)silyl]oxy)methylpentyl methanesulfonate

(2S)-5-Azido-2-([tert-butyl(dimethyl)silyl]oxy)methylpentan-1-ol was treated in analogous fashion to example 33, step 7, to afford the title compound. ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 0.05 (s, 6H), 0.87 (s, 9H), 1.28-1.43 (m, 2H), 1.56-1.63 (m, 2H), 1.82-1.88 (m, 1H), 3.16 (s, 3H), 3.31-3.35 (m, 2H), 3.52-3.62 (m, 2H), 4.16 (d, *J* 5.6, 2H).

Step 3: methyl (7R)-7-(3-azidopropyl)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

The title compound was prepared from methyl 3-[(1R, 2S) or (1S, 2R)-2-fluorocyclohexyl]-2-(2-hydroxyphenyl)-1H-indole-6-carboxylate (prepared as described in International patent application WO2007054741) and (2R)-5-azido-2-([tert-butyl(dimethyl)silyl]oxy)methylpentyl methanesulfonate, using the same methodology described for the 3-azidoethyl analog, example 33 steps 8-11, (25 % overall). (ES⁺) *m/z* 491 (M+H)⁺; [α]_D²⁰ + 47.9 (c = 1.05, CHCl₃).

Step 4: methyl (7R)-7-(3-aminopropyl)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

25 To a solution of methyl (7R)-7-(3-azidopropyl)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.23 M) in dry MeOH under N₂ was added acetic acid (1 eq), then Pd/C (0.15 weight eq). The atmosphere in the reaction vessel was charged with H₂ and the reaction stirred vigorously under a H₂ atmosphere (balloon) overnight. The reaction was flushed with N₂ and filtered through a plug of celite. The filtrate
30 was then concentrated *in vacuo* and the residue partitioned between sat. aq. NaHCO₃ and EtOAc. The combined organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the title compound (100 %) which was used without further purification; (ES⁺) *m/z* 465 (M+H)⁺.

Step 5: methyl (7R)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7-[3-(methylamino)propyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

35 A solution of methyl (7R)-7-(3-aminopropyl)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (0.17 M) in THF was treated dropwise with 2,2,2-trifluoroethyl formate (1.5 eq) and stirred overnight at RT. The volatiles

- 97 -

were removed *in vacuo* and the residue dissolved (0.09 M) in THF and treated dropwise with BH₃·DMS complex (2M in THF; 5 eq). The resulting solution was stirred at RT for 3 h. The reaction was quenched by the careful addition of HCl/MeOH (1.25 M) and the resulting solution refluxed for 2 h. The volatiles were then removed *in vacuo* and the residue partitioned between sat. aq. NaHCO₃ and EtOAc. The combined organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was used in the subsequent step without further purification (100 %). (ES⁺) *m/z* 479 (M+H)⁺.

Step 6: methyl (7R)-7-{3-[{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}(methyl)amino]propyl}-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

tert-Butyl methyl(2-oxoethyl)carbamate (2 eq) (prepared as described in *Tetrahedron*. **2002**, 58, 1719) was added to a solution of methyl (7R)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7-[3-(methylamino)propyl]-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (0.17 M) in THF at RT followed by HOAc (cat.). After 1 h all volatiles were removed *in vacuo* and the residue redissolved (0.17 M) in MeOH. NaCNBH₃ (3 eq) were added and the resulting solution stirred for 2 h at RT. The reaction was diluted with EtOAc and washed with sat. aq. NaHCO₃. The combined organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was used in the subsequent step without further purification (100 %). MS (ES⁺) *m/z* 636 (M+H)⁺.

Step 7: methyl (7R)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7-(3-{methyl[2-(methylamino)ethyl]amino}propyl)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

Methyl (7R)-7-{3-[{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}(methyl)amino]propyl}-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (0.10 M) in DCM was treated with TFA (25 eq) and stirred at RT overnight. The volatiles were then removed *in vacuo* and the residue partitioned between sat. aq. NaHCO₃ and EtOAc. The combined organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product as a white foam (100 %) that was used without further purification. (ES⁺) *m/z* 536 (M+H)⁺.

Step 8: (7R)-7-{3-[{2-[(aminosulfonyl)(methyl)amino]ethyl}(methyl)amino]propyl}-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid

The title compound was prepared from methyl (7R)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7-(3-{methyl[2-(methylamino)ethyl]amino}propyl)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate using the same methodology described in example 34 steps 8-10, (80 % overall). (ES⁺) *m/z* 601 (M+H)⁺.

Step 9: (7R)-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-21-methyl-7,8-dihydro-6H-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

To a solution of (7R)-7-{3-[{2-[(aminosulfonyl)(methyl)amino]ethyl}(methyl)amino]propyl}-14-[(1R,2S) or (1S,2R)-2-fluorocyclohexyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid (0.05 M) in DCM were added EDC (2 eq) and DMAP (3.5 eq). The mixture was stirred at 50 °C for 2 h before cooling to RT and diluting with EtOAc. The mixture was washed with 1N HCl (aq) then brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by RP-HPLC (Waters Sunfire column; MeCN/H₂O/0.1 % TFA gradient).
Fractions containing the pure compound were combined and lyophilized to afford the product as a white powder (20 %). ¹H NMR (600 MHz, DMSO-*d*₆ + TFA, 300 K) δ 0.98-1.14 (m, 2H), 1.42-1.64 (m, 5H), 1.74-1.83 (m, 1H), 1.88-2.09 (m, 3H), 2.20-2.27 (m, 1H), 2.42-2.50 (m, 1H), 2.79-2.84 (m, 1H), 2.87 (s, 3H), 3.10 (s, 3H), 3.16-3.26 (m, 2H), 3.30-3.39 (m, 1H), 3.59-3.69 (m, 3H), 3.84-3.98 (m, 2H), 4.38-4.49 (m, 2H), 5.10 (dm, *J*_{HF} 50.7, 1H), 7.32-7.33 (m, 2H), 7.47-7.48 (m, 2H), 7.54-7.56 (m, 1H), 7.95 (d, *J* 8.4, 1H), 8.04 (s, 1H); (ES⁺) *m/z* 583 (M+H)⁺. [α]_D²⁰ + 8.1 (c = 0.88, MeOH).

Compounds A1-A40 were assayed in the above described cell-based HCV replication assay (example ii))and results are reported as IC₅₀ activity ranges in Table A.

Table A: Inhibition of HCV subgenomic replication by compounds A1-A40.

Compound	IC ₅₀ (nM)	Compound	IC ₅₀ (nM)
A1	+++	A21	+++
A2	+++	A22	++
A3	+++	A23	++
A4	+++	A24	++
A5	+++	A25	+++
A6	++	A26	+++
A7	++	A27	+++
A8	+++	A28	+++
A9	++	A29	+++
A10	++	A30	++
A11	+++	A31	+++
A12	+++	A32	+++
A13	++	A33	+++
A14	+++	A34	++
A15	+	A35	+++
A16	++	A36	++
A17	++	A37	+++

A18	+++	A38	+++
A19	+++	A39	+++
A20	++	A40	+++

Activity ranges:

+++ : < 25 nM; ++ : 25 – 150 nM; + : 150 – 500 nM; * > 500 nM

5 The following tables show some of these and further non-limiting examples:

Table 1: 16 membered macrocycles

Example no.	Compound name	IC ₅₀ [*] (nM)	procedure	m/z (ES ⁺)
101	14-cyclohexyl-18,22-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(ethanoiminopropanoiminothioiminomethano)indolo [1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	C	565
102	(7 <i>R</i>)-21-[2-(benzyloxy)ethyl]-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	700
103	(7 <i>R</i>)-14-cyclohexyl-21-(2-hydroxyethyl)-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	610
104	(7 <i>R</i>)-14-cyclohexyl-21-isobutyl-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	622
105	(7 <i>R</i>)-14-cyclohexyl-21-(<i>N,N</i> -dimethylglycyl)-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	651
106	(7 <i>R</i>)-14-cyclohexyl-21-ethyl-18-(2-hydroxyethyl)-24-methyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	624
107	(7 <i>R</i>)-14-cyclohexyl-21,24-diethyl-18-methyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	608

* Inhibition of HCV subgenomic replication

Table 2: Various macrocycles

Example no.	Compound name	IC ₅₀ [*] (nM)	Proce- dure	m/z (ES ⁺)
201	20-benzyl-13-cyclohexyl-17,23-dimethyl-6,7-dihydro-5 <i>H</i> -6,10-(epiminoethanoiminoethanoiminothioiminomethano) indolo[2,1- <i>a</i>][2]benzazepin-14-one 16,16-dioxide	*	A	640
202	(7 <i>R</i>)-14-cyclohexyl-2-fluoro-18,21,24-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A	598
203	(7 <i>R</i>)-14-cyclohexyl-21-ethyl-3-fluoro-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A,B	612
204	(7 <i>R</i>)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	A,B	598
205	(7 <i>R</i>)-14-cyclohexyl-21-ethyl-2-fluoro-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A,B	612
206	(7 <i>R</i>)-14-cyclohexyl-21-ethyl-2-fluoro-18-methyl-24-(pyridin-3-ylmethyl)-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A,B	689
207	(7 <i>R</i>)-14-cyclohexyl-3-fluoro-21-isopropyl-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A,B	626
208	(7 <i>R</i>)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-24-[2-(methylamino)ethyl]-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano) indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	A,B	655

209	(7 <i>R</i>)-14-cyclohexyl-2-fluoro-21-isopropyl-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A,B	626
210	(7 <i>R</i>)-14-cyclohexyl-21-ethyl-3-methoxy-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A,B	624
211	(7 <i>R</i>)-14-cyclohexyl-21-ethyl-18,24-dimethyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A,B	701
212	(7 <i>R</i>)-14-cyclohexyl-18,21,24-trimethyl-4-propyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	A,B	622
213	(7 <i>R</i>)-14-cyclohexyl-21-isopropyl-18,24-dimethyl-4-propyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	A,B	650
214	(7 <i>R</i>)-14-cyclohexyl-21-ethyl-24-(2-hydroxyethyl)-3,18-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A,B	638
215	(7 <i>R</i>)-14-cyclohexyl-21-ethyl-3,18,24-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A,B	608
216	(7 <i>R</i>)-14-cyclohexyl-3,18,21,24-tetramethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	594
217	(7 <i>R</i>)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-21-ethyl-18-methyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	651

218	(7 <i>R</i>)-14-cyclohexyl-21-isopropyl-3,18,24-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	622
219	(7 <i>R</i>)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-21-ethyl-4,18-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	665
220	(7 <i>R</i>)-14-cyclohexyl-21-[2-(dimethylamino)ethyl]-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	637

* Inhibition of HCV subgenomic replication

Table 3: Various macrocycles

Example no.	Compound name	IC ₅₀ [*] (nM)	Proce- dure	m/z (ES ⁺)
301	(18 <i>R</i>)-29-cyclohexyl-10,17-dimethyl-20-oxa-9-thia-1,8,10,13,17-pentaazahexacyclo[16.9.1.1 ^{2,6} .1 ^{3,27} .1 ^{13,16} .0 ^{21,26}]hentriaconta-2(31),3,5,21,23,25,27(29)-heptaen-7-one 9,9-dioxide	+++	A	592
302	(3 <i>R</i>)-31-cyclohexyl-2,22-dimethyl-5-oxa-21-thia-2,13,20,22,25-pentaazahexacyclo[23.2.2.1 ^{3,13} .1 ^{12,15} .1 ^{14,18} .0 ^{6,11}]dotriaconta-6,8,10,12(31),14(30),15,17-heptaen-19-one 21,21-dioxide	+++	A	606
303	(5 <i>R</i>)-31-cyclohexyl-4,24-dimethyl-7-oxa-23-thia-1,4,15,22,24-pentaazahexacyclo[23.2.2.1 ^{5,15} .1 ^{14,17} .1 ^{16,20} .0 ^{8,13}]dotriaconta-8,10,12,14(31),16(30),17,19-heptaen-21-one 23,23-dioxide	+++	C	606
304	(20 <i>R</i>)-31-cyclohexyl-21-methyl-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.3.2.1 ^{5,9} .1 ^{8,11} .1 ^{10,20} .0 ^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide	+++	A	592
305	(5 <i>R</i>)-31-cyclohexyl-4,24-dimethyl-7-oxa-23-thia-1,4,15,22,24-pentaazahexacyclo[23.2.2.1 ^{5,15} .1 ^{14,17} .1 ^{16,20} .0 ^{8,13}]dotriaconta-8,10,12,14(31),16(30),17,19-heptaen-21-one 23,23-dioxide	+++	C	620

306	(20 <i>R</i>)-31-cyclohexyl-21-methyl-18,24-dioxa-2-thia-1,3,10,21-tetraazahexacyclo[23.2.2.1 ^{5,9} .1 ^{8,11} .1 ^{10,20} .0 ^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide	+	C	593
307	(20 <i>R</i>)-31-cyclohexyl-21-[2-(dimethylamino)ethyl]-18,24-dioxa-2-thia-1,3,10,21-tetraazahexacyclo[23.2.2.1 ^{5,9} .1 ^{8,11} .1 ^{10,20} .0 ^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide	+	C	650
308	(20 <i>R</i>)-30-cyclohexyl-21-(2-fluoroethyl)-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.2.2.1 ^{5,9} .1 ^{8,11} .1 ^{10,20} .0 ^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide	++	A	610
309	(20 <i>R</i>)-21-benzyl-31-cyclohexyl-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.3.2.1 ^{5,9} .1 ^{8,11} .1 ^{10,20} .0 ^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide	+	A	668

* Inhibition of HCV subgenomic replication

Table 4: Various macrocycles

Example no.	Compound name	IC ₅₀ [*] (nM)	Procedure	m/z (ES ⁺)
401	(7 <i>S</i>)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	A	566
402	(7 <i>R</i>)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-18-methyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanooxyethanoiminiothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	C	624
403	(7 <i>R</i>)-4-allyl-14-cyclohexyl-21-ethyl-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	A, B	634
404	(7 <i>R</i>)-14-cyclohexyl-21-ethyl-4-fluoro-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminiothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	612

405	(7 <i>R</i>)-14-cyclohexyl-4-fluoro-21-isopropyl-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	626
406	(7 <i>R</i>)-14-cyclohexyl-4-[(dimethylamino)methyl]-21-ethyl-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+	A, B	662
407	(7 <i>R</i>)-14-cyclohexyl-4-(cyclopropylmethyl)-18,21,24-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	634
408	2-[(7 <i>R</i>)-14-cyclohexyl-18,21-dimethyl-17,17-dioxido-15-oxo-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-24-yl]acetamide	++	A, B	623
409	(7 <i>R</i>)-14-cyclohexyl-18,21-dimethyl-24-[(1-methyl-1 <i>H</i> -pyrazol-4-yl)methyl]-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	660
410	(7 <i>R</i>)-14-cyclohexyl-18,24-dimethyl-4-(morpholin-4-ylmethyl)-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	A, B	665
411	(7 <i>R</i>)-4-(benzyloxy)-14-cyclohexyl-18,21,24-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	A, B	686
412	(7 <i>R</i>)-14-cyclohexyl-4-methoxy-18,21,24-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	610
413	(7 <i>R</i>)-14-[(1 <i>R</i> ,2 <i>S</i>) or (1 <i>S</i> ,2 <i>R</i>)-2-fluorocyclohexyl]-18,21,24-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	598

* Inhibition of HCV subgenomic replication

Table 5: Various macrocycles

Example no.	Compound name	IC ₅₀ [*] (nM)	Proce- dure	m/z (ES ⁺)
501	14-[(1 <i>R</i> ,2 <i>S</i>) or (1 <i>S</i> 2 <i>R</i>)-2-fluorocyclohexyl]-18,22-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(ethanoiminopropanoiminothioiminomethano)indolo [1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	C	583
502	30-[(1 <i>R</i> ,2 <i>S</i>)-2-fluorocyclohexyl]-23-methyl-18-oxa-2-thia-1,3,10,23-tetraazahexacyclo[22.2.2.1 ^{5,9} .1 ^{8,11} .1 ^{10,20} .0 ^{12,17}]hentria conta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide	++	A	595
503	30-[(1 <i>R</i> ,2 <i>S</i>)-2-fluorocyclohexyl]-22-methyl-18-oxa-2-thia-1,3,10,22-tetraazahexacyclo[22.2.2.1 ^{5,9} .1 ^{8,11} .1 ^{10,20} .0 ^{12,17}]hentria conta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide	++	C	595
504	30-cyclohexyl-23-methyl-6-oxa-22-thia-1,14,21,23-tetraazahexacyclo[22.2.2.1 ^{4,14} .1 ^{13,16} .1 ^{15,19} .0 ^{7,12}]hentri aconta-7,9,11,13(30),15(29),16,18-heptaen-20-one 22,22-dioxide	++	C	577
505	(7 <i>R</i>) or (7 <i>S</i>)-14-cyclohexyl-22-methyl-18-(2-pyrrolidin-1-ylethyl)-7,8-dihydro-6 <i>H</i> -7,11-(ethanoiminopropanoiminothioiminomethano)indolo [1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	C	648
506	(7 <i>R</i>) or (7 <i>S</i>)-14-cyclohexyl-22-isopropyl-18-methyl-7,8-dihydro-6 <i>H</i> -7,11-(ethanoiminopropanoiminothioiminomethano)indolo [1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	C	593
507	(7 <i>R</i>) or (7 <i>S</i>)-14-cyclohexyl-22-(2-hydroxyethyl)-18-methyl-7,8-dihydro-6 <i>H</i> -7,11-(ethanoiminopropanoiminothioiminomethano)indolo [1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	C, B	595
508	31-cyclohexyl-18-oxa-2-thia-1,3,10,24-tetraazahexacyclo[22.3.2.1 ^{5,9} .1 ^{8,11} .1 ^{10,20} .0 ^{12,17}]dotriac onta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide	++	C	577
509	14-cyclohexyl-21-isopropyl-18-methyl-7,8-dihydro-6 <i>H</i> -7,11-(propanoiminoethanoiminothioiminomethano)indolo [1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	C	593
510	(7 <i>R</i>)-14-cyclohexyl-4-methoxy-18,21-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(propanoiminoethanoiminothioiminomethano)indolo [1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	C	595
511	(7 <i>R</i>)-14-cyclohexyl-18,21-dimethyl-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6 <i>H</i> -7,11-(propanoiminoethanoiminothioiminomethano)indolo [1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A, B	678

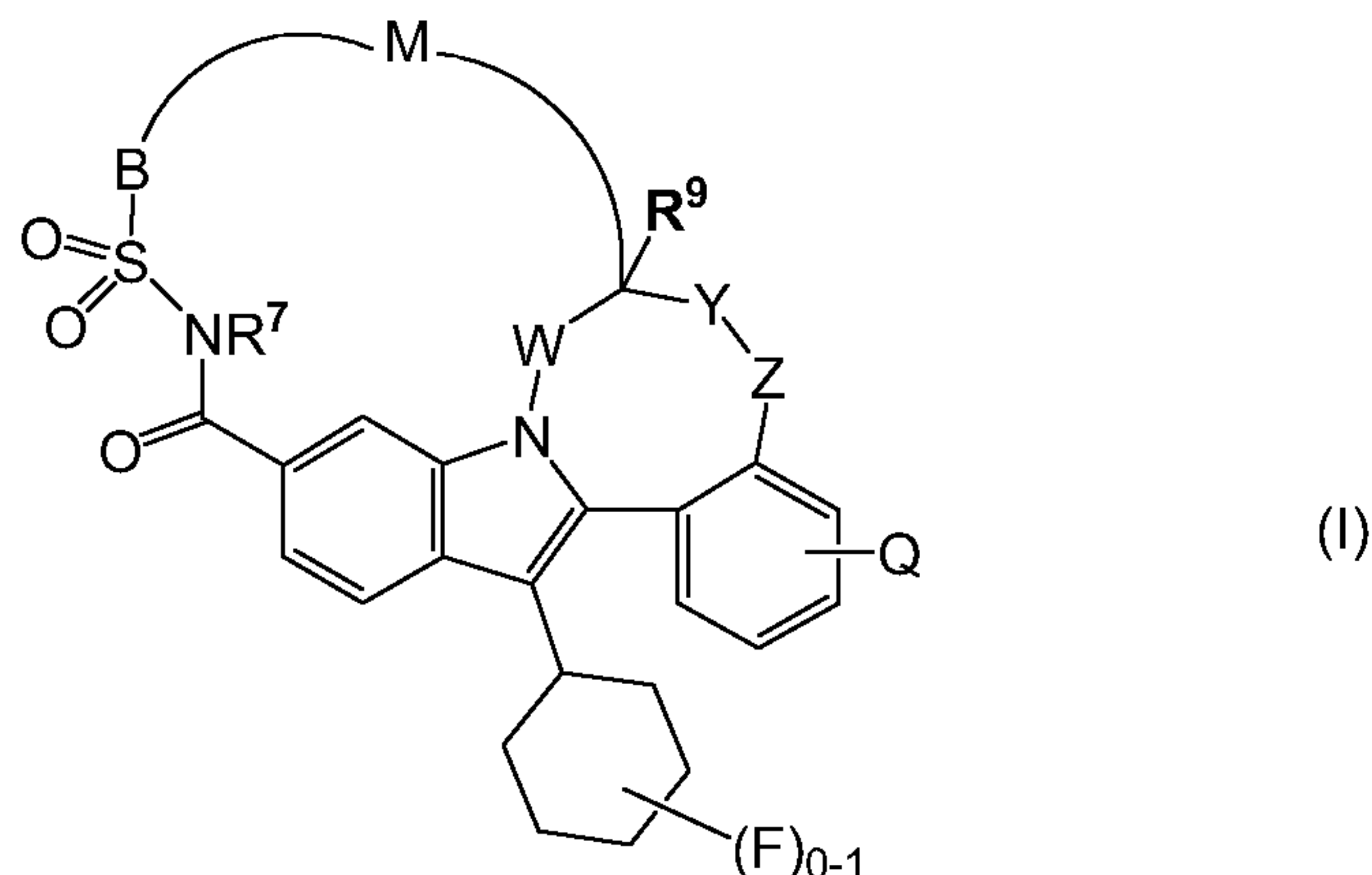
512	(7 <i>R</i>)-14-cyclohexyl-18,21,21,24-tetramethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminopentanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+	C	593
513	(7 <i>R</i>)-14-[(1 <i>R</i> ,2 <i>S</i>)-2-fluorocyclohexyl]-4,18,21-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	C	597
514	2-[(7 <i>R</i>)-14-cyclohexyl-4,18,24-trimethyl-17,17-dioxido-15-oxo-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-21-yl]- <i>N,N</i> -dimethylacetamide	+++	A,B	665
515	(7 <i>R</i>)-14-cyclohexyl-4,18,24-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A	580
516	(7 <i>R</i>)-14-cyclohexyl-4,18,21,24-tetramethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A,B	594
517	(7 <i>R</i>)-14-cyclohexyl-4,18,24-trimethyl-21-[(1-methyl-1 <i>H</i> -pyrazol-4-yl)methyl]-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	A,B	674
518	(7 <i>R</i>)-14-cyclohexyl-4-methoxy-18,24-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(epiminoethanooxyethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	++	C	597
519	(7 <i>R</i>)-14-cyclohexyl-4,18,21-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	C	579
520	(7 <i>R</i>)-14-cyclohexyl-4,18,22-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	C	579
521	(7 <i>R</i>)-14-cyclohexyl-22-[2-(dimethylamino)ethyl]-4,18-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	C	636
522	(20 <i>R</i>)-30-cyclohexyl-15-methoxy-23-methyl-18-oxa-2-thia-1,3,10,23-tetraazahexacyclo[22.2.2.1 ^{5,9} .1 ^{8,11} .1 ^{10,20} .0 ^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide	+++	C	607

523	(7 <i>R</i>)-14-cyclohexyl-20,20-difluoro-3-methoxy-18,22-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(ethanoiminopropanoiminothioiminomethano)indolo [1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide	+++	C	631
-----	---	-----	---	-----

*Inhibition of HCV subgenomic replication

Claims

1. A compound of the formula (I):



- 5 wherein Q is hydrogen, halogen, hydroxy, a group $(O)_{0-1}(CR^eR^f)_{0-3}R^8$ wherein R^e is hydrogen or C_{1-6} alkyl; R^f is hydrogen or C_{1-6} alkyl; and R^8 is hydrogen, C_{1-5} alkyl optionally substituted by C_{3-6} cycloalkyl, or R^8 is aryl, C_{1-6} alkoxy, heteroaryl or a 4-, 5-, 6- or 7-membered heteroaliphatic ring optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy, or a
- 10 group NR^aR^b , or $CONR^aR^b$, wherein R^a and R^b are each independently selected from hydrogen, C_{1-4} alkyl and $C(O)C_{1-4}$ alkyl; or R^a , R^b and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy; and wherein said C_{1-4} alkyl, C_{1-4} alkoxy and aryl groups are optionally substituted by halogen or hydroxy;
- 15 W is a bond, $C=O$, O, $S(O)_{0-2}$ or $-(CR^{10}R^{11})-(CR^{12}R^{13})_{0-1}-$;
Y is a bond, $C=O$, O, $-CR^{14}R^{15}-$ or NR^{14} ;
Z is a bond, $C=O$, O, $S(O)_{0-2}$, $-(CR^{10}R^{11})-(CR^{12}R^{13})_{0-1}-$ or NR^{10} ;
and none, one or two of W, Y and Z are a bond;
 R^9 is a bond, hydrogen, fluoro or hydroxyl;
- 20 R^{10} , R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, $C(O)C_{1-6}$ alkyl, a heteroaliphatic ring of 4 to 7 ring atoms containing 1, 2 or 3 heteroatoms selected from N, O or S or a group $S(O)$, $S(O)_2$, NH or NC_{1-4} alkyl, or R^{10} , R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from $(CH_2)_{0-3}NR^{16}R^{17}$, $C(O)(CH_2)_{0-3}NR^{16}R^{17}$, $NHC(O)(CH_2)_{0-3}NR^{16}R^{17}$, $O(CH_2)_{1-3}NR^{16}R^{17}$, $S(O)_{0-2}(CH_2)_{0-3}NR^{16}R^{17}$, $NMeC(O)(CH_2)_{0-3}NR^{16}R^{17}$ and $C(O)(CH_2)_{0-3}OR^{16}$; or one of R^{10} , R^{14} and R^9 is linked to R^{20} or R^{21} to form a 4-10 membered carbocyclic ring, where said ring is optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy; or, when Z is $-CR^{10}R^{11}-$ or NR^{10} , R^{10} is joined to R^9 to form a $-(CH_2)_{-1-4}$ group, optionally substituted by C_{1-4} alkyl; or R^9 is joined with an atom of the linker M to form an aliphatic ring of 4-7 ring atoms, said aliphatic ring optionally containing
- 30 one or two heteroatoms selected from O, N or S or a group $S(O)$, $S(O)_2$, NH or NC_{1-4} alkyl;

- R^{16} and R^{17} are independently selected from hydrogen, C_{1-6} alkyl and $(CH_2)_{0-4}NR^{18}R^{19}$; or R^{16} , R^{17} and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, which ring may optionally contain 1 or 2 more heteroatoms selected from O or S or a group S(O), S(O)₂, NH or NC₁₋₄alkyl, and which ring is optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy;
- R^{18} and R^{19} are independently selected from hydrogen and C_{1-6} alkyl; or R^{18} , R^{19} and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, which ring may optionally contain 1 or 2 more heteroatoms selected from O or S or a group S(O), S(O)₂, NH or NC₁₋₄alkyl, and which ring is optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy;
- R^7 is hydrogen or C_{1-6} alkyl;
- B is NR²⁰- and R^{20} is hydrogen, C_{1-6} alkyl optionally substituted by 1-3 fluoro, C_{2-6} alkenyl, $(CH_2)_{0-3}C_{3-6}$ cycloalkyl, $(CH_2)_{1-3}OH$, C_{1-6} alkoxy, C(O) C_{1-6} alkyl, $(CH_2)_{0-3}$ aryl, $(CH_2)_{0-3}$ Het, $(CH_2)_{0-3}$ heteroaryl, $(CH_2)_{1-3}NR^{16}R^{17}$, C(O) $(CH_2)_{1-3}NR^{16}R^{17}$, S(O)₀₋₂ $(CH_2)_{1-3}NR^{16}R^{17}$, C(O) $(CH_2)_{1-3}OR^{16}$, $(CH_2)_{1-3}O(CH_2)_{0-3}$ aryl, or R^{20} is linked to one of R^{10} , R^{14} and R^9 to form a ring of 4 to 10 atoms as hereinbefore described, or the R^{20} and a R^{21} group can be joined to form a $-(CH_2)_{1-3}$ group, optionally substituted by C_{1-2} alkyl;
- and M is C_{3-7} alkylene or C_{3-7} alkenylene, optionally substituted by one or two groups R^{21} which can be substituents on the same carbon atom where R^{21} is halo, C_{1-4} alkyl optionally substituted by 1-3 fluoro, $(CH_2)_{0-3}C_{3-8}$ cycloalkyl, $(CH_2)_{0-3}$ aryl, $(CH_2)_{0-3}$ heteroaryl, $(CH_2)_{0-3}$ Het, oxo or $(CH_2)_{0-3}NR^{16}R^{17}$, or R^{21} is linked to one of R^{10} , R^{14} and R^9 to form a ring of 4 to 10 atoms as hereinbefore described; and 1, 2 or 3 of the carbon atoms in the C_{3-7} alkylene or C_{3-7} alkenylene groups is optionally replaced by O, NR²², S, SO, SO₂, piperidinyl, piperazinyl, homopiperazinyl or pyrrolidinyl;
- and each group R^{22} is independently hydrogen, C_{1-6} alkyl optionally substituted with 1-3 fluoro, C_{2-6} alkenyl, $(CH_2)_{0-3}C_{3-6}$ cycloalkyl, $(CH_2)_{1-3}OH$, C_{1-6} alkoxy, C(O) C_{1-6} alkyl, $(CH_2)_{0-3}$ aryl, $(CH_2)_{0-3}$ Het, $(CH_2)_{0-3}$ heteroaryl, $(CH_2)_{1-3}NR^{16}R^{17}$, C(O) $(CH_2)_{1-3}NR^{16}R^{17}$, $(CH_2)_{1-3}C(O)NR^{16}R^{17}$, S(O)₀₋₂ $(CH_2)_{1-3}NR^{16}R^{17}$, C(O) $(CH_2)_{1-3}OR^{16}$, $(CH_2)_{1-3}O(CH_2)_{0-3}$ aryl, or where 1, 2 or 3 of the carbon atoms in the C_{3-7} alkylene or C_{3-7} alkenylene group are replaced by NR²², then the R^{20} and R^{22} groups can be joined to form a $-(CH_2)_{1-3}$ group, optionally substituted by C_{1-2} alkyl;
- and pharmaceutically acceptable salts thereof.

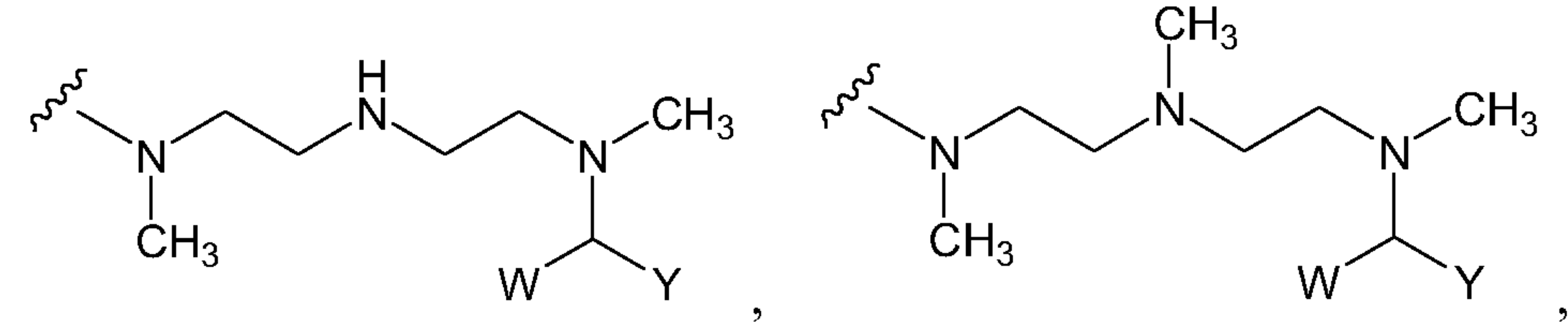
2. A compound as claimed in claim 1 wherein, Q is hydrogen, halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy or O₀₋₁ $(CH_2)_{0-3}R^{23}$ where R^{23} is a 5- or 6- membered heteroaliphatic ring, or heteroaryl.

3. A compound as claimed in claim 1 or claim 2 wherein W is $-CH_2-$, Z is O and Y is $-CH_2-$.

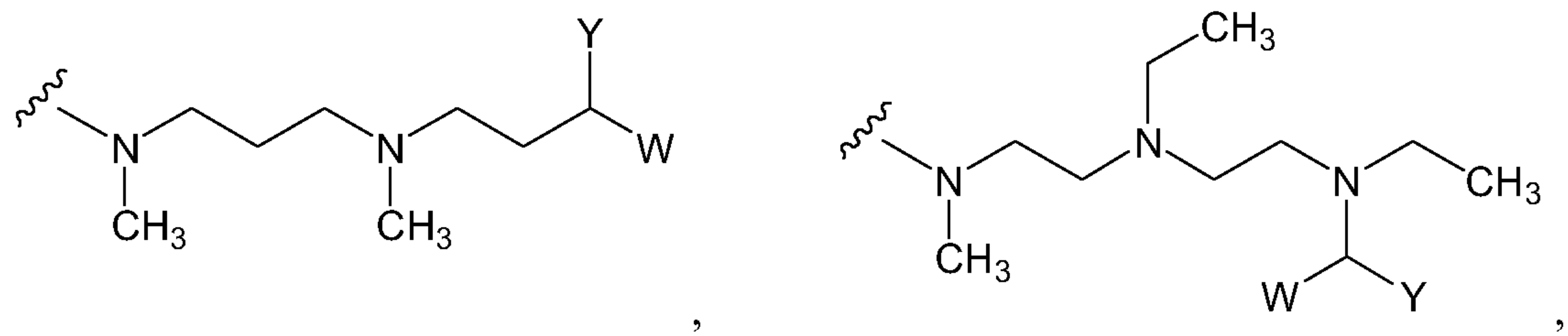
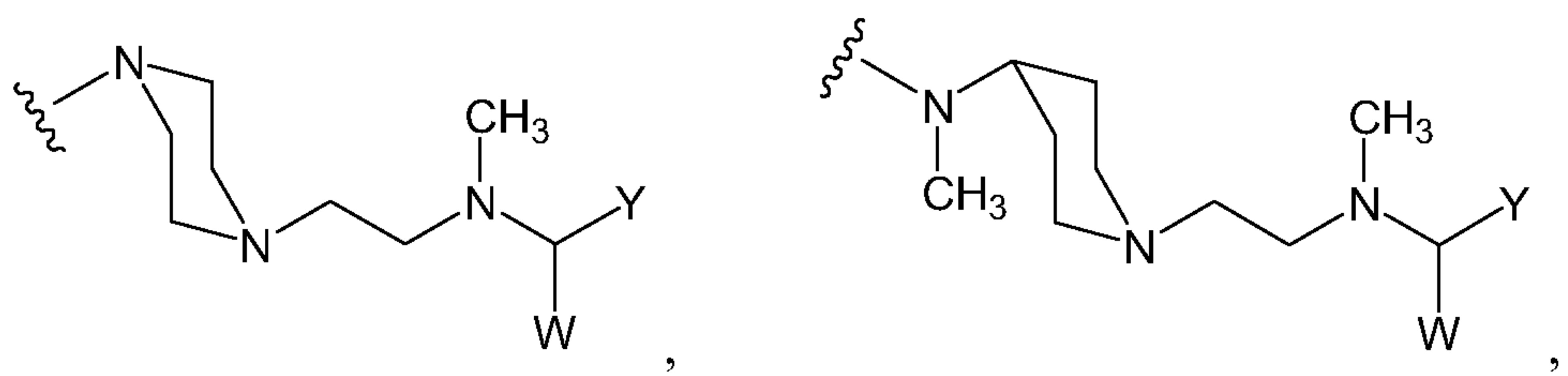
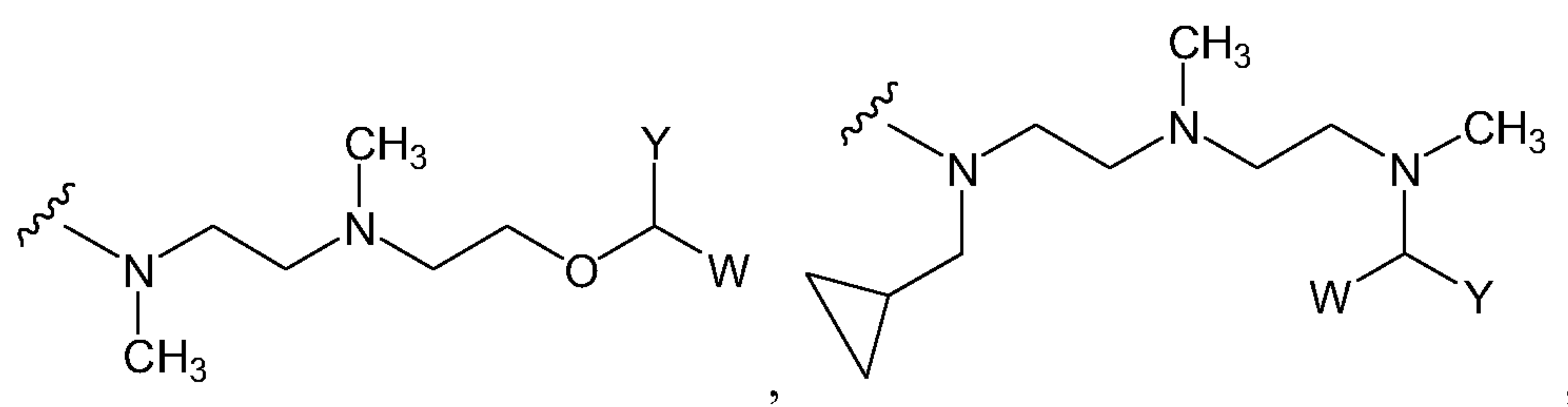
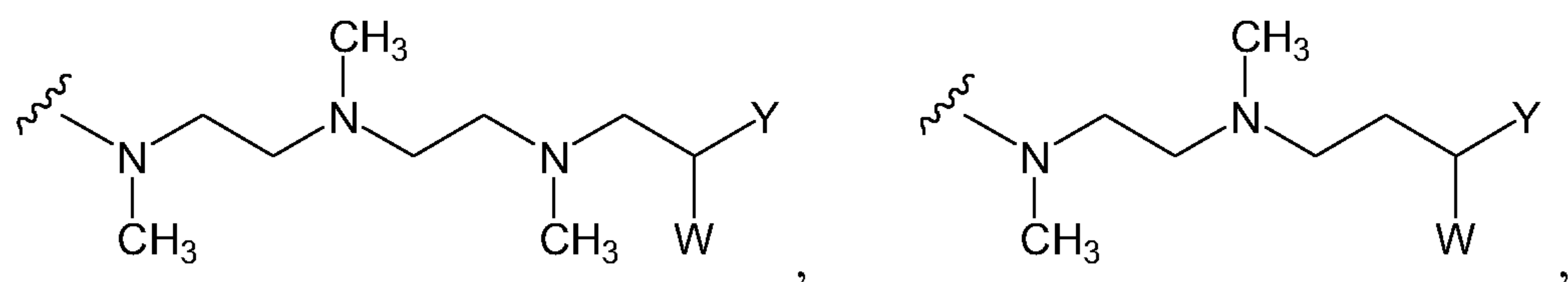
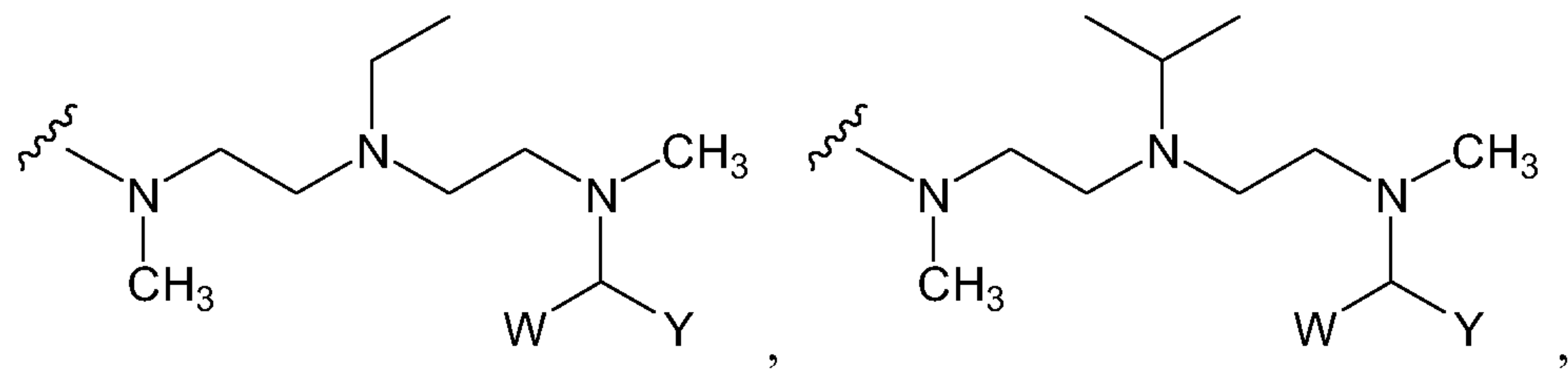
4. A compound as claimed in any one of claims 1 to 3 wherein R⁷ and R⁹ are both independently hydrogen.

5. A compound as claimed in Claim 1 where B-M is independently selected from:

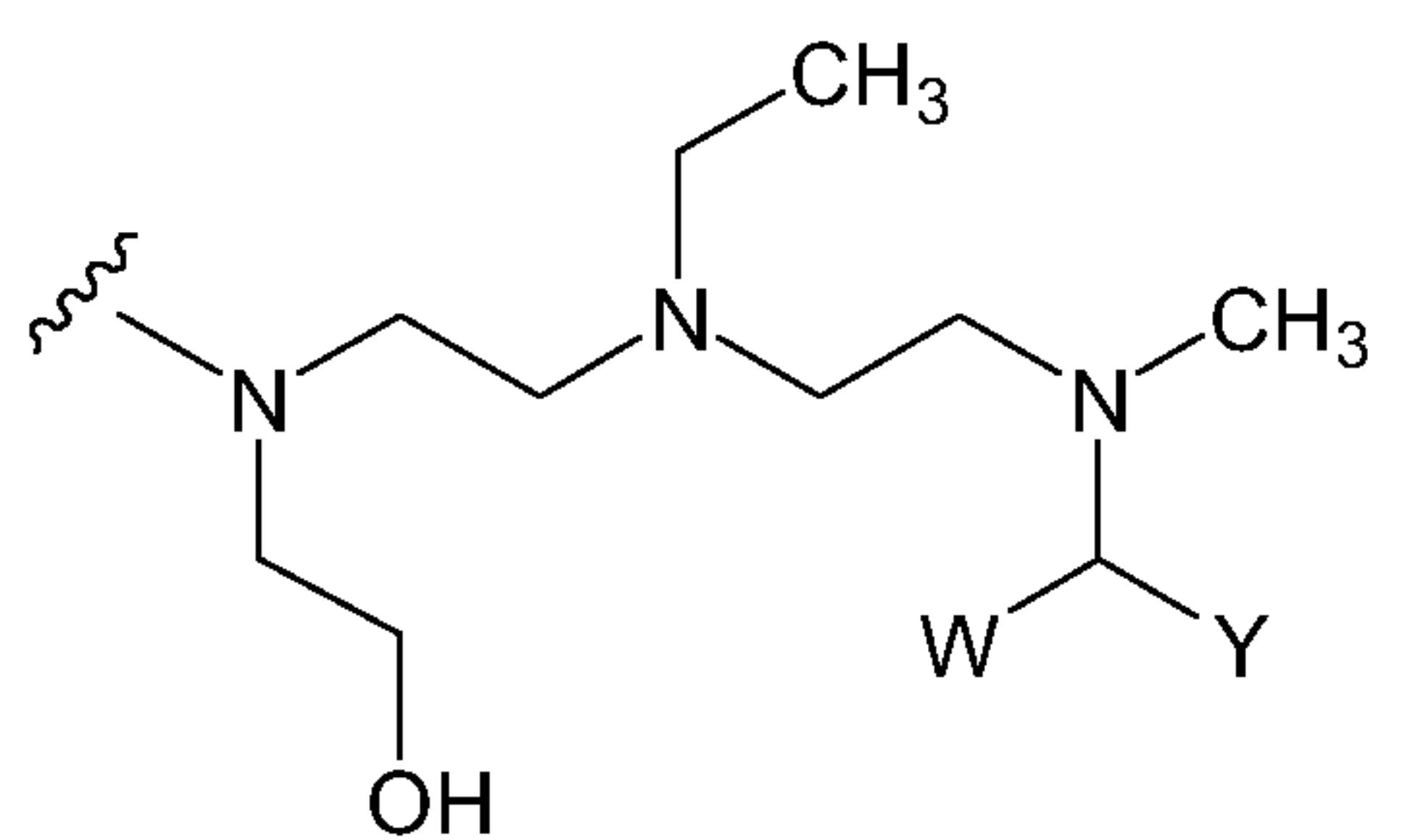
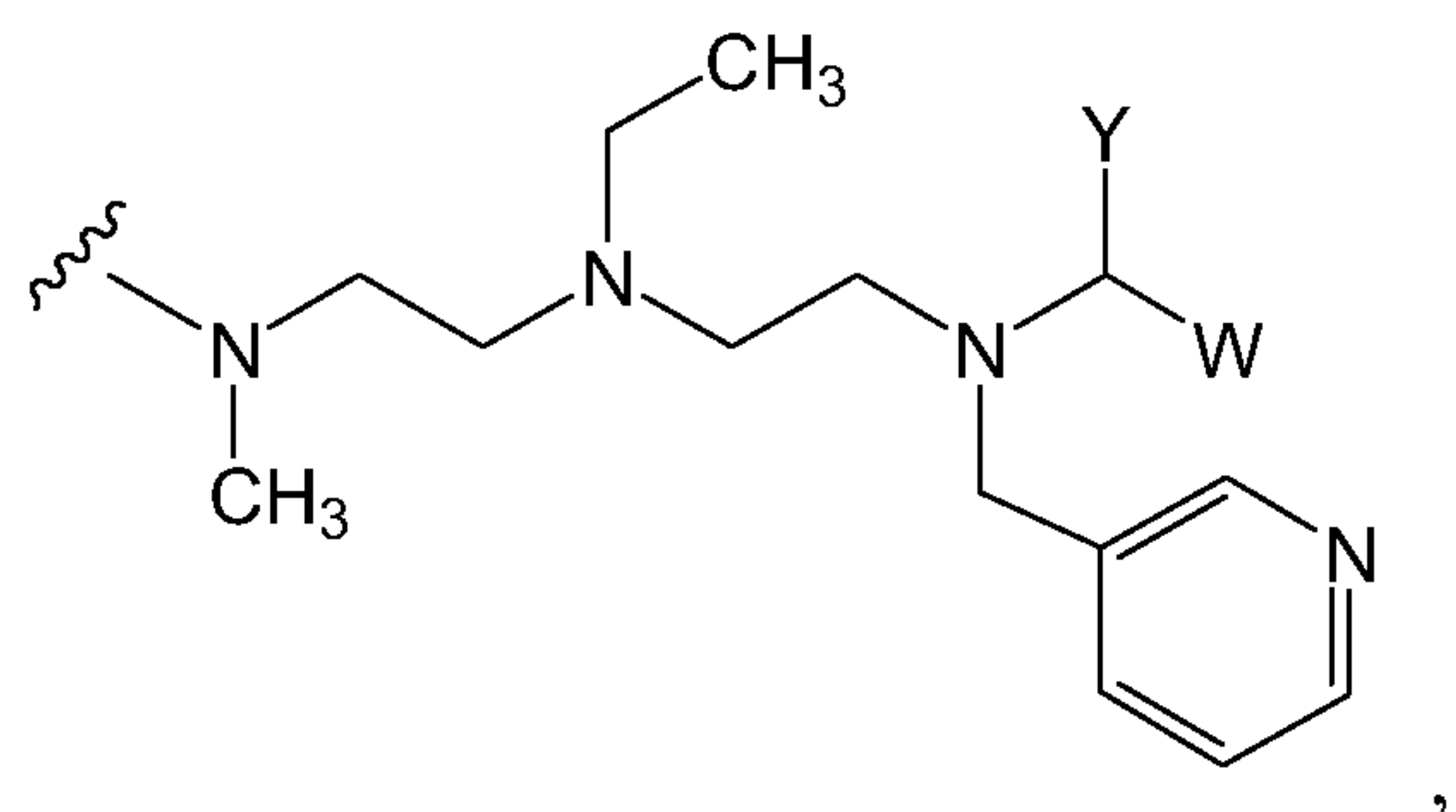
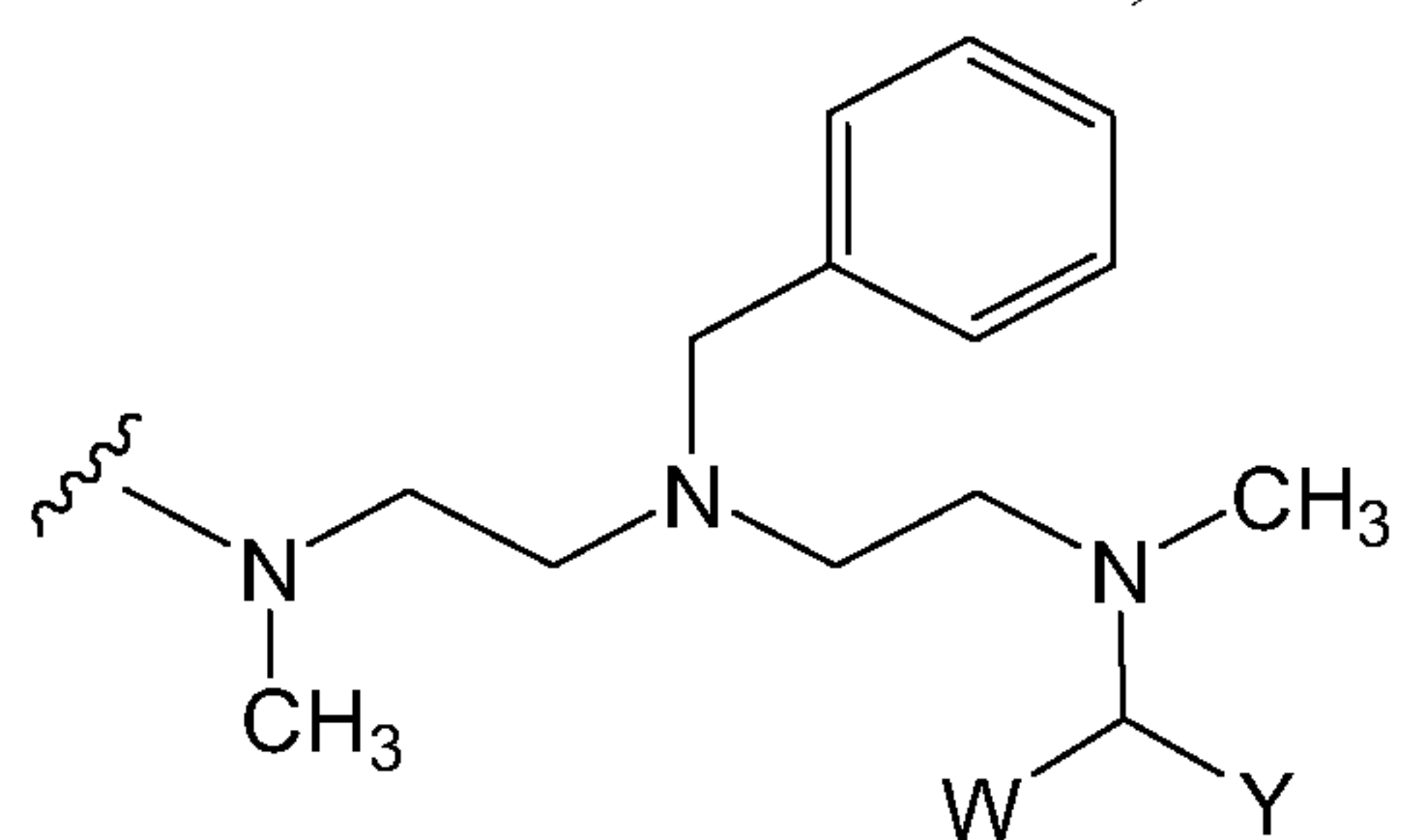
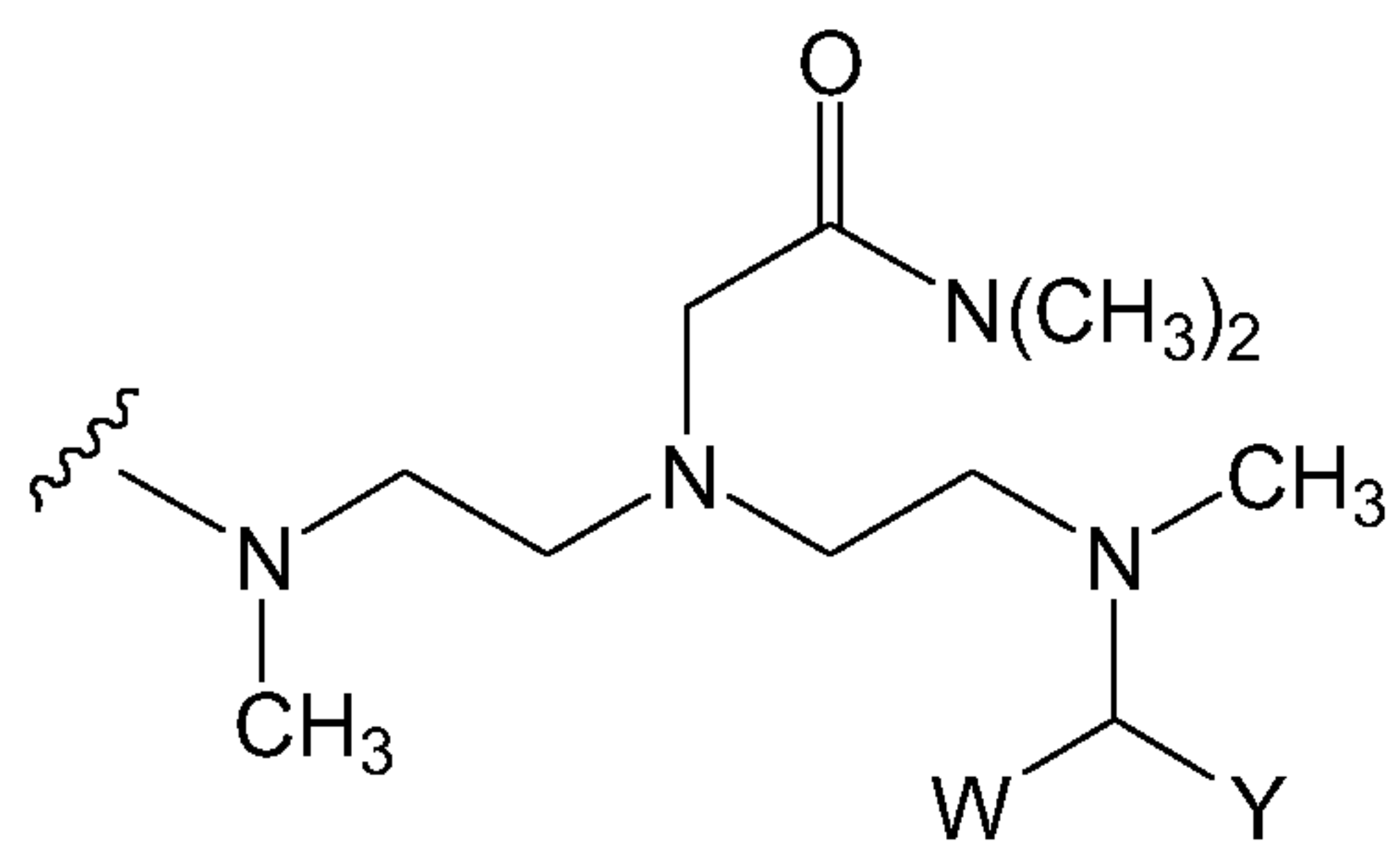
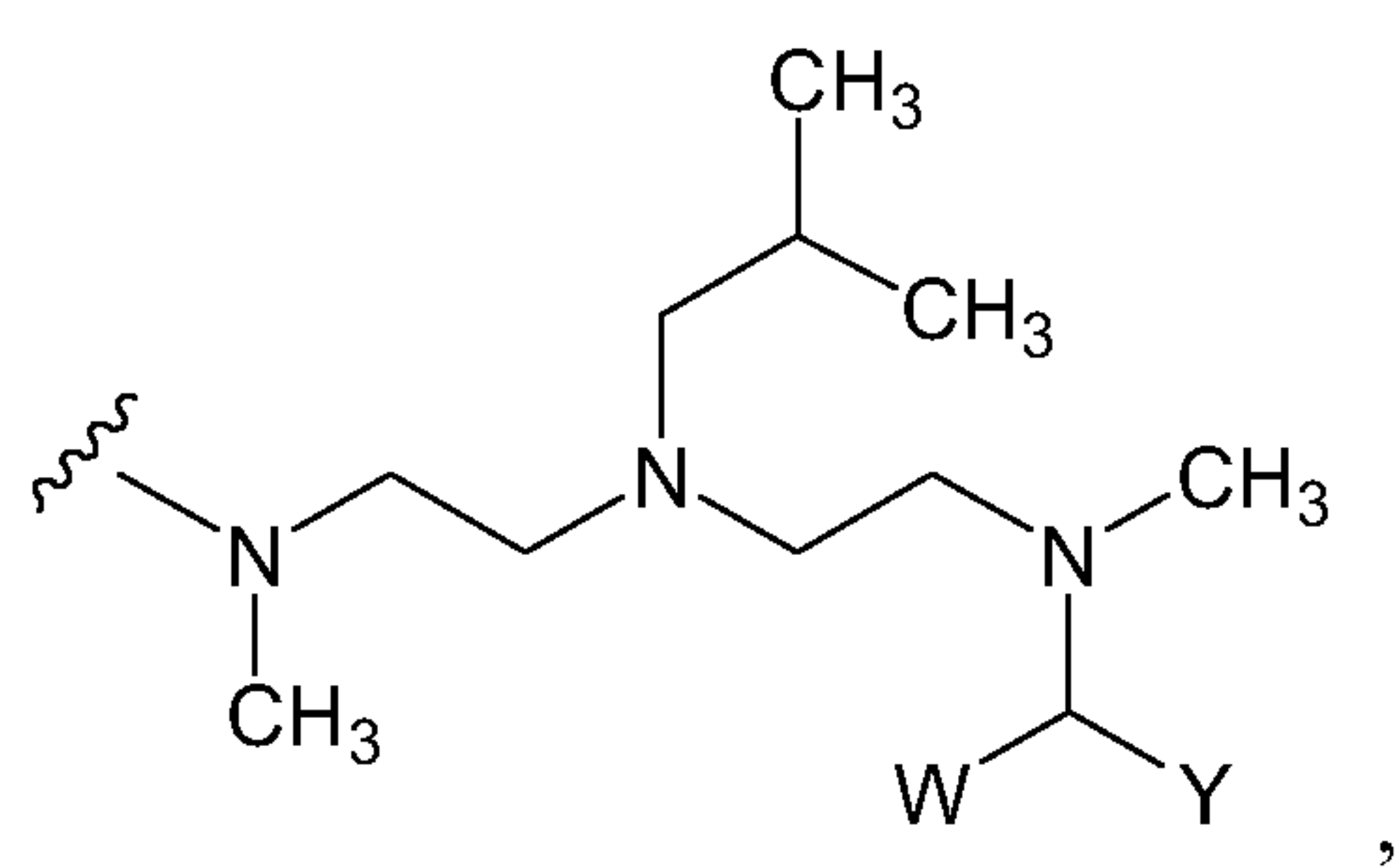
5



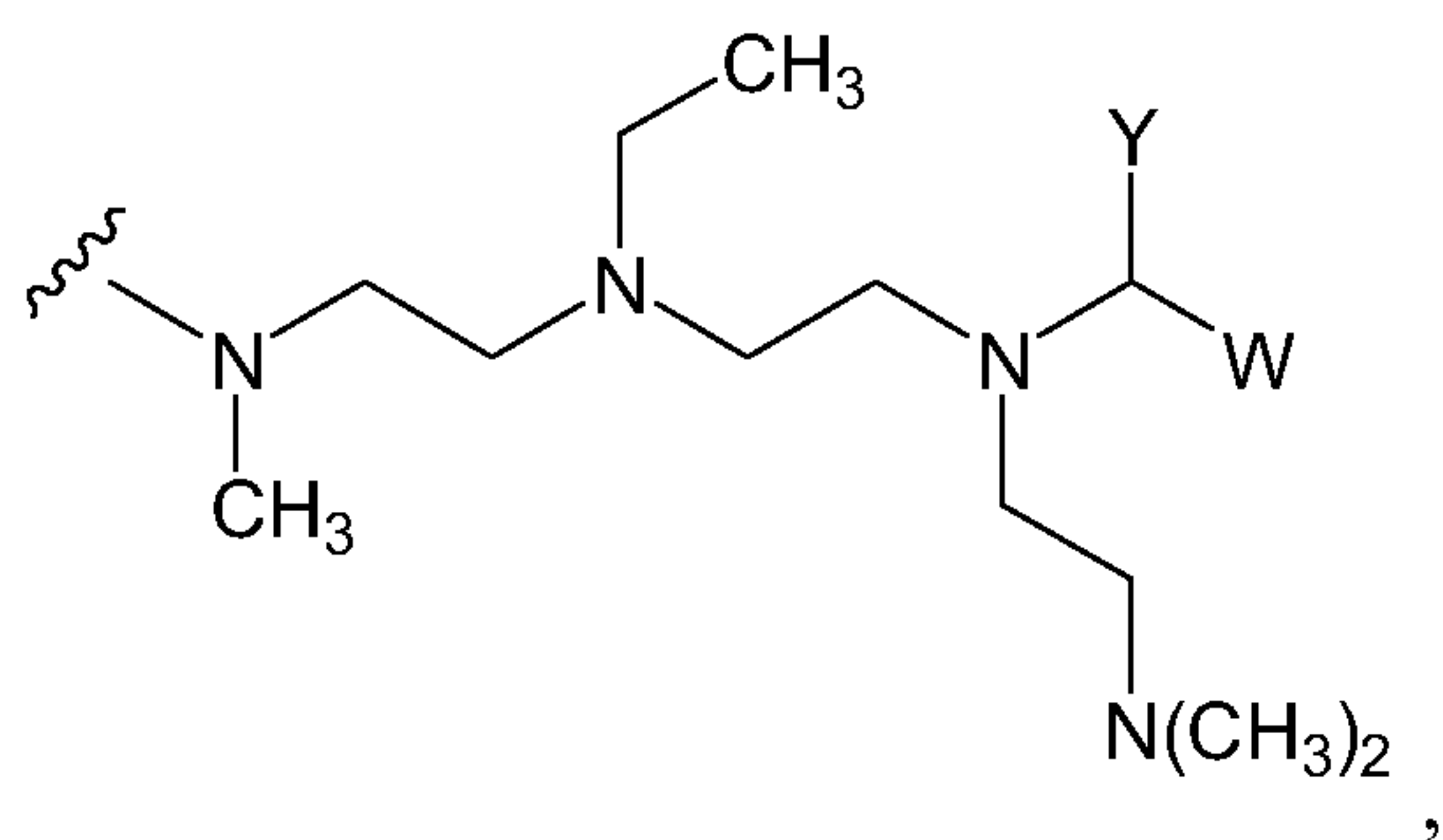
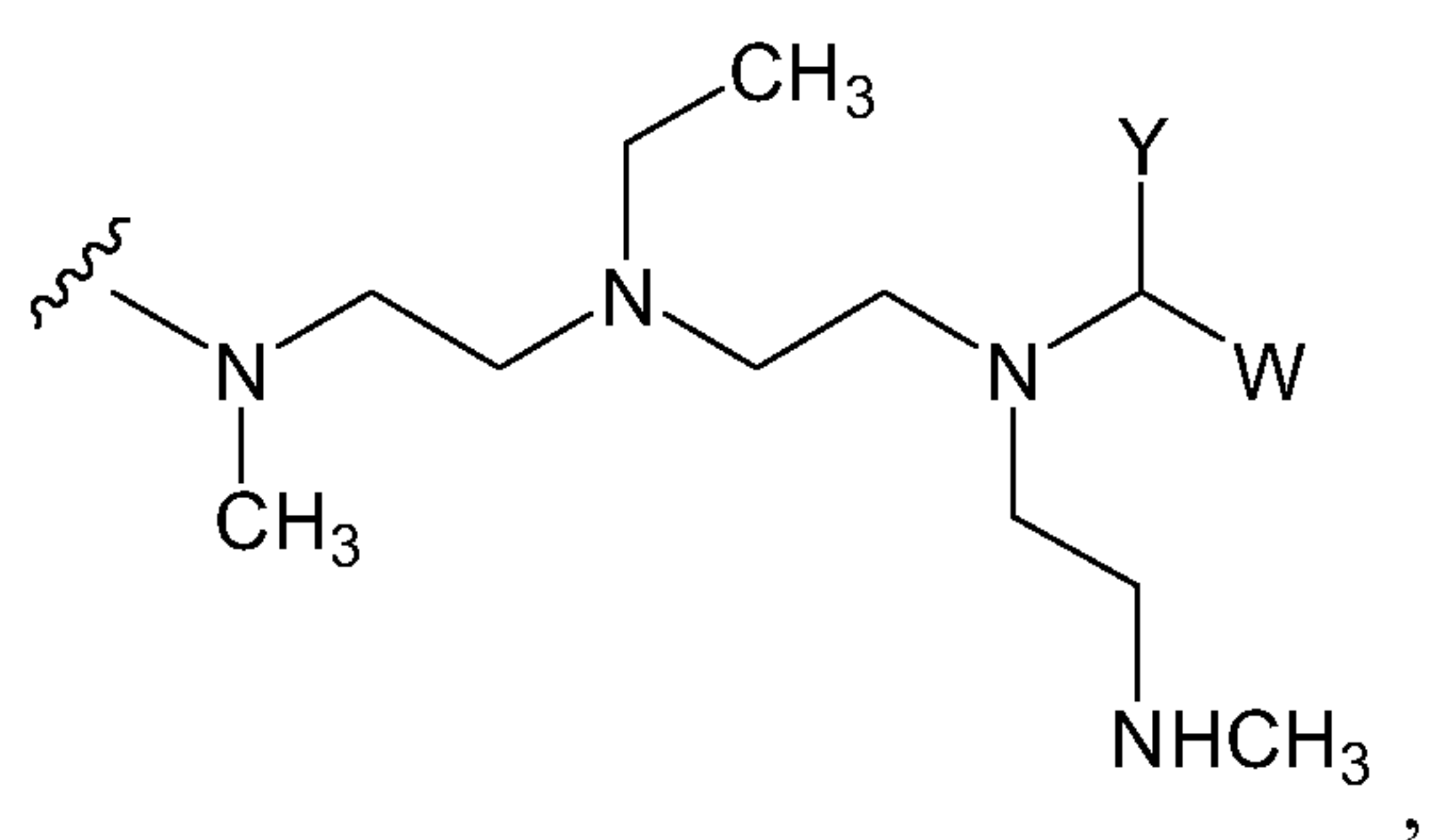
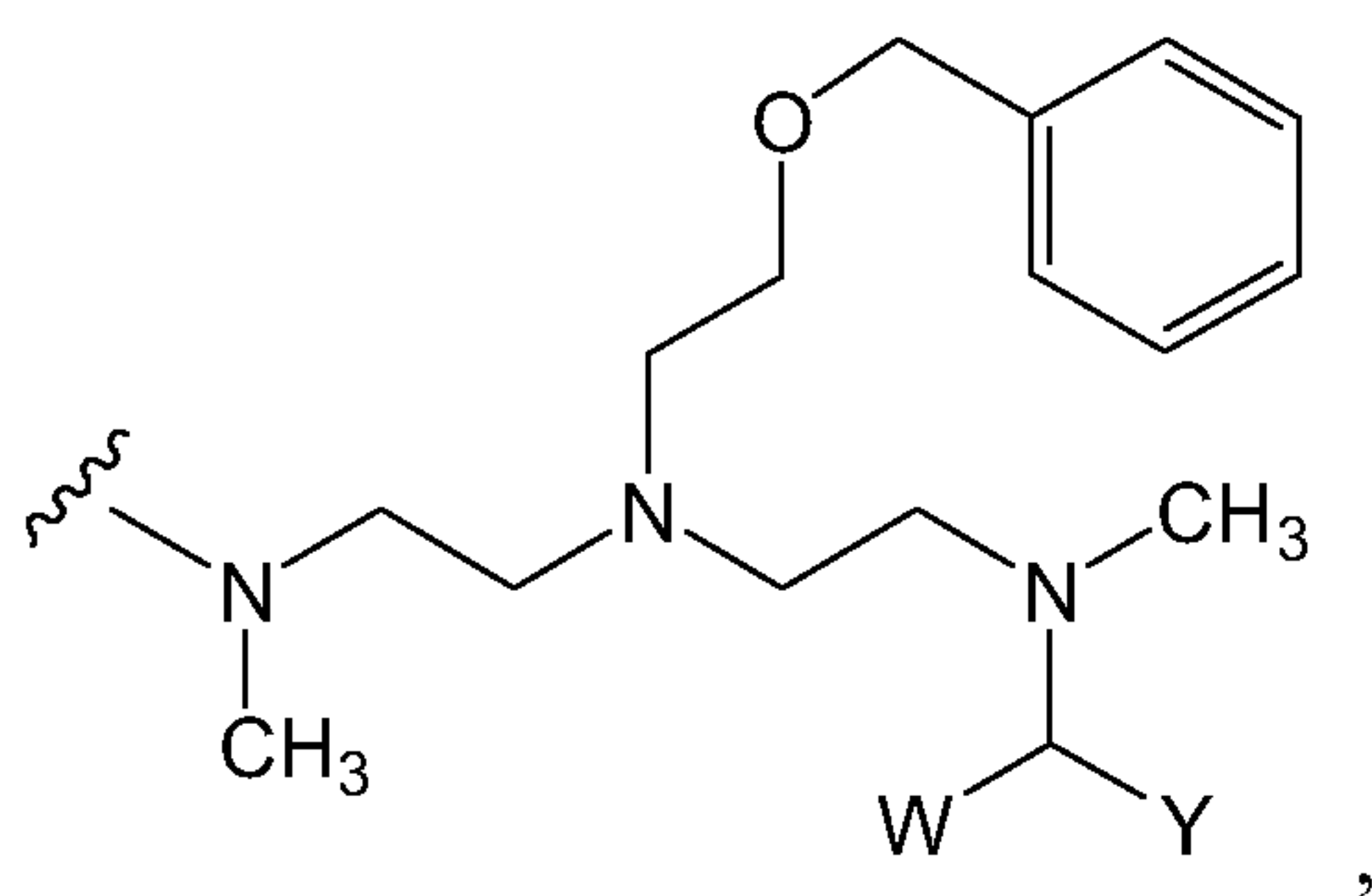
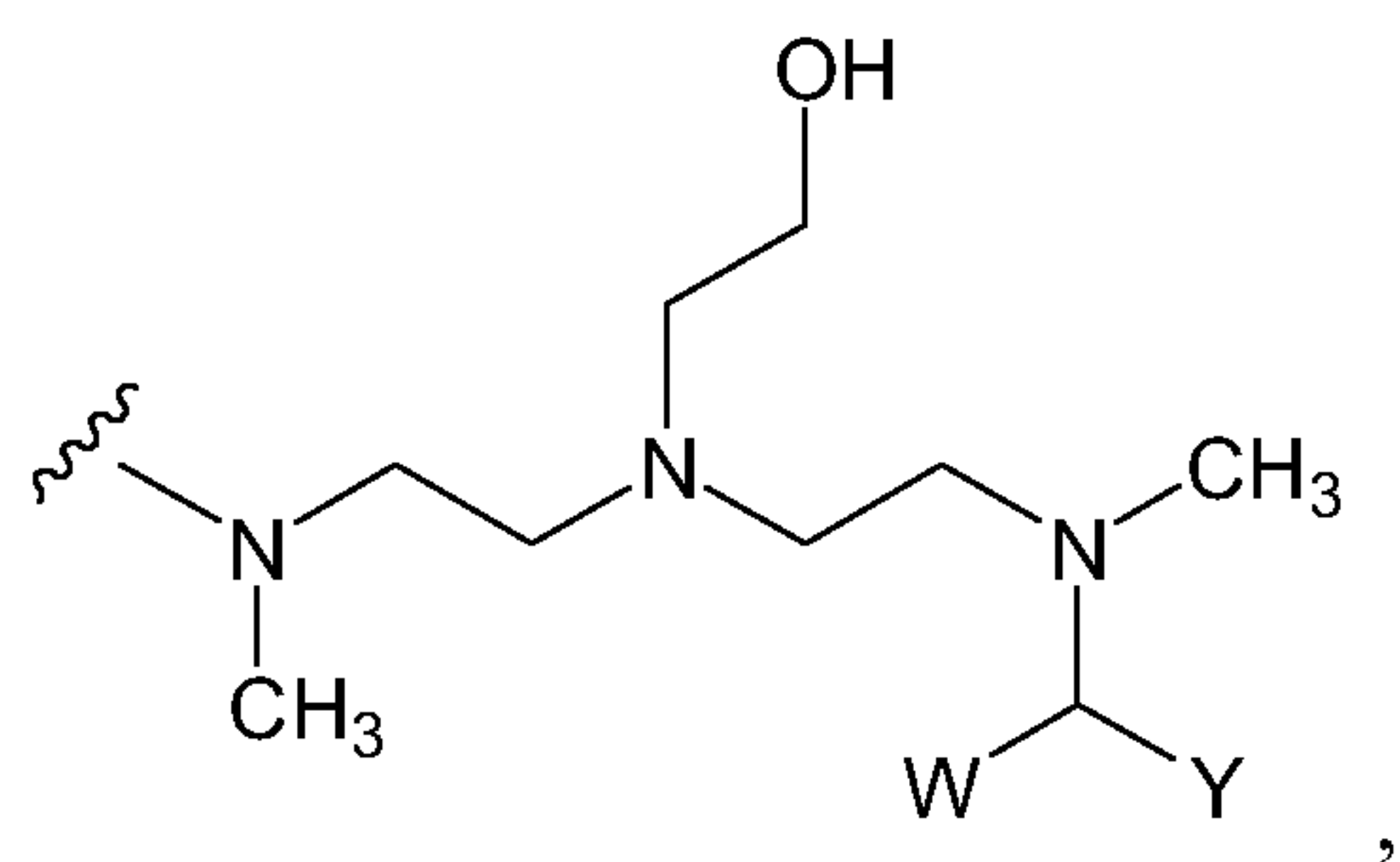
10

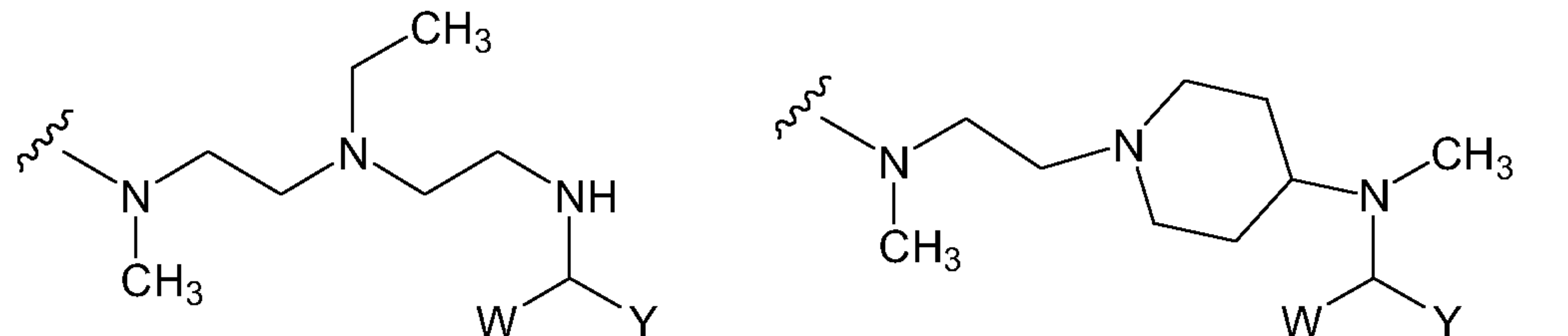
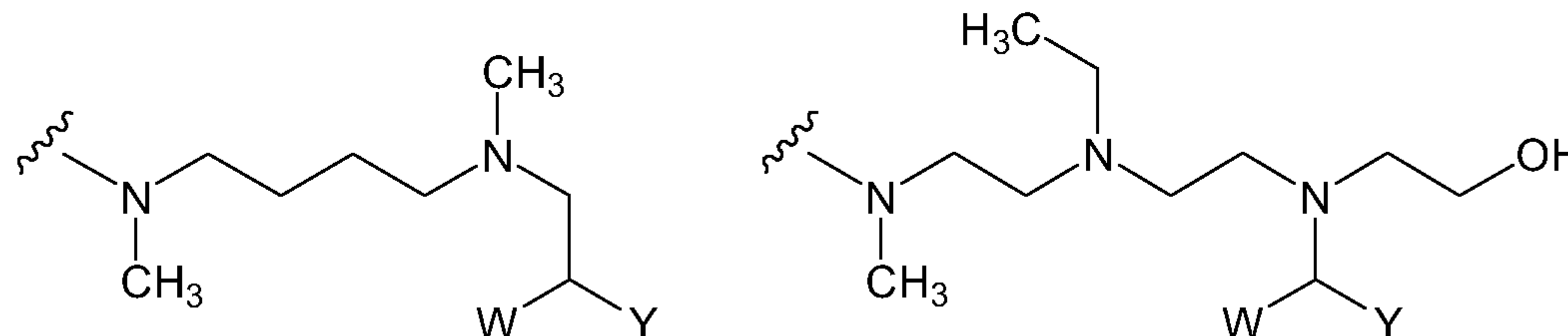
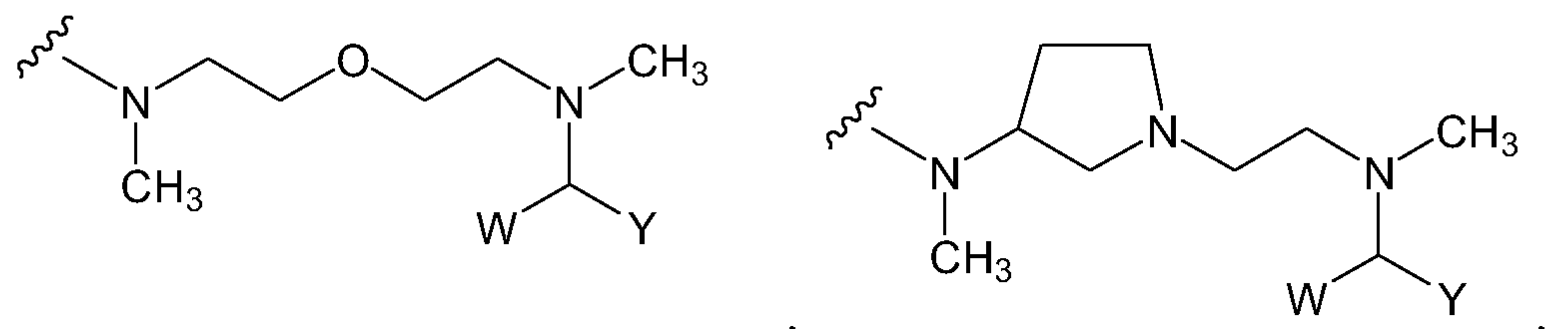
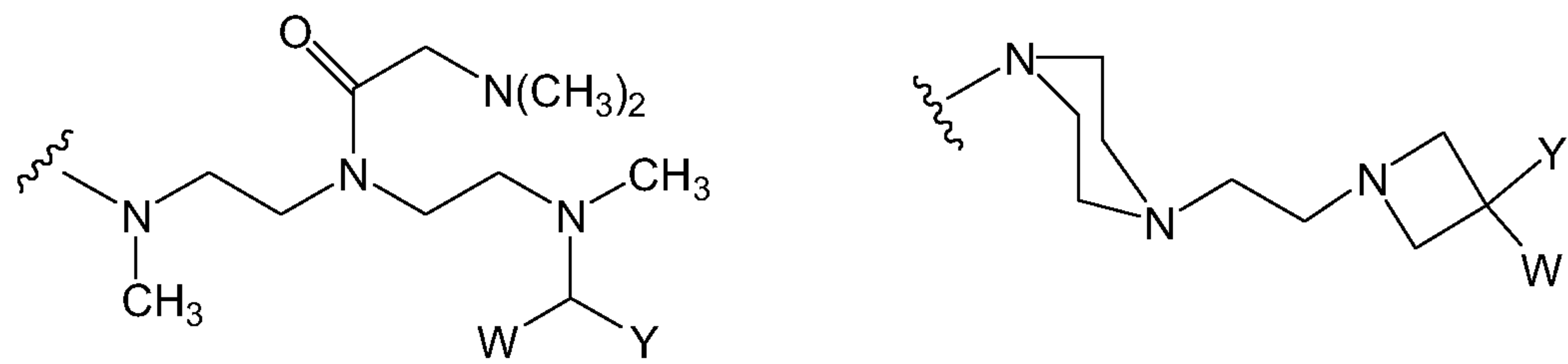


15

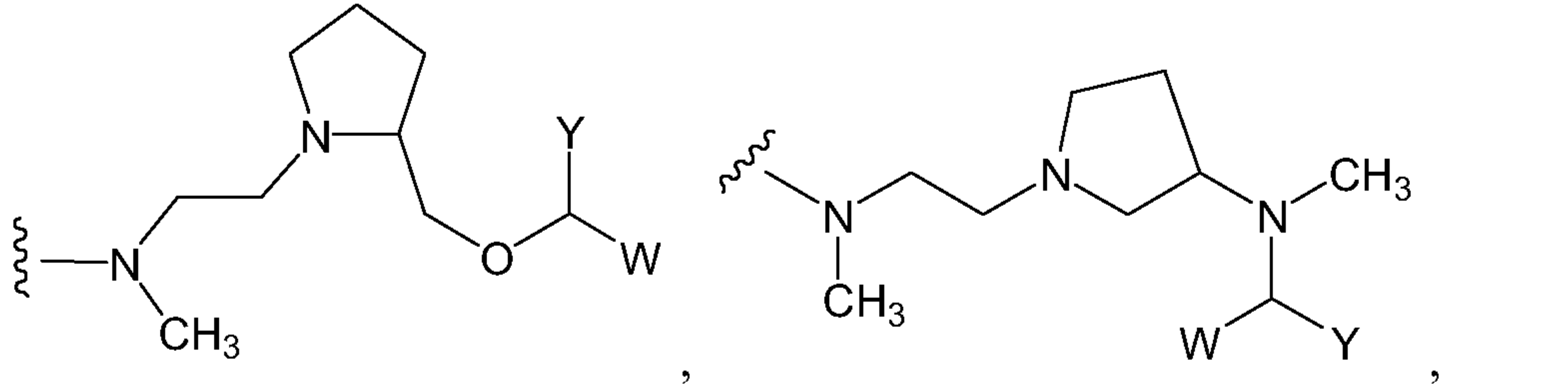
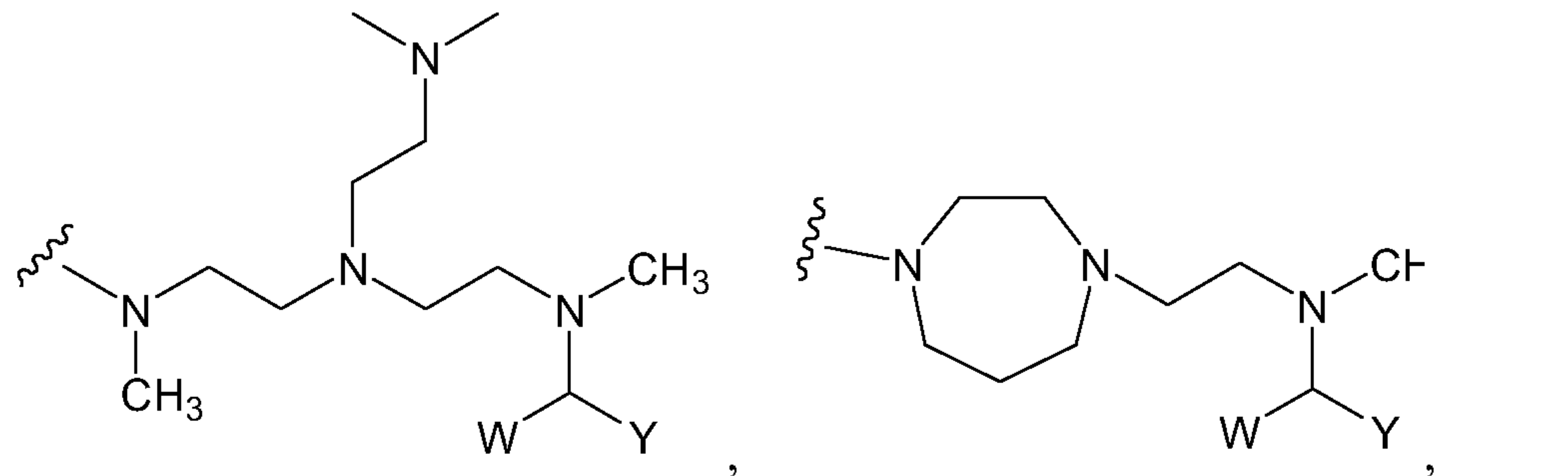


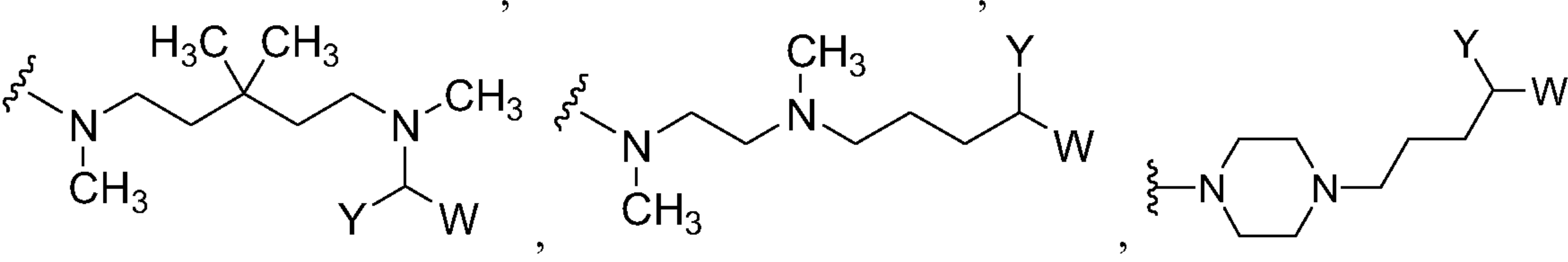
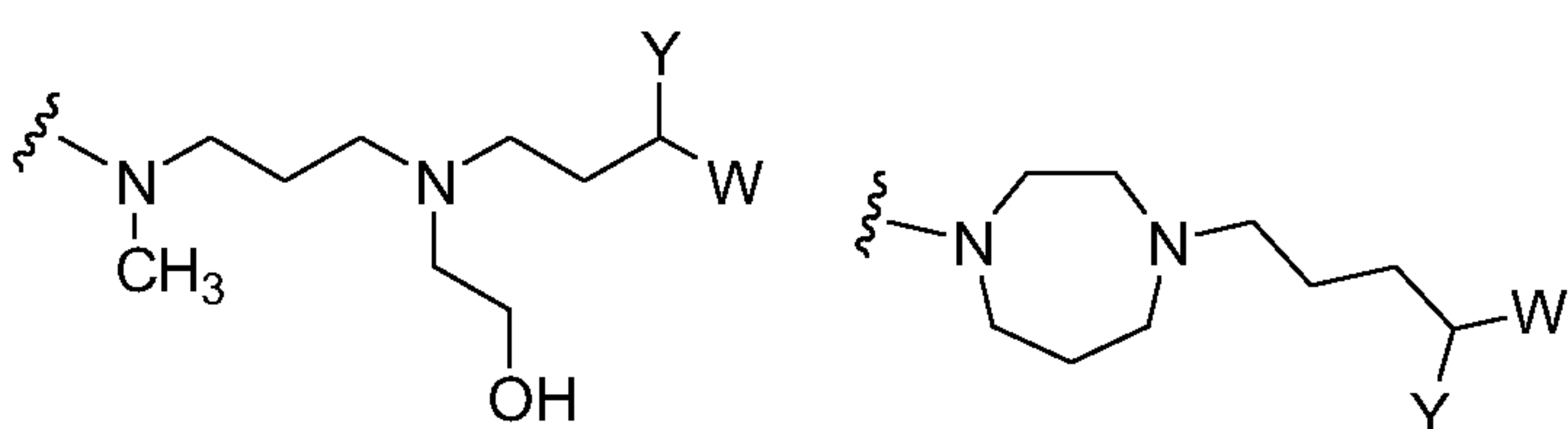
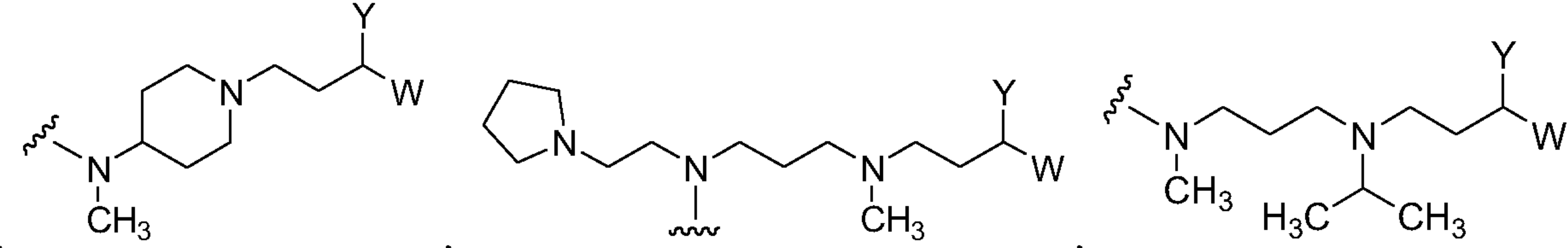
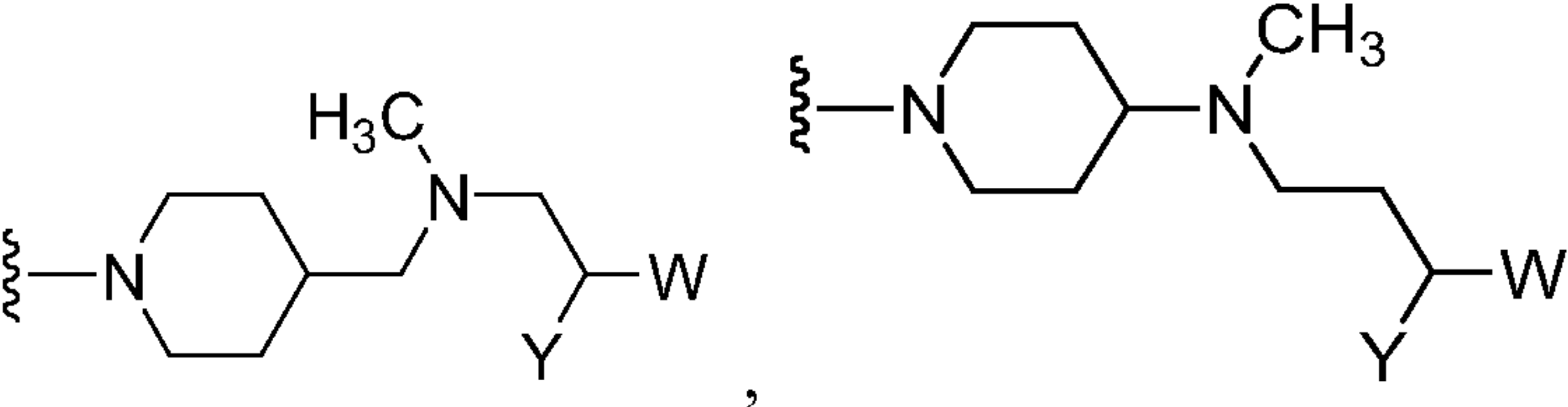
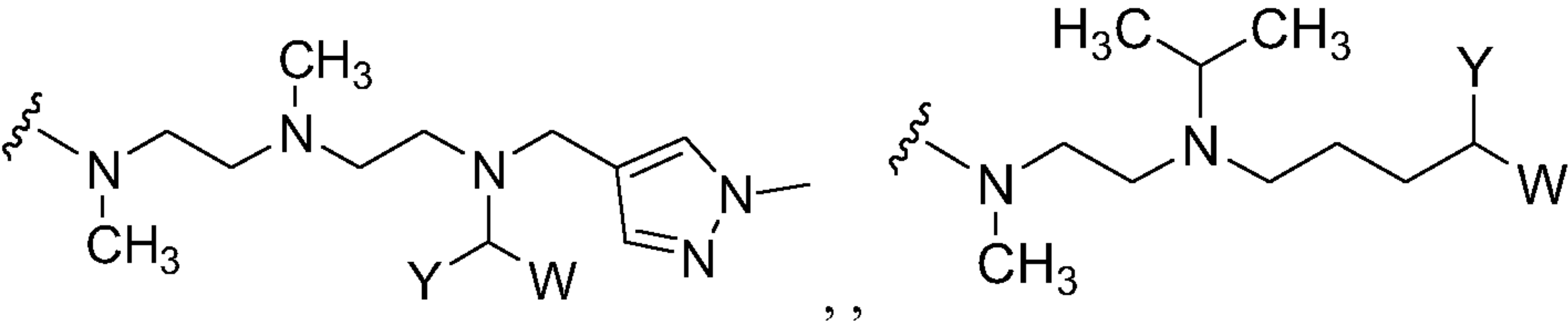
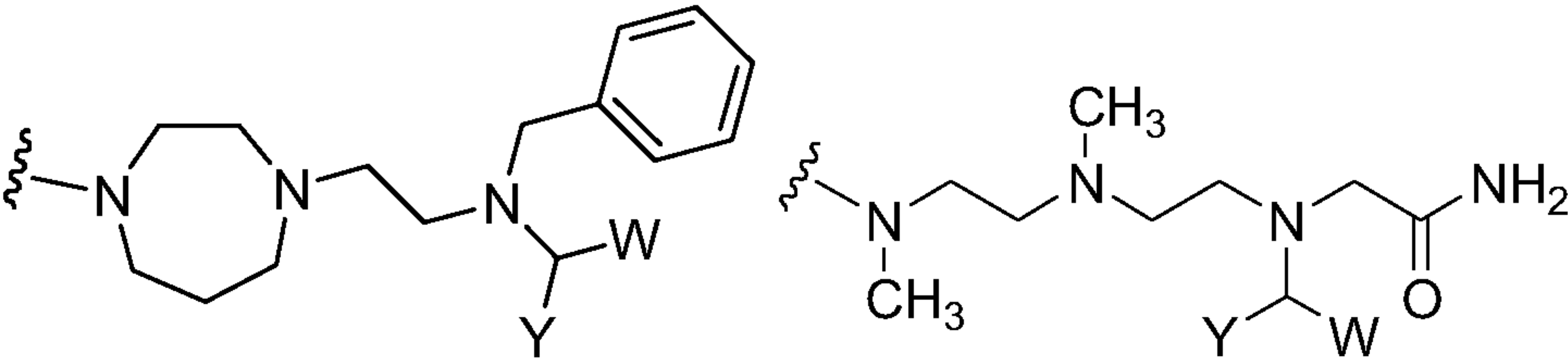
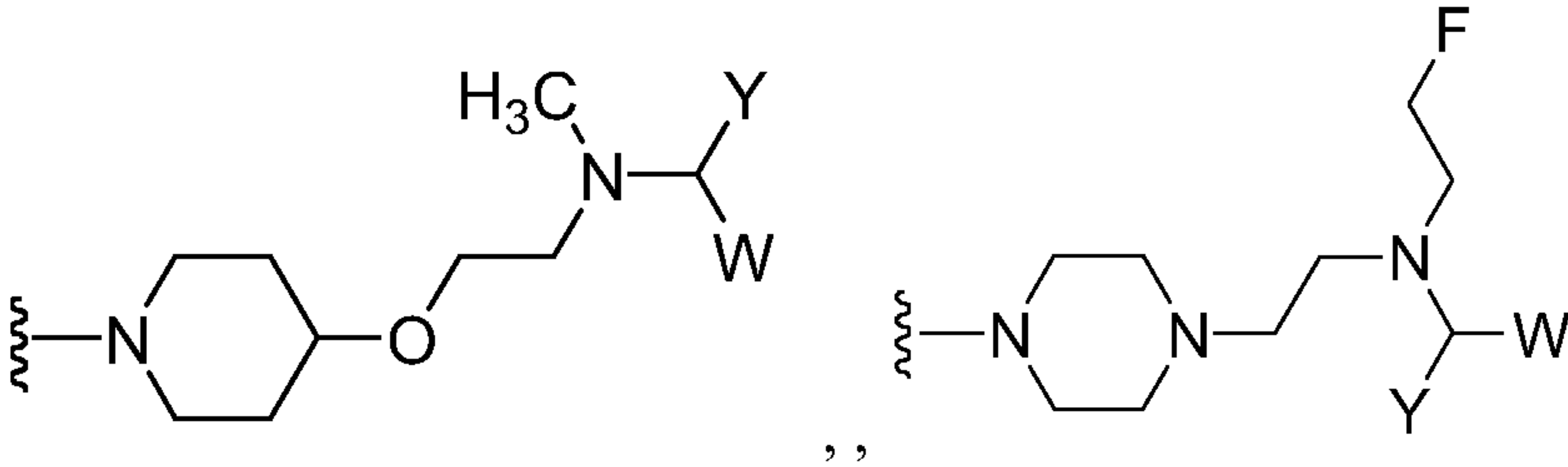
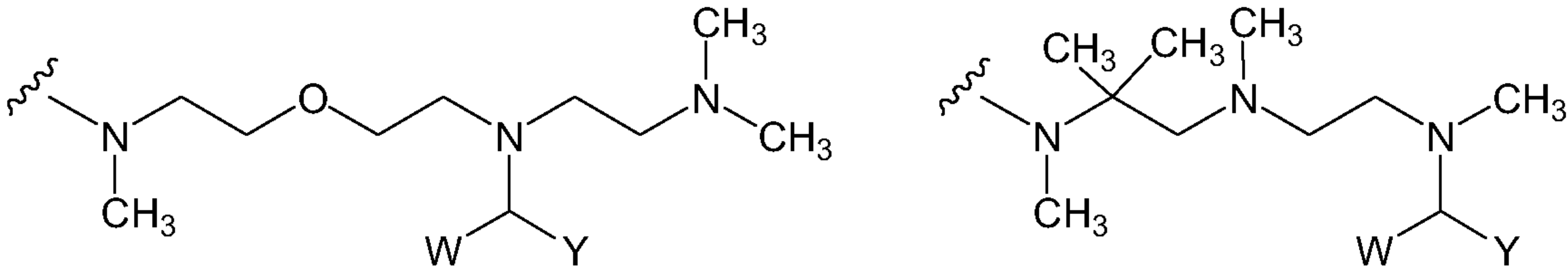
5



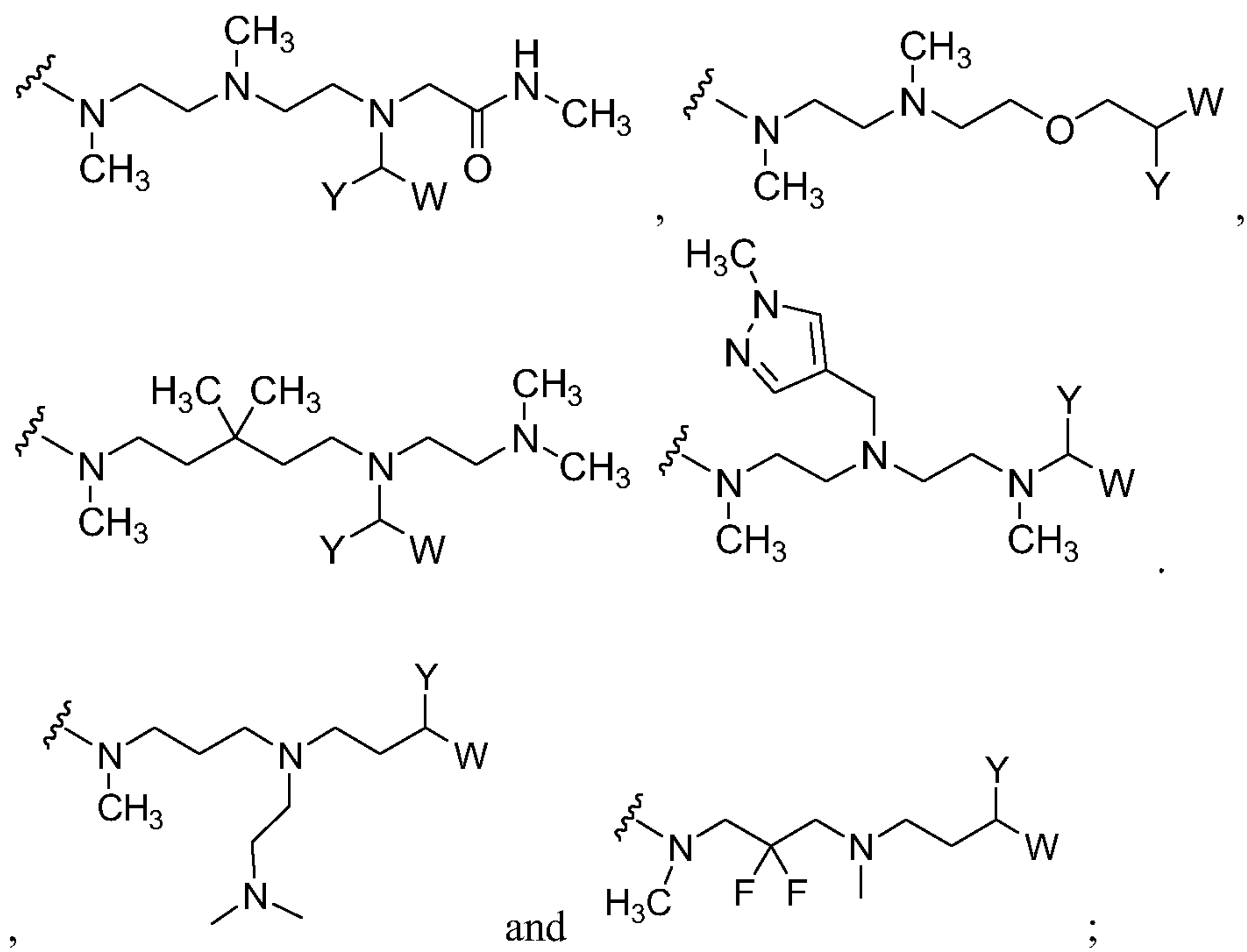


5



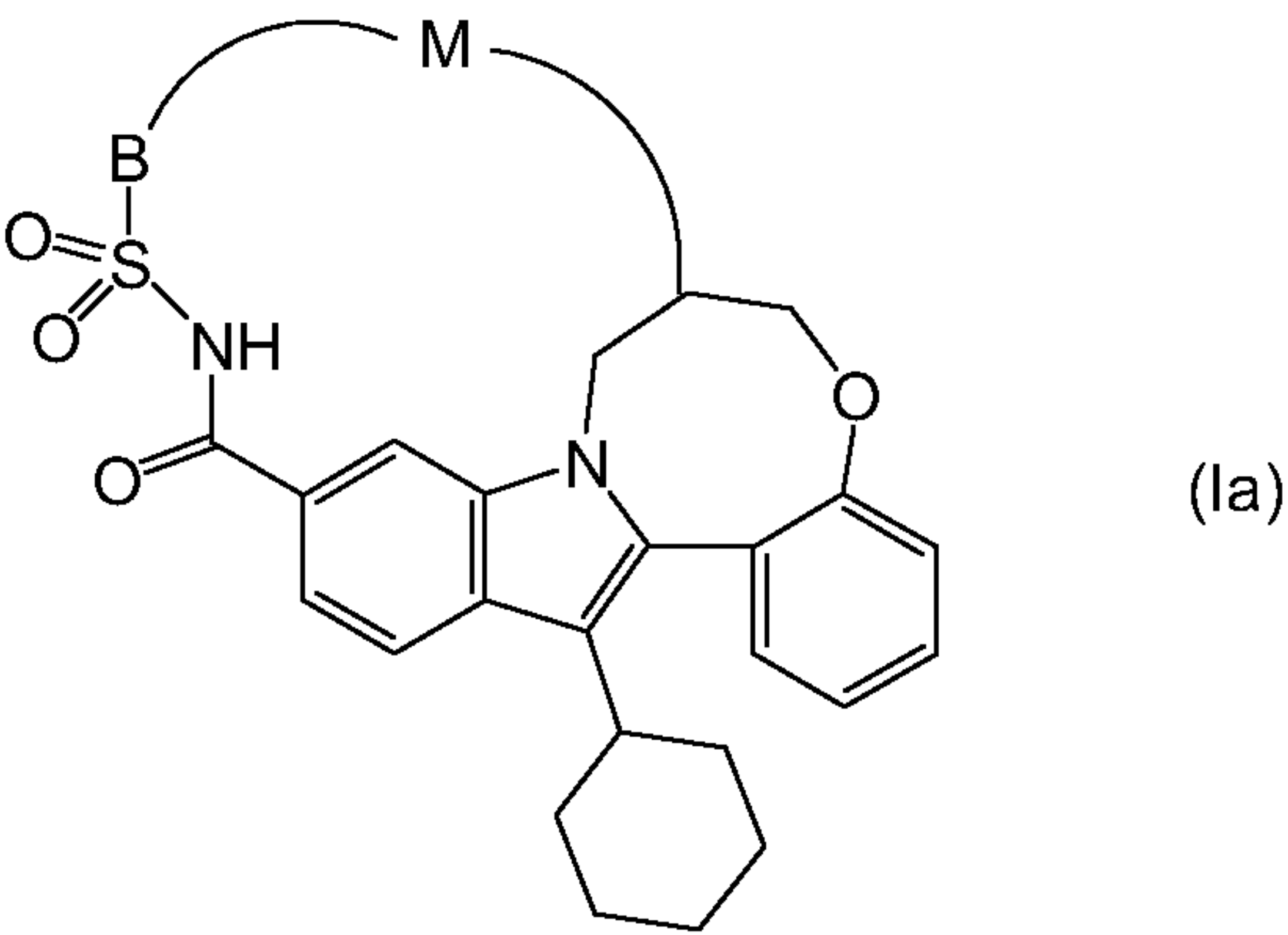


- 114 -



where R⁹ is hydrogen.

6. A compound as claimed in Claim 1 of formula (Ia):



or a pharmaceutically acceptable salt thereof, wherein M and B are as defined in relation to formula (I).

7. A compound as claimed in Claim 1 which is selected from:

- (7*R*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;

- (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-isopropyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 5 (7*R*)-14-cyclohexyl-18-(cyclopropylmethyl)-21,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 (20*R*)-30-cyclohexyl-21-methyl-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- (7*S*)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(epoxyethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 15 (7*R*)-14-cyclohexyl-18,21,24-trimethyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 13-cyclohexyl-5,17,20,23-tetramethyl-6,7-dihydro-5*H*-10,6-(methanoiminothioiminoethanoiminoethanoiminomethano)indolo[1,2-*d*][1,4]benzodiazepin-14-one 16,16-dioxide;
- 20 13-cyclohexyl-3-methoxy-17,20-dimethyl-6,7-dihydro-5*H*-6,10-(ethanoiminoethanoiminothioiminomethano)indolo[2,1-*a*][2]benzazepin-14-one 16,16-dioxide;
- (7*R*)-14-cyclohexyl-3-fluoro-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 25 (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-21-ethyl-3-fluoro-18-methyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)-indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 30 (+)-14-cyclohexyl-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (-)-14-cyclohexyl-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 35 (7*S*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;

- (7*R,S*)-14-[(1*R,2S*) or (1*S,2R*)-2-fluorocyclohexyl]-18,23-dimethyl-7,8-dihydro-6*H*-11,7-(methanoiminothioiminobutanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (20*S*)-31-cyclohexyl-10-methyl-19,22-dioxa-9-thia-1,8,10,13-
- 5 tetraazahexacyclo[18.9.1.1^{2,6}.1^{3,29}.0^{13,17}.0^{23,28}]dotriaconta-2(32),3,5,23,25,27,29(31)-heptaen-7-one 9,9-dioxide;
- (18*R*)-29-cyclohexyl-10,17-dimethyl-20-oxa-9-thia-1,8,10,14,17-pentaazahexacyclo[16.9.1.1^{2,6}.1^{3,27}.1^{11,14}.0^{21,26}]hentriaconta-2(31),3,5,21,23,25,27(29)-heptaen-7-one 9,9-dioxide;
- 10 (7*R*)-14-cyclohexyl-21-ethyl-4,18,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoxyethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
- 15 17,17-dioxide;
- (16*S,18R*)-29-cyclohexyl-10,17-dimethyl-20-oxa-9-thia-1,8,10,13,17-pentaazahexacyclo[16.9.1.1^{2,6}.1^{3,27}.1^{13,16}.0^{21,26}]hentriaconta-2(31),3,5,21,23,25,27(29)-heptaen-7-one 9,9-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-4-propyl-7,8-dihydro-6*H*-7,11-
- 20 (epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 31-cyclohexyl-8-oxa-24-thia-1,4,16,23,25-pentaazaheptacyclo[23.2.2.1^{4,6}.1^{6,16}.1^{15,18}.1^{17,21}.0^{9,14}]tritriaconta-9,11,13,15(31),17(30),18,20-heptaen-22-one 24,24-dioxide;
- 25 (7*R*)-14-cyclohexyl-18,19,19,21,24-pentamethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
- 30 dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-methoxy-18,24-dimethyl-7,8-dihydro-6*H*-7,11-
- 35 (epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;

- (7*R*)-14-cyclohexyl-21-ethyl-4-methoxy-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-methoxy-18,24-dimethyl-21-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 2-[(7*R*)-14-cyclohexyl-18,21-dimethyl-17,17-dioxido-15-oxo-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-24-yl]-*N*-methylacetamide;
- (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-18,21,21-trimethyl-7,8-dihydro-6*H*-7,11-(epiminopentanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-18,21,24-trimethyl-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-methoxy-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 30-cyclohexyl-18-oxa-2-thia-1,3,10,24-tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- (-)-14-cyclohexyl-3-methoxy-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (+)-14-cyclohexyl-3-methoxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (-)-14-cyclohexyl-3-methoxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-3-methoxy-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R* or 7*S*)-14-cyclohexyl-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(methanooxyethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;

- 14-cyclohexyl-18,22-dimethyl-7,8-dihydro-6*H*-7,11-
(ethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-
dioxide;
- (7*R*)-21-[2-(benzyloxy)ethyl]-14-cyclohexyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-
5 (epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-(2-hydroxyethyl)-18,24-dimethyl-7,8-dihydro-6*H*-7,11-
(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
17,17-dioxide;
- 10 (7*R*)-14-cyclohexyl-21-isobutyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-
(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-(*N,N*-dimethylglycyl)-18,24-dimethyl-7,8-dihydro-6*H*-7,11-
(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
15 17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-18-(2-hydroxyethyl)-24-methyl-7,8-dihydro-6*H*-7,11-
(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
17,17-dioxide;
- (7*R*)-14-cyclohexyl-21,24-diethyl-18-methyl-7,8-dihydro-6*H*-7,11-
20 (epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
17,17-dioxide;
- 20-benzyl-13-cyclohexyl-17,23-dimethyl-6,7-dihydro-5*H*-6,10-
(epiminoethanoiminoethanoiminothioiminomethano)indolo[2,1-*a*][2]benzazepin-14-one 16,16-
dioxide;
- 25 (7*R*)-14-cyclohexyl-2-fluoro-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-
(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-3-fluoro-18,24-dimethyl-7,8-dihydro-6*H*-7,11-
(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
30 17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-7,8-dihydro-6*H*-7,11-
(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-2-fluoro-18,24-dimethyl-7,8-dihydro-6*H*-7,11-
35 (epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one
17,17-dioxide;

- (7*R*)-14-cyclohexyl-21-ethyl-2-fluoro-18-methyl-24-(pyridin-3-ylmethyl)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-3-fluoro-21-isopropyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 5 (7*R*)-14-cyclohexyl-21-ethyl-3-fluoro-18-methyl-24-[2-(methylamino)ethyl]-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 (7*R*)-14-cyclohexyl-21-ethyl-3-methoxy-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 15 (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-3-(pyridin-2-ylmethoxy)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-18,21,24-trimethyl-4-propyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 20 (7*R*)-14-cyclohexyl-21-isopropyl-18,24-dimethyl-4-propyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 25 (7*R*)-14-cyclohexyl-21-ethyl-24-(2-hydroxyethyl)-3,18-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-ethyl-3,18,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 30 (7*R*)-14-cyclohexyl-3,18,21,24-tetramethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-21-ethyl-18-methyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 35

- (7*R*)-14-cyclohexyl-21-isopropyl-3,18,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 5 (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-21-ethyl-4,18-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-21-[2-(dimethylamino)ethyl]-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 (18*R*)-29-cyclohexyl-10,17-dimethyl-20-oxa-9-thia-1,8,10,13,17-pentaazahexacyclo[16.9.1.1^{2,6}.1^{3,27}.1^{13,16}.0^{21,26}]hentriaconta-2(31),3,5,21,23,25,27(29)-heptaen-7-one 9,9-dioxide;
- (3*R*)-31-cyclohexyl-2,22-dimethyl-5-oxa-21-thia-2,13,20,22,25-pentaazahexacyclo[23.2.2.1^{3,13}.1^{12,15}.1^{14,18}.0^{6,11}]dotriaconta-6,8,10,12(31),14(30),15,17-heptaen-15 19-one 21,21-dioxide;
- (5*R*)-31-cyclohexyl-4,24-dimethyl-7-oxa-23-thia-1,4,15,22,24-pentaazahexacyclo[23.2.2.1^{5,15}.1^{14,17}.1^{16,20}.0^{8,13}]dotriaconta-8,10,12,14(31),16(30),17,19-heptaen-21-one 23,23-dioxide;
- 20 (20*R*)-31-cyclohexyl-21-methyl-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.3.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide;
- (5*R*)-31-cyclohexyl-4,24-dimethyl-7-oxa-23-thia-1,4,15,22,24-pentaazahexacyclo[23.2.2.1^{5,15}.1^{14,17}.1^{16,20}.0^{8,13}]dotriaconta-8,10,12,14(31),16(30),17,19-heptaen-21-one 23,23-dioxide;
- 25 (20*R*)-31-cyclohexyl-21-methyl-18,24-dioxa-2-thia-1,3,10,21-tetraazahexacyclo[23.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide;
- (20*R*)-31-cyclohexyl-21-[2-(dimethylamino)ethyl]-18,24-dioxa-2-thia-1,3,10,21-tetraazahexacyclo[23.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-30 one 2,2-dioxide;
- (20*R*)-30-cyclohexyl-21-(2-fluoroethyl)-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- (20*R*)-21-benzyl-31-cyclohexyl-18-oxa-2-thia-1,3,10,21,24-pentaazahexacyclo[22.3.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-35 one 2,2-dioxide;

- (7*S*)-14-cyclohexyl-21-isopropyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-24-[2-(dimethylamino)ethyl]-18-methyl-7,8-dihydro-6*H*-7,11-(epiminoethanooxyethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 5 (7*R*)-4-allyl-14-cyclohexyl-21-ethyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 10 (7*R*)-14-cyclohexyl-21-ethyl-4-fluoro-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-fluoro-21-isopropyl-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 15 (7*R*)-14-cyclohexyl-21-ethyl-18,24-dimethyl-4-(trifluoromethyl)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-(cyclopropylmethyl)-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 20 2-[(7*R*)-14-cyclohexyl-18,21-dimethyl-17,17-dioxido-15-oxo-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-24-yl]acetamide;
- 25 (7*R*)-14-cyclohexyl-18,21-dimethyl-24-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-18,24-dimethyl-4-(morpholin-4-ylmethyl)-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 30 (7*R*)-4-(benzyloxy)-14-cyclohexyl-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-methoxy-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 35

- (7*R*)-14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 5 30-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-23-methyl-18-oxa-2-thia-1,3,10,23-tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- 10 30-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-22-methyl-18-oxa-2-thia-1,3,10,22-tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- 30-cyclohexyl-23-methyl-6-oxa-22-thia-1,14,21,23-tetraazahexacyclo[22.2.2.1^{4,14}.1^{13,16}.1^{15,19}.0^{7,12}]hentriaconta-7,9,11,13(30),15(29),16,18-heptaen-15 20-one 22,22-dioxide;
- (7*R*) or (7*S*)-14-cyclohexyl-22-methyl-18-(2-pyrrolidin-1-ylethyl)-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*) or (7*S*)-14-cyclohexyl-22-isopropyl-18-methyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 20 (7*R*) or (7*S*)-14-cyclohexyl-22-(2-hydroxyethyl)-18-methyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 25 31-cyclohexyl-18-oxa-2-thia-1,3,10,24-tetraazahexacyclo[22.3.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide;
- 14-cyclohexyl-21-isopropyl-18-methyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 30 (7*R*)-14-cyclohexyl-4-methoxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-18,21-dimethyl-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 35 (7*R*)-14-cyclohexyl-18,21,21,24-tetramethyl-7,8-dihydro-6*H*-7,11-(epiminopentanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;

- 14-[(1*R*,2*S*) or (1*S*,2*R*)-2-fluorocyclohexyl]-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 30-[(1*R*,2*S*)-2-fluorocyclohexyl]-23-methyl-18-oxa-2-thia-1,3,10,23-tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- 5 30-[(1*R*,2*S*)-2-fluorocyclohexyl]-22-methyl-18-oxa-2-thia-1,3,10,22-tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- 10 30-cyclohexyl-23-methyl-6-oxa-22-thia-1,14,21,23-tetraazahexacyclo[22.2.2.1^{4,14}.1^{13,16}.1^{15,19}.0^{7,12}]hentriaconta-7,9,11,13(30),15(29),16,18-heptaen-20-one 22,22-dioxide;
- (7*R*) or (7*S*)-14-cyclohexyl-22-methyl-18-(2-pyrrolidin-1-ylethyl)-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 15 (7*R*) or (7*S*)-14-cyclohexyl-22-isopropyl-18-methyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*) or (7*S*)-14-cyclohexyl-22-(2-hydroxyethyl)-18-methyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 20 31-cyclohexyl-18-oxa-2-thia-1,3,10,24-tetraazahexacyclo[22.3.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]dotriaconta-5(32),6,8,11(31),12,14,16-heptaen-4-one 2,2-dioxide;
- 25 14-cyclohexyl-21-isopropyl-18-methyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-methoxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 30 (7*R*)-14-cyclohexyl-18,21-dimethyl-4-(2-pyrrolidin-1-ylethoxy)-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-18,21,21,24-tetramethyl-7,8-dihydro-6*H*-7,11-(epiminopentanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- 35 (7*R*)-14-[(1*R*,2*S*)-2-fluorocyclohexyl]-4,18,21-trimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;

- 2-[(7*R*)-14-cyclohexyl-4,18,24-trimethyl-17,17-dioxido-15-oxo-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-21-yl]-*N,N*-dimethylacetamide;
- (7*R*)-14-cyclohexyl-4,18,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4,18,21,24-tetramethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4,18,24-trimethyl-21-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclopentyl-18,21,24-trimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4-methoxy-18,24-dimethyl-7,8-dihydro-6*H*-7,11-(epiminoethanooxyethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4,18,21-trimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-4,18,22-trimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (7*R*)-14-cyclohexyl-22-[2-(dimethylamino)ethyl]-4,18-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- (20*R*)-30-cyclohexyl-15-methoxy-23-methyl-18-oxa-2-thia-1,3,10,23-tetraazahexacyclo[22.2.2.1^{5,9}.1^{8,11}.1^{10,20}.0^{12,17}]hentriaconta-5(31),6,8,11(30),12,14,16-heptaen-4-one 2,2-dioxide;
- (7*R*)-14-cyclohexyl-20,20-difluoro-3-methoxy-18,22-dimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide;
- or a pharmaceutically acceptable salts thereof.
8. A pharmaceutical composition comprising a compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

- 125 -

9. A combination of a compound according to any one of claims 1 to 8 in admixture with one or more other agents for the treatment of viral infections.

5 10. A compound of any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof for use in therapy

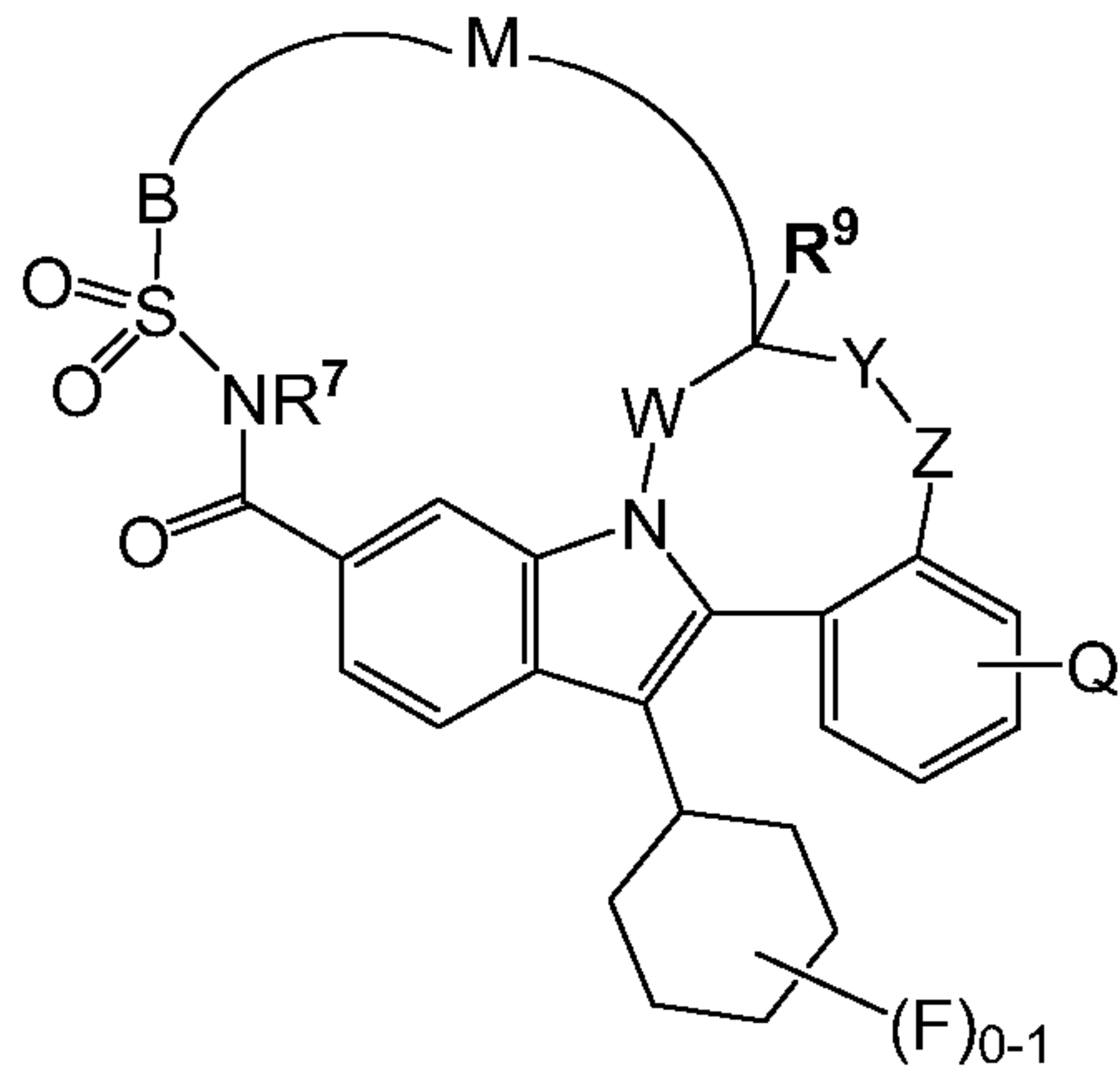
11. A compound of any one of claims 1-9 or a pharmaceutically acceptable salt thereof for use in the treatment and prevention of infection by hepatitis C virus in human or animal.

10

12. Use of a compound of any one of claims 1-9 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of infection by hepatitis C in human or animal.

15 13. A method on inhibiting hepatitis C virus protease and/or of treating or preventing an illness due to hepatitis C virus, the method involving administering to a human or animal subject suffering from the condition a therapeutically or prophylactically effective amount of the pharmaceutical composition claimed in Claim 8 or Claim 9 or of a compound of any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof.

20



(I)