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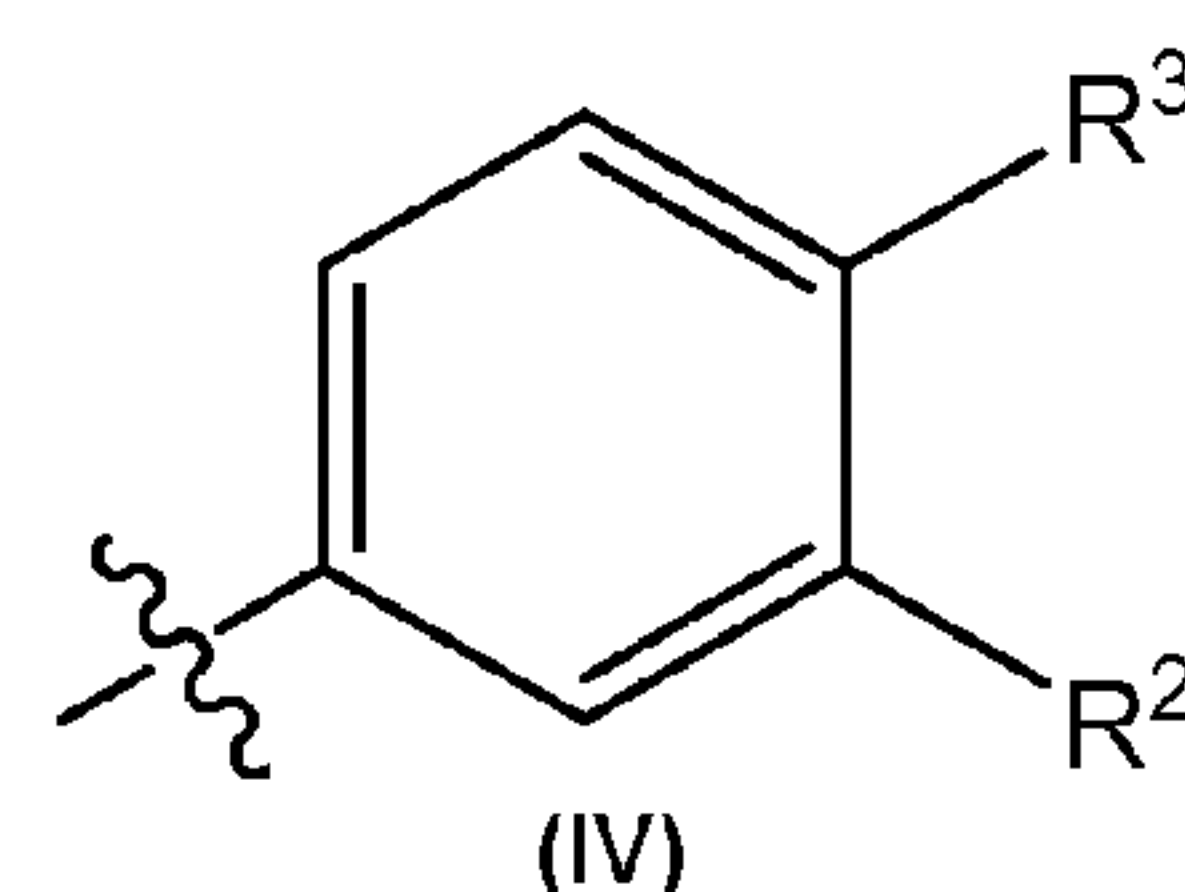
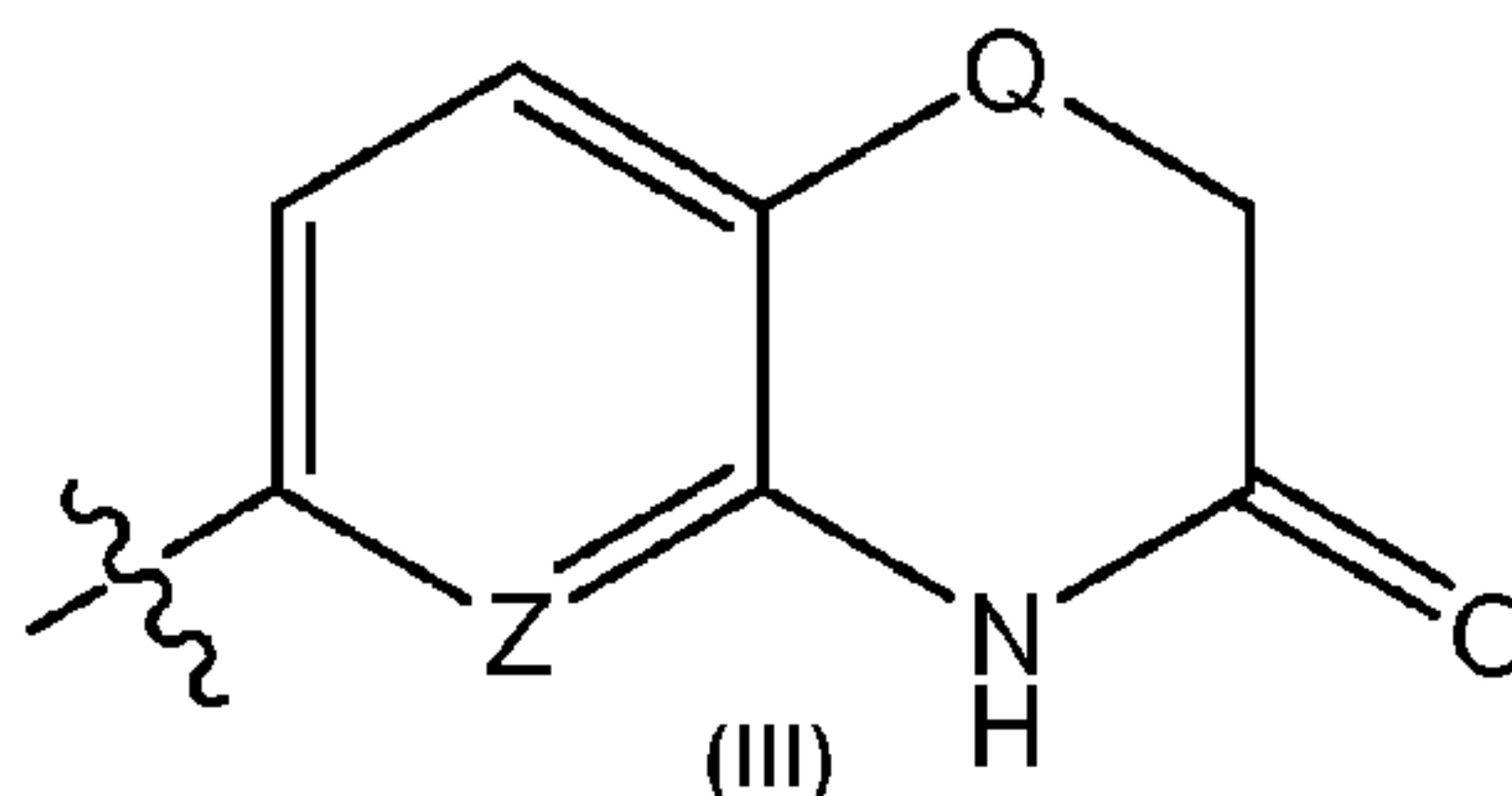
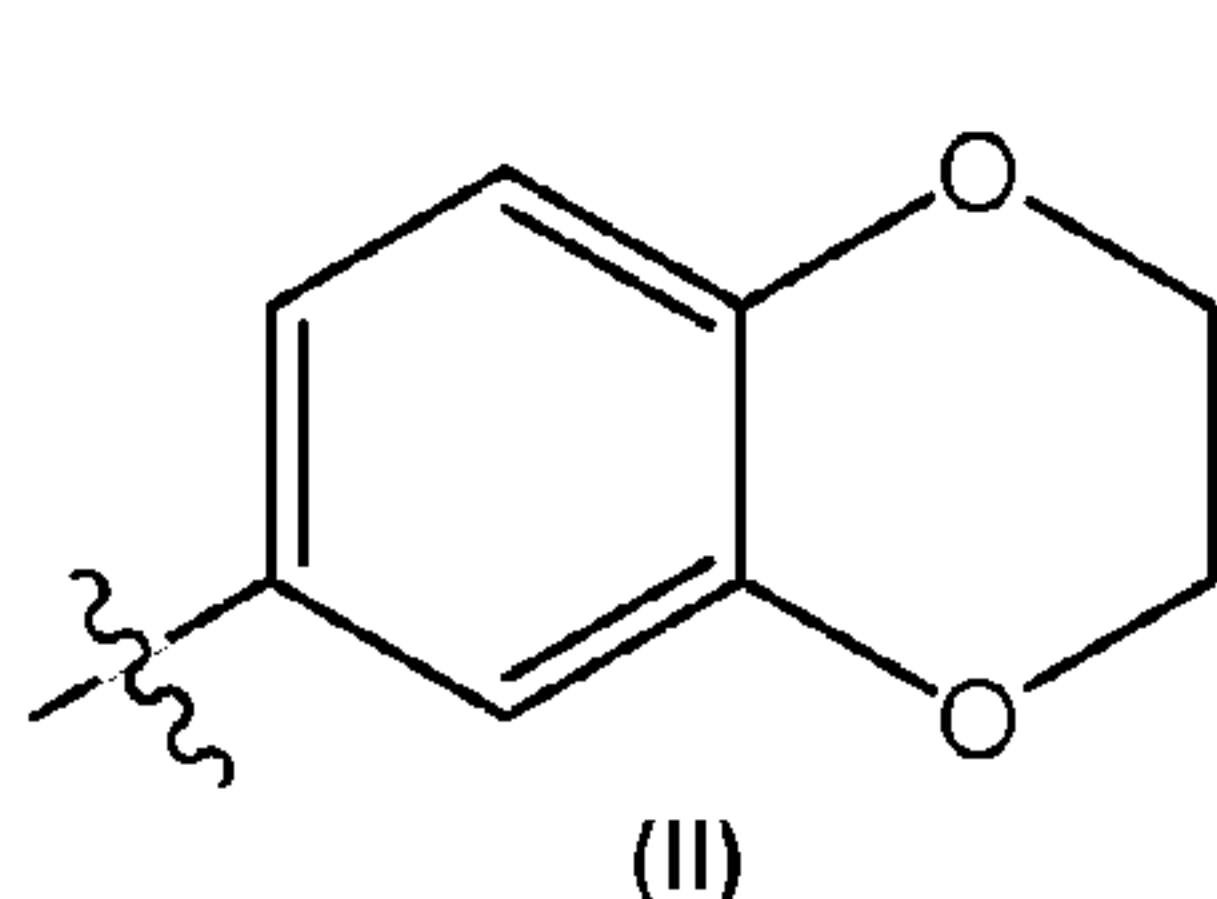
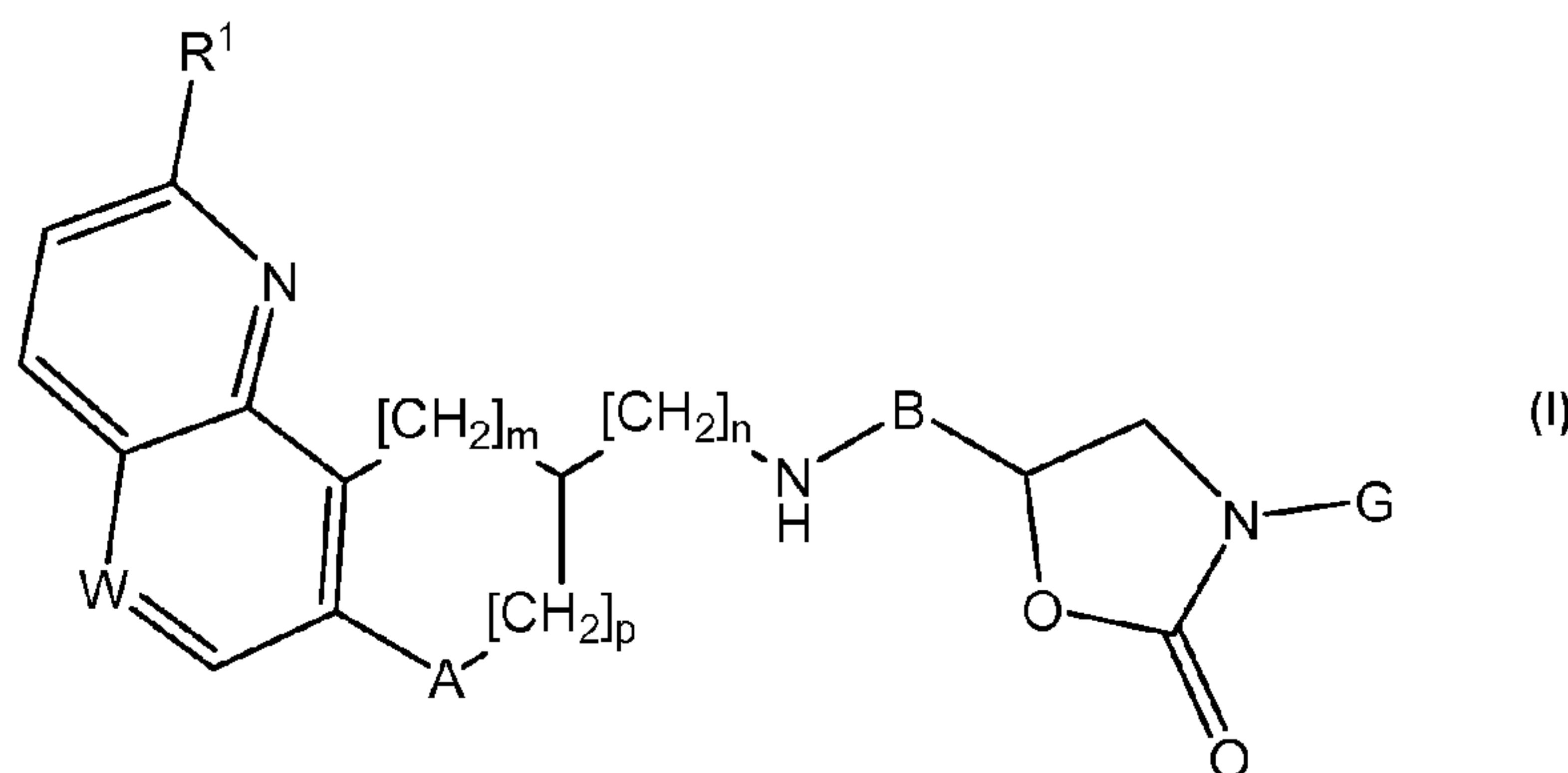
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(54) Titre : DERIVES D'ALKYLAMINOMETHYLOXAZOLIDINONE TRICYCLIQUES

(54) Title: TRICYCLIC ALKYLAMINOMETHYLOXAZOLIDINONE DERIVATIVES



(57) Abrégé/Abstract:

The invention relates to antibacterial compounds of formula (I) wherein R¹ is alkoxy or halogen; W is CH or N; A is O or NH; B is CO or (CH₂)_q; G is a group having one of the three formulae (II), (III) and (IV) below wherein Q represents O or S, Z represents CH or N, R² represents halogen and R³ represents alkyl; m is 0 or 1; and n is 1 or 2; p is 0 or 1, provided m and p are not each 0; and q is 1 or 2; and salts of such compounds.



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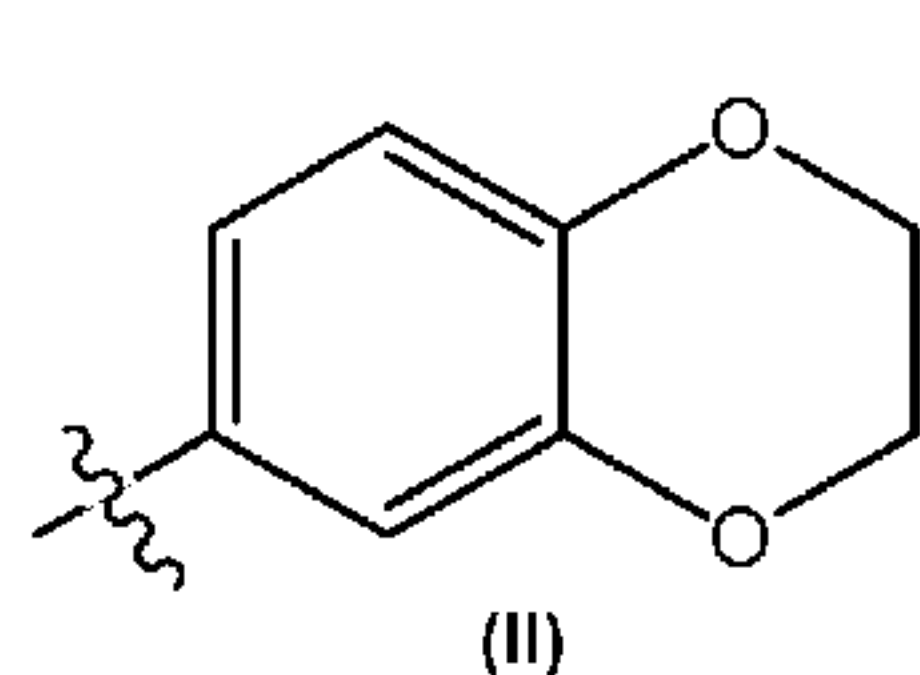
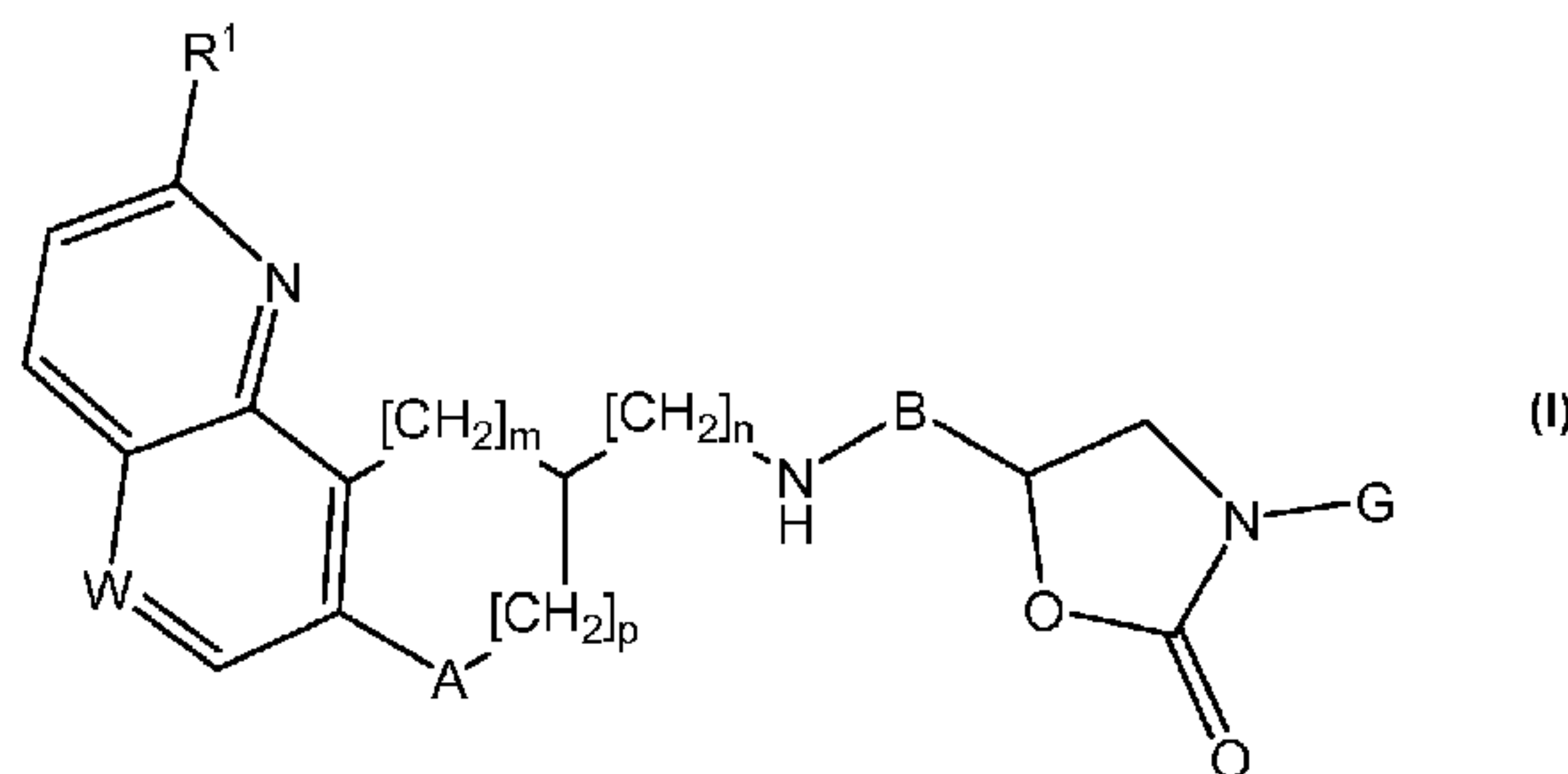
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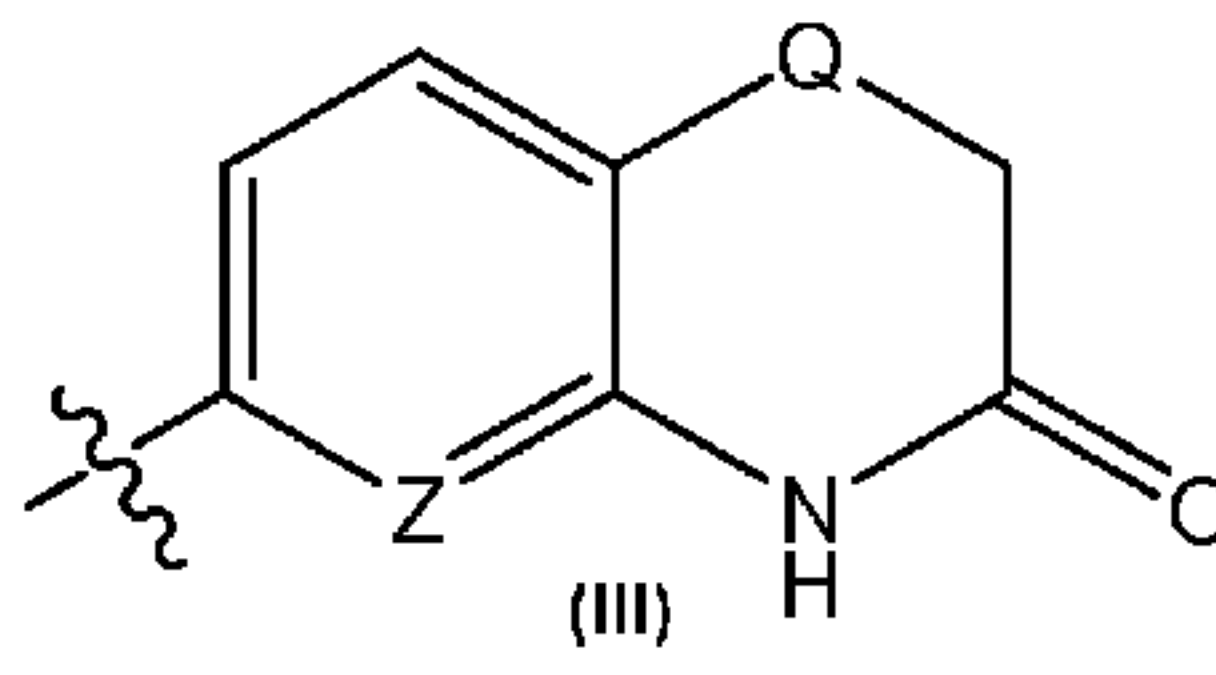
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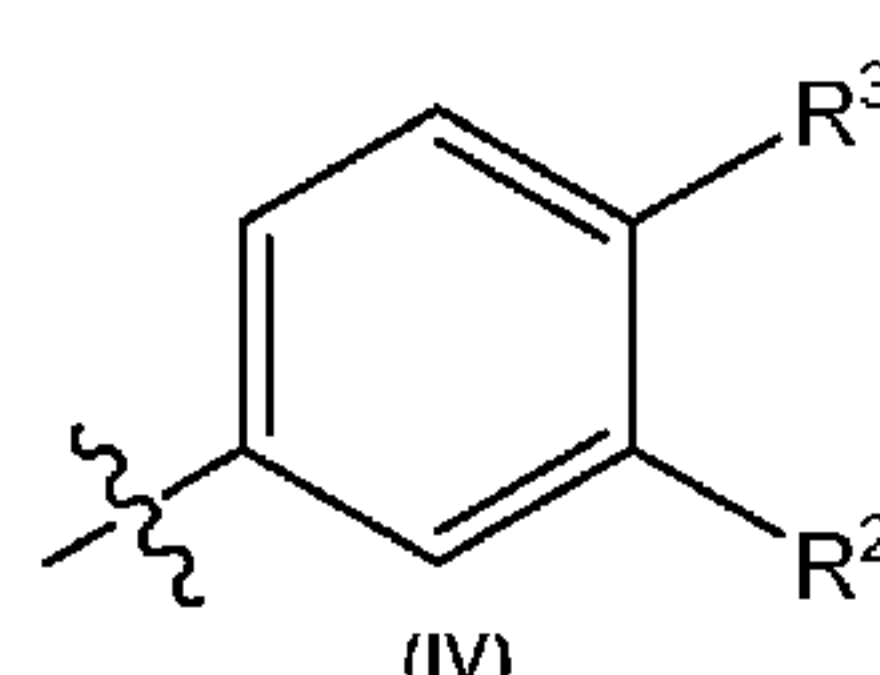
(54) Title: TRICYCLIC ALKYLAMINOMETHYLOXAZOLIDINONE DERIVATIVES



(II)



(III)



(IV)

(57) Abstract: The invention relates to antibacterial compounds of formula (I) wherein R^1 is alkoxy or halogen; W is CH or N; A is O or NH; B is CO or $(CH_2)_q$; G is a group having one of the three formulae (II), (III) and (IV) below wherein Q represents O or S, Z represents CH or N, R^2 represents halogen and R^3 represents alkyl; m is 0 or 1; and n is 1 or 2; p is 0 or 1, provided m and p are not each 0; and q is 1 or 2; and salts of such compounds.

TRICYCLIC ALKYLAMINOMETHYLOXAZOLIDINONE DERIVATIVES

The present invention concerns tricyclic alkylaminomethyloxazolidinone derivatives, a pharmaceutical antibacterial composition containing them and the use of these compounds in the manufacture of a medicament for the treatment of infections (e.g. bacterial
5 infections). These compounds are useful antimicrobial agents effective against a variety of human and veterinary pathogens including among others Gram-positive and Gram-negative aerobic and anaerobic bacteria and mycobacteria.

The intensive use of antibiotics has exerted a selective evolutionary pressure on microorganisms to produce genetically based resistance mechanisms. Modern medicine
10 and socio-economic behaviour exacerbates the problem of resistance development by creating slow growth situations for pathogenic microbes, e.g. in artificial joints, and by supporting long-term host reservoirs, e.g. in immuno-compromised patients.

In hospital settings, an increasing number of strains of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus spp.*, and *Pseudomonas aeruginosa*, major
15 sources of infections, are becoming multi-drug resistant and therefore difficult if not impossible to treat:

- *S. aureus* is resistant to β -lactams, quinolones and now even to vancomycin;
- *S. pneumoniae* is becoming resistant to penicillin or quinolone antibiotics and even to new macrolides;
- 20 - *Enterococci* are quinolone and vancomycin resistant and β -lactam antibiotics are inefficacious against these strains;
- *Enterobacteriaceae* are cephalosporin and quinolone resistant;
- *P. aeruginosa* are β -lactam and quinolone resistant.

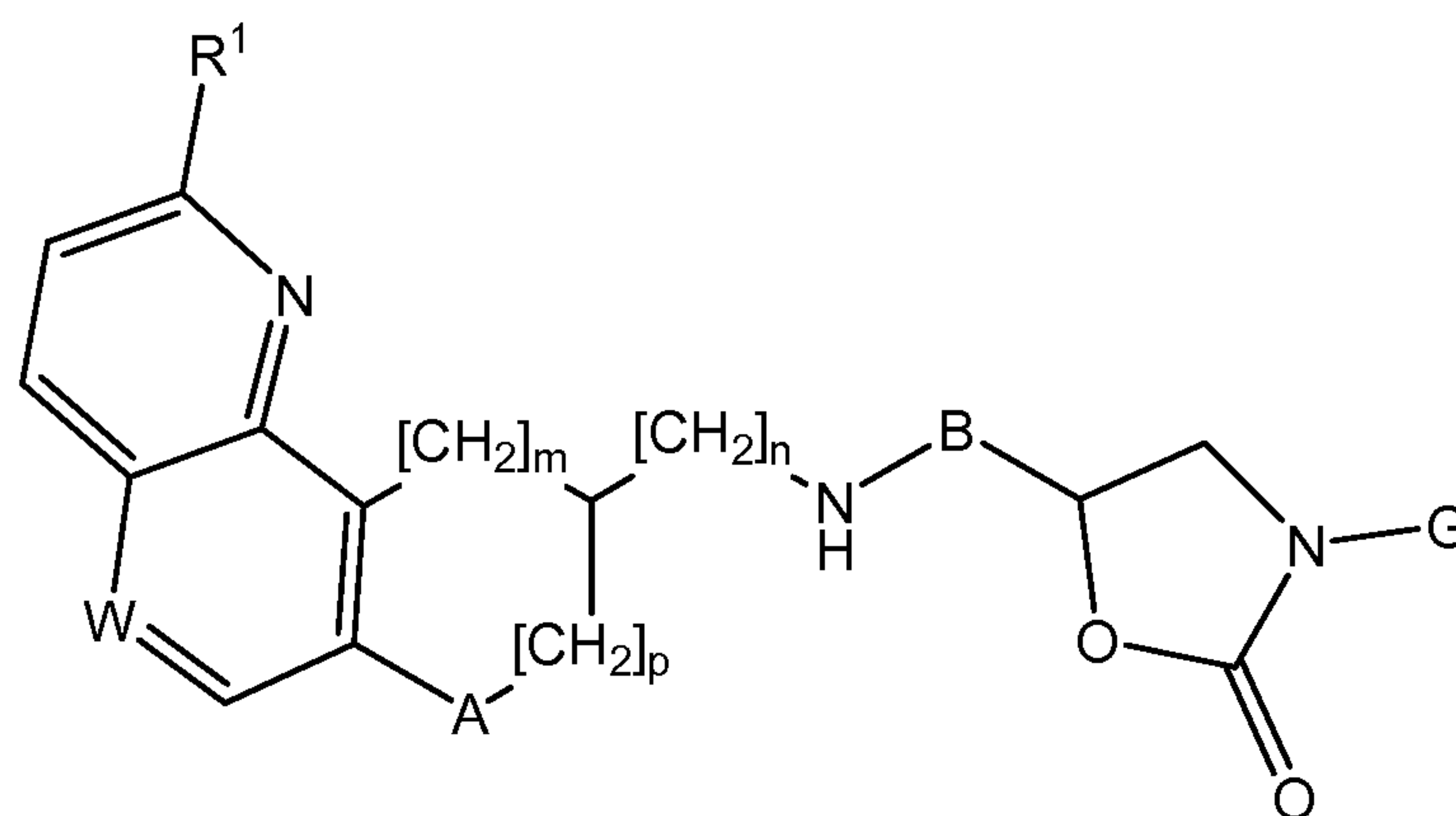
Furthermore, the incidence of multi-drug-resistant Gram-negative strains such as *Enterobacteriaceae* and *Pseudomonas aeruginosa*, is steadily increasing and new emerging organisms like *Acinetobacter spp.* or *Clostridium difficile*, which have been selected during therapy with the currently used antibiotics, are becoming a real problem in hospital settings. Therefore, there is a high medical need for new antibacterial agents which overcome multidrug-resistant Gram-negative bacilli such as *A. baumannii*, ESBL-producing *E. coli* and *Klebsiella* species and *Pseudomonas aeruginosa* (*Clinical Infectious Diseases* (2006), **42**, 657-68).

In addition, microorganisms that are causing persistent infections are increasingly being recognized as causative agents or cofactors of severe chronic diseases like peptic ulcers or heart diseases.

Certain antibacterial compounds comprising both a quinoline or naphthyridine moiety and an oxazolidinone group have been described in WO 2008/026172. In these compounds however, unlike the compounds of formula I described hereafter, the oxazolidinone is part of a spiro group and the quinoline or naphthyridine moiety is not part of a tricyclic group.

Various embodiments of the invention are presented hereafter.

i) The invention firstly relates to compounds of formula I



I

wherein

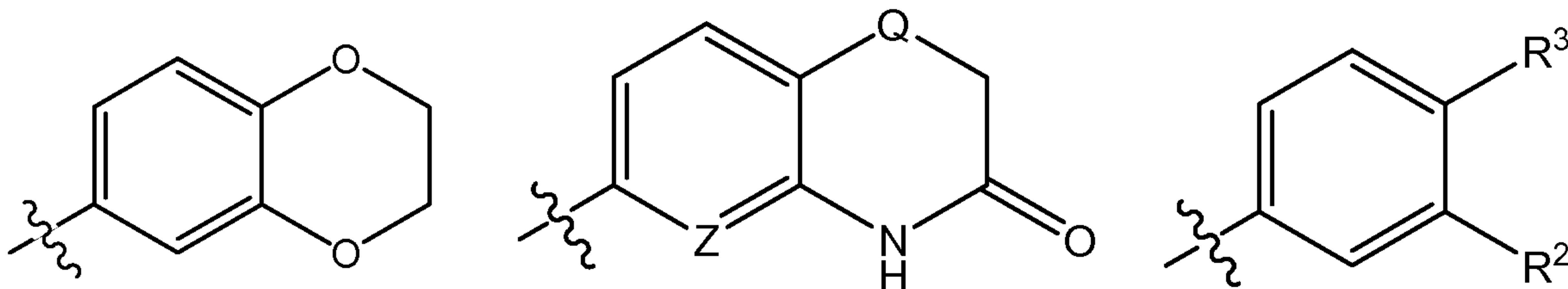
R^1 is alkoxy or halogen;

W is CH or N;

A is O or NH;

B is CO or (CH₂)_q;

G is a group having one of the three formulae below



wherein Q represents O or S, Z represents CH or N (notably CH), R² represents halogen (notably fluorine) and R³ represents alkyl;

5 m is 0 or 1;

n is 1 or 2;

p is 0 or 1, provided m and p are not each 0; and

q is 1 or 2;

and to salts (in particular pharmaceutically acceptable salts) of compounds of formula I.

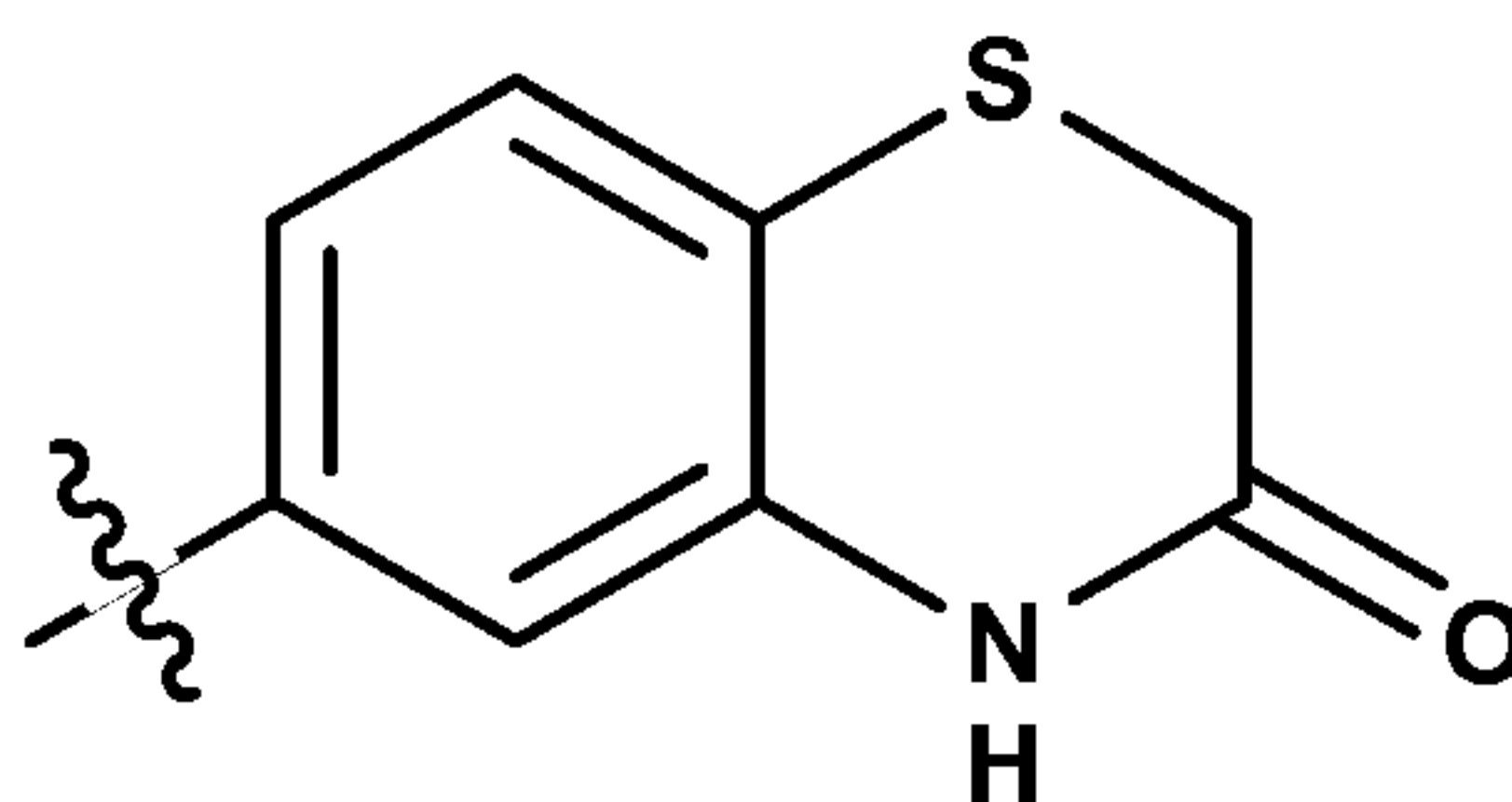
10 The following paragraphs provide definitions of the various chemical moieties for the compounds according to the invention and are intended to apply uniformly throughout the specification and claims, unless an otherwise expressly set out definition provides a broader or narrower definition:

❖ The term “alkyl”, used alone or in combination, refers to a saturated straight or
15 branched chain alkyl group containing from one to four carbon atoms. Representative examples of alkyl groups include methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl. The term “(C₁-C_x)alkyl” (x being an integer) refers to a straight or branched chain alkyl group containing 1 to x carbon atoms.

❖ The term “alkoxy”, used alone or in combination, refers to a saturated straight or
20 branched chain alkoxy group containing from one to four carbon atoms. Representative examples of alkoxy groups include methoxy, ethoxy, propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. The term “(C₁-C_x)alkoxy” refers to a straight or branched chain alkoxy group containing 1 to x carbon atoms.

❖ The term “halogen” refers to fluorine, chlorine, bromine or iodine, preferably to
25 fluorine or chlorine.

In this text, a bond interrupted by a wavy line shows a point of attachment of the radical drawn to the rest of the molecule. For example, the radical drawn below



is the 3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-6-yl group.

The compounds of formula I according to this invention may contain one or more
5 stereogenic or asymmetric centers, such as one or more asymmetric carbon atoms. The compounds of formula I may thus be present as mixtures of stereoisomers or, preferably, as pure stereoisomers. Mixtures of stereoisomers may be separated in a manner known to a person skilled in the art.

Whenever the absolute stereochemistry indication “(*R*)” or “(*S*)” is omitted in the name of
10 a compound although there is a corresponding asymmetric carbon atom, it is meant thereby that this compound name refers to either the (*R*)-configured compound or the (*S*)-configured compound.

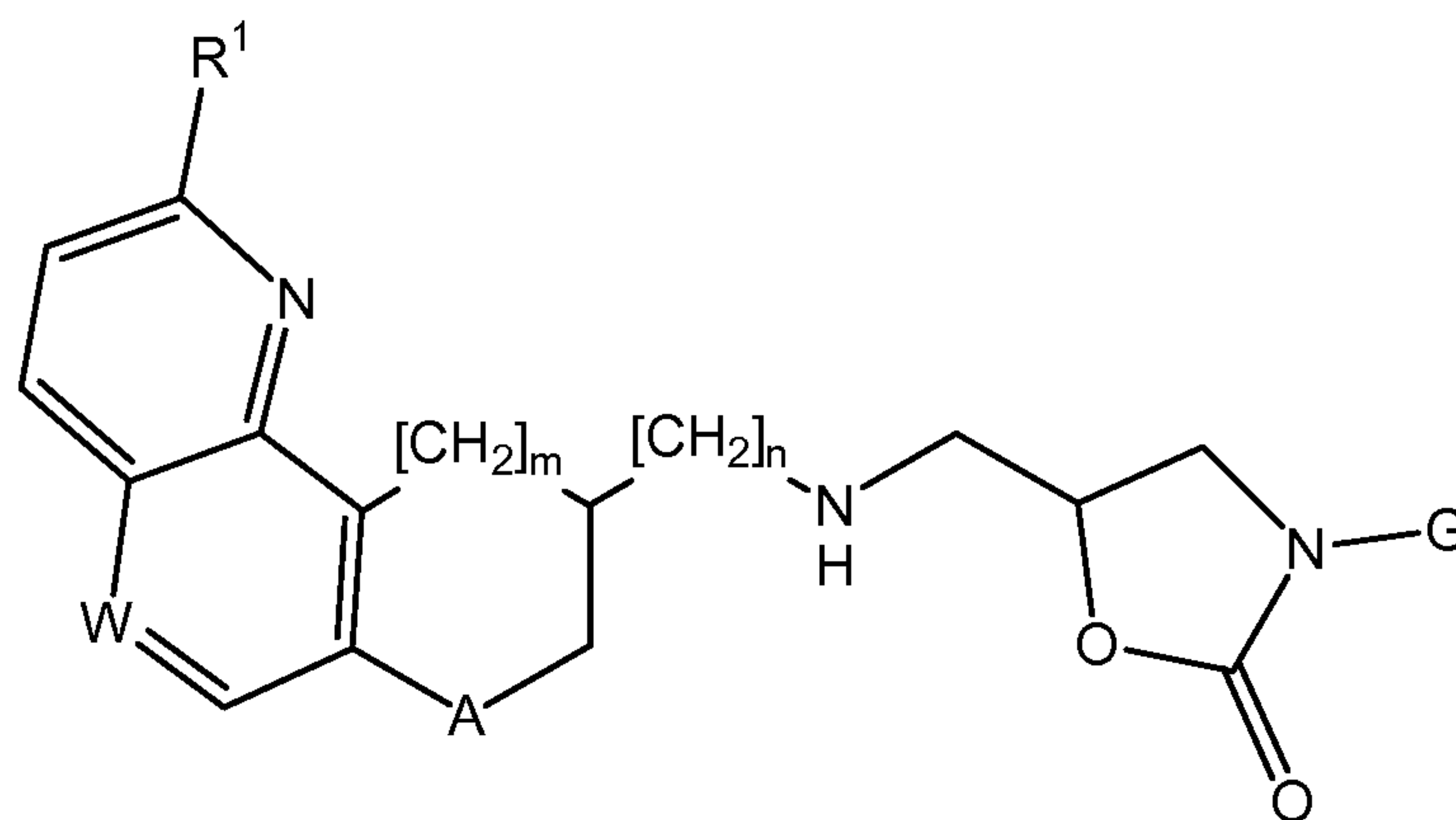
The present invention also includes isotopically labelled, especially ^2H (deuterium) labelled compounds of formula I, which compounds are identical to the compounds of
15 formula I except that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially ^2H (deuterium) labelled compounds of formula I and salts thereof are within the scope of the present invention. Substitution of hydrogen with the heavier isotope ^2H (deuterium) may lead to greater metabolic stability, resulting
20 e.g. in increased *in-vivo* half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one variant of the invention, the compounds of formula I are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-variant, the compounds of formula I are not isotopically labelled at all. Isotopically labelled compounds of formula I
25 may be prepared in analogy to the methods described hereinafter, but using the appropriate isotopic variation of suitable reagents or starting materials.

The term "pharmaceutically acceptable salts" refers to non-toxic, inorganic or organic acid and/or base addition salts. Reference can be made to "Salt selection for basic drugs", *Int. J. Pharm.* (1986), **33**, 201-217.

Besides, the term "room temperature" as used herein refers to a temperature of 25°C.

- 5 Unless used regarding temperatures, the term "about" placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term "about" placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus
10 10°C to Y plus 10°C, and preferably to an interval extending from Y minus 5°C to Y plus 5°C.

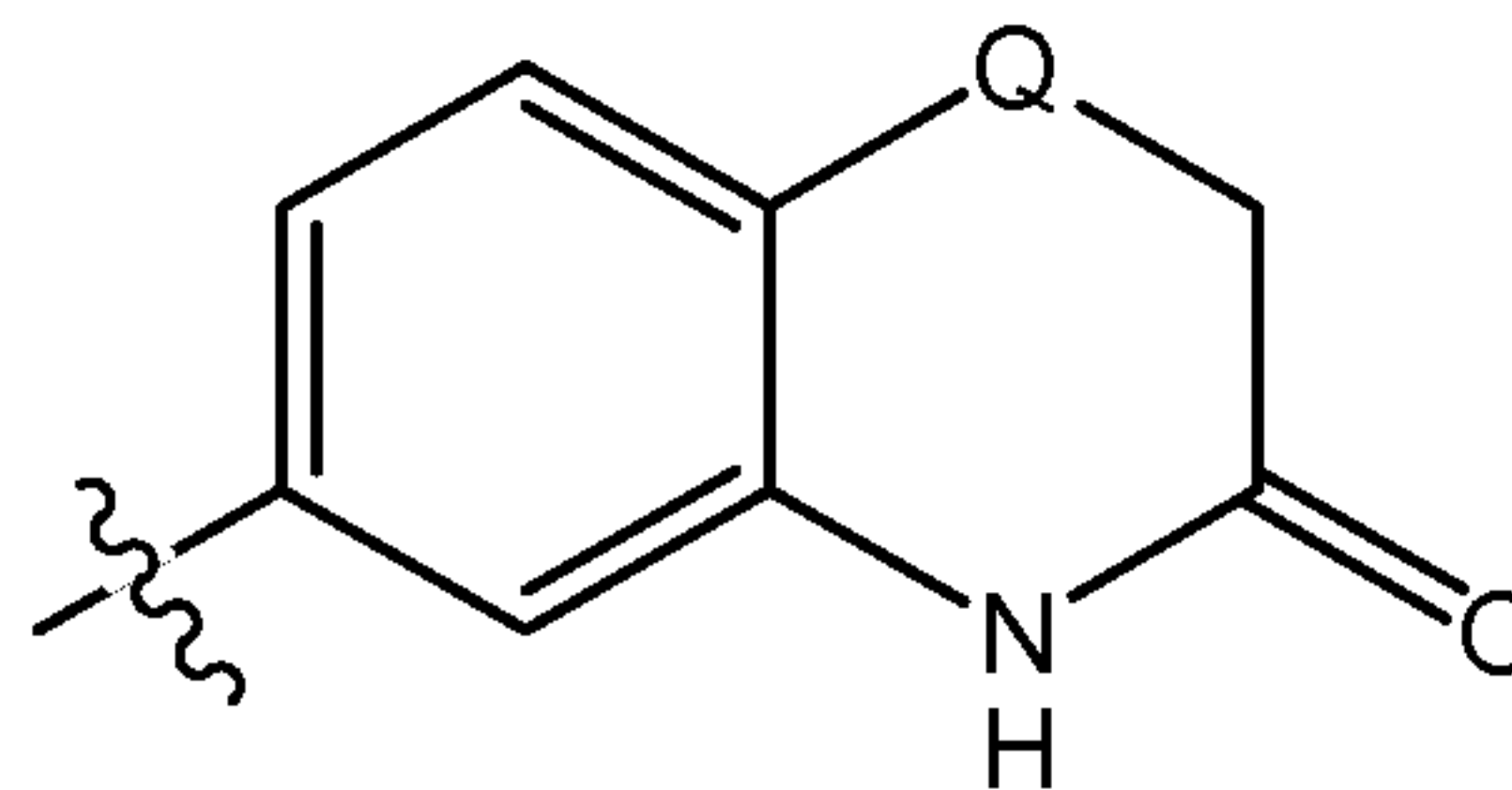
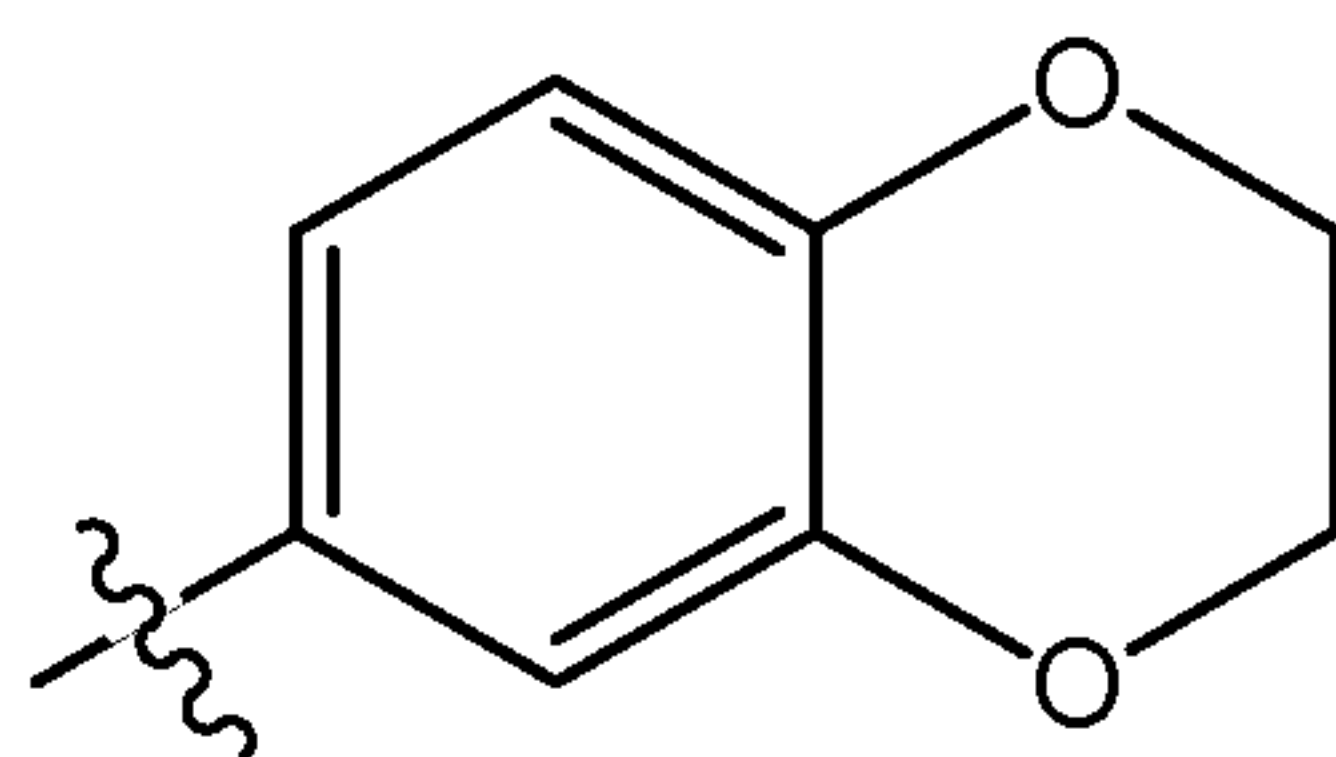
ii) The invention furthermore relates to compounds of formula I as defined in embodiment i) that are also compounds of formula I_p

I_p

wherein

- 15 R¹ is alkoxy or halogen;
W is CH or N;
A is O or NH;

G is a group having one of the two formulae below



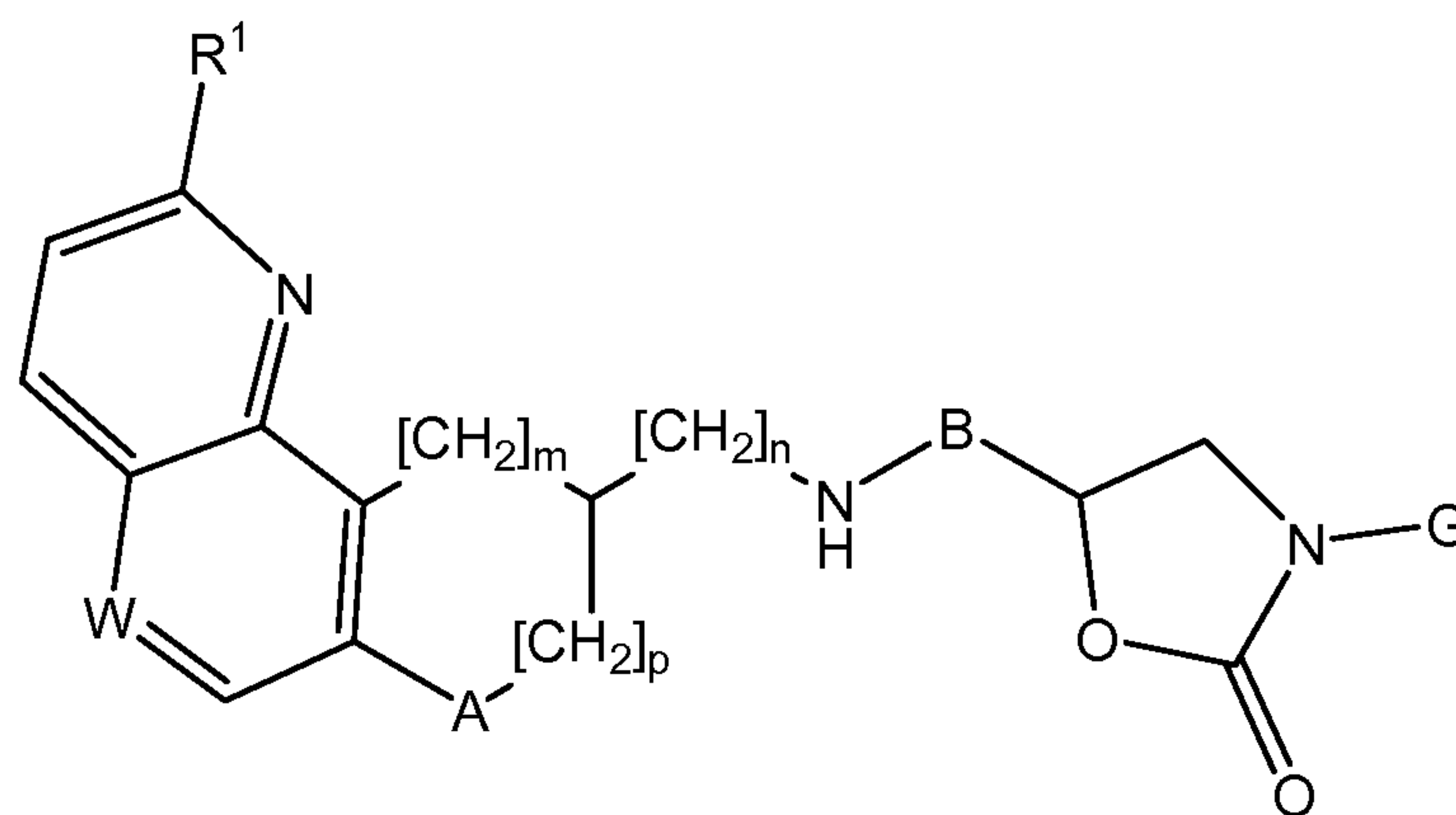
wherein Q represents O or S;

m is 0 or 1; and

n is 1 or 2;

5 and to salts (in particular pharmaceutically acceptable salts) of compounds of formula I_p.

iii) In particular, the invention relates to compounds of formula I as defined in embodiment i) that are also compounds of formula I_{CE}



I_{CE}

wherein

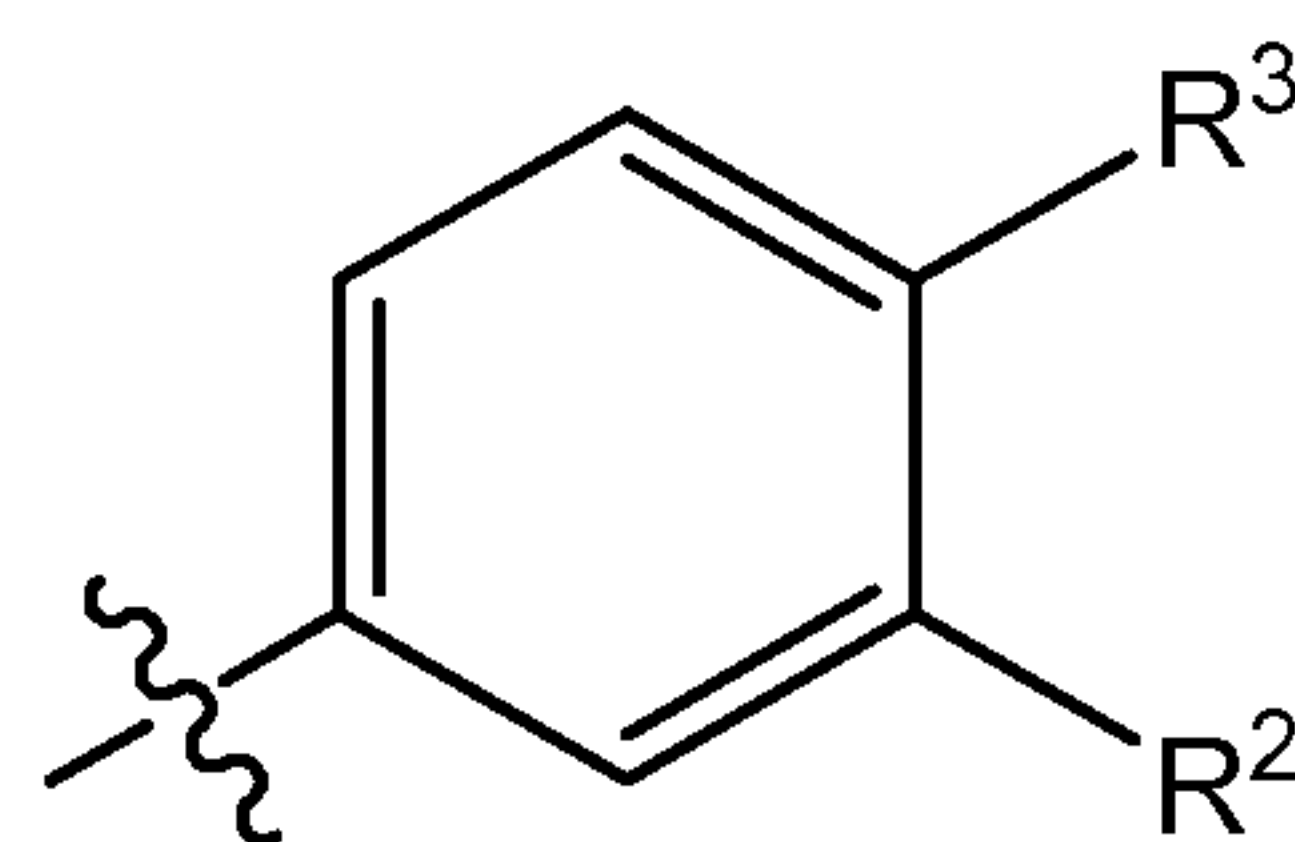
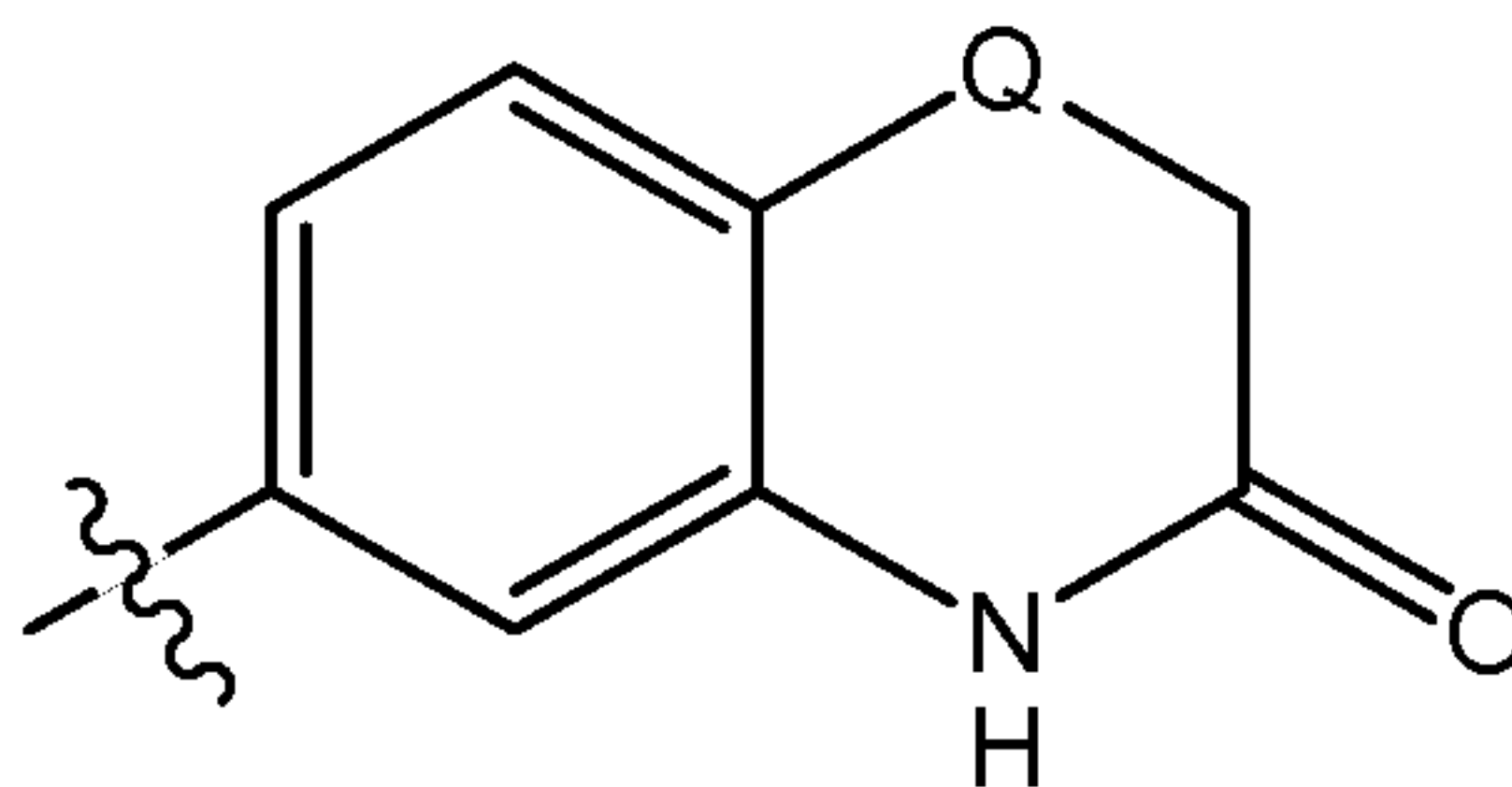
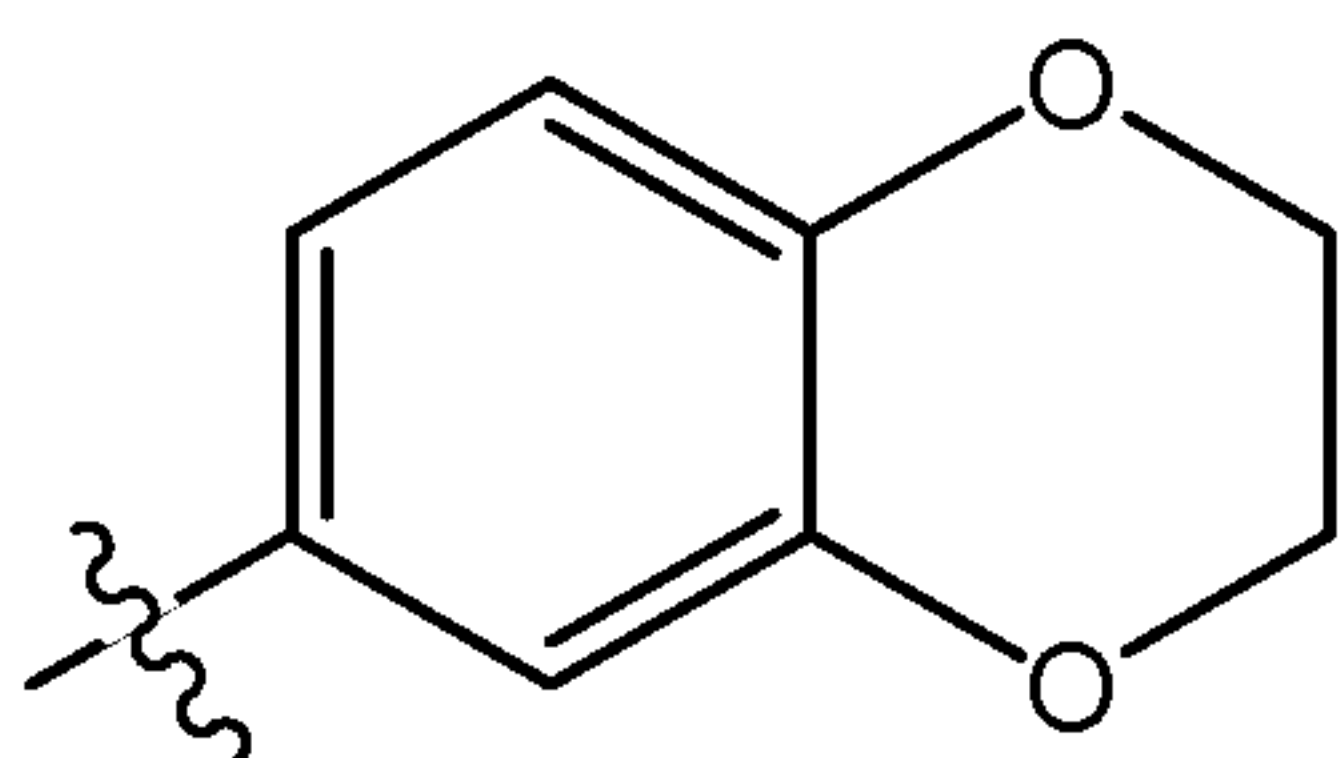
R¹ is alkoxy (especially methoxy);

10 W is CH or N;

A is O or NH;

B is CO or (CH₂)_q;

G is a group of the formula



wherein Q represents O or S, R^2 represents halogen (notably fluorine) and R^3 represents alkyl (notably methyl);

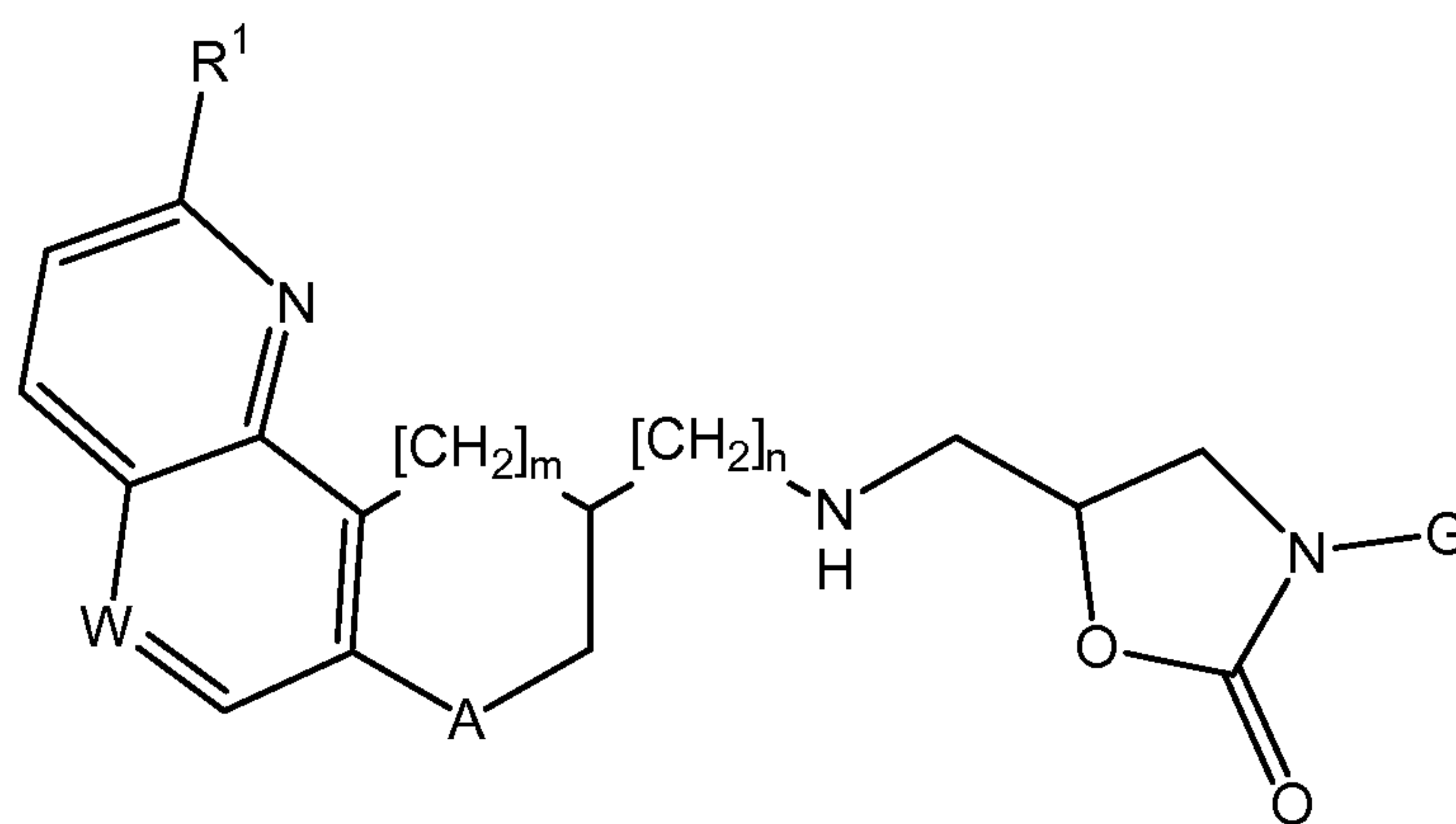
m is 0 and n is 1 or 2 or m is 1 and n is 1;

p is 0 or 1, provided m and p are not each 0; and

5 q is 1 or 2;

and to salts (in particular pharmaceutically acceptable salts) of compounds of formula I_{CE}.

iv) The invention furthermore relates to compounds of formula I_P as defined in embodiment ii) that are also compounds of formula I_{CEP}



I_{CEP}

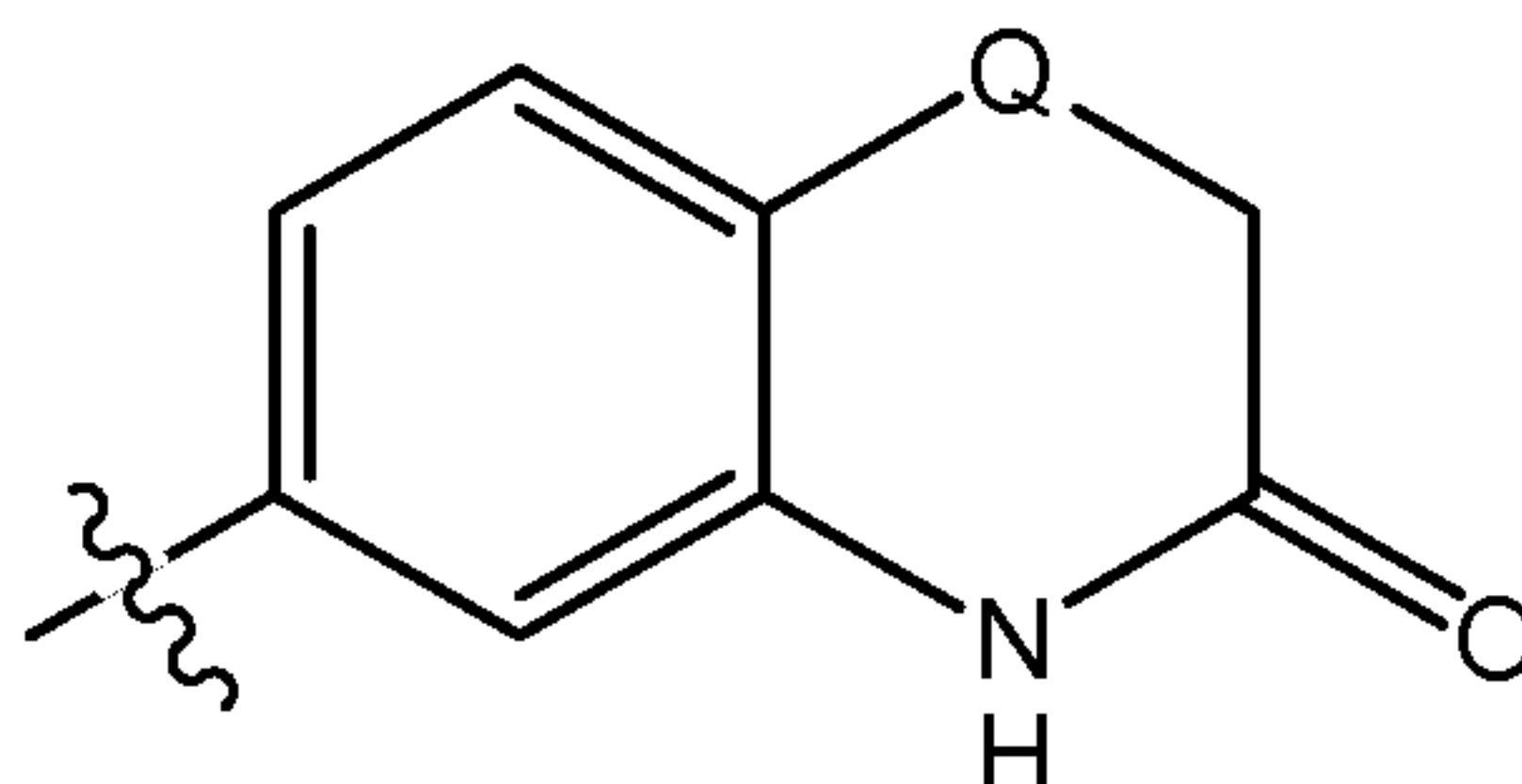
wherein

10 R^1 is alkoxy (especially methoxy);

W is CH or N;

A is O or NH;

G is a group of the formula



wherein Q represents O or S;

15 m is 0 and n is 1 or 2 or m is 1 and n is 1;

and to salts (in particular pharmaceutically acceptable salts) of compounds of formula I_{CEP}.

v) According to a preferred embodiment of this invention, the compounds of formula I as defined in one of embodiments i) to iv) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that R¹ is (C₁-C₄)alkoxy or fluorine (and preferably (C₁-C₃)alkoxy, in particular methoxy or ethoxy, especially methoxy) in the case of compounds of formula I as defined in embodiment i) or iii) or salts thereof, or such that R¹ is (C₁-C₄)alkoxy (and preferably (C₁-C₃)alkoxy, in particular methoxy or ethoxy, especially methoxy) in the case of compounds of formula I as defined in embodiment ii) or iv) or salts thereof.

vi) Another embodiment of this invention relates to the compounds of formula I as defined in one of embodiments i) to v) above or their salts (among which the pharmaceutically acceptable salts will be preferred) wherein W is CH.

vii) Yet another embodiment of this invention relates to the compounds of formula I as defined in one of embodiments i) to v) above or their salts (among which the pharmaceutically acceptable salts will be preferred) wherein W is N.

viii) According to one main variant of this invention, the compounds of formula I as defined in one of embodiments i) to vii) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that A is O (and notably such that A is O and p, if present, is 1).

ix) According to the other main variant of this invention, the compounds of formula I as defined in one of embodiments i) to vii) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that A is NH (and notably such that A is NH and each of m and p, if present, is 1).

x) According to one particular embodiment of this invention, the compounds of formula I as defined in one of embodiments i) to ix) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that p, if present, is 0 and m is 1.

xi) According to another particular embodiment of this invention, the compounds of formula I as defined in one of embodiments i) to ix) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that p, if present, is 1.

xii) One sub-embodiment of embodiment xi) relates to the compounds of formula I as defined in embodiment xi) above or their salts (among which the pharmaceutically acceptable salts will be preferred) wherein m is 0, n is 1 and B, if present, is $(CH_2)_q$, q being 1.

5 xiii) Another sub-embodiment of embodiment xi) relates to the compounds of formula I as defined in embodiment xi) above or their salts (among which the pharmaceutically acceptable salts will be preferred) wherein m is 0, n is 2 and B, if present, is $(CH_2)_q$, q being 1.

10 xiv) Yet another sub-embodiment of embodiment xi) relates to the compounds of formula I as defined in embodiment xi) above or their salts (among which the pharmaceutically acceptable salts will be preferred) wherein m is 1, n is 1 and B, if present, is $(CH_2)_q$, q being 1.

15 xv) Yet a further sub-embodiment of embodiment xi) relates to the compounds of formula I as defined in embodiment xi) above or their salts (among which the pharmaceutically acceptable salts will be preferred) wherein B, if present, is $(CH_2)_q$, q being 2 (and notably such that m is 0, n is 2 and B, if present, is $(CH_2)_q$, q being 2).

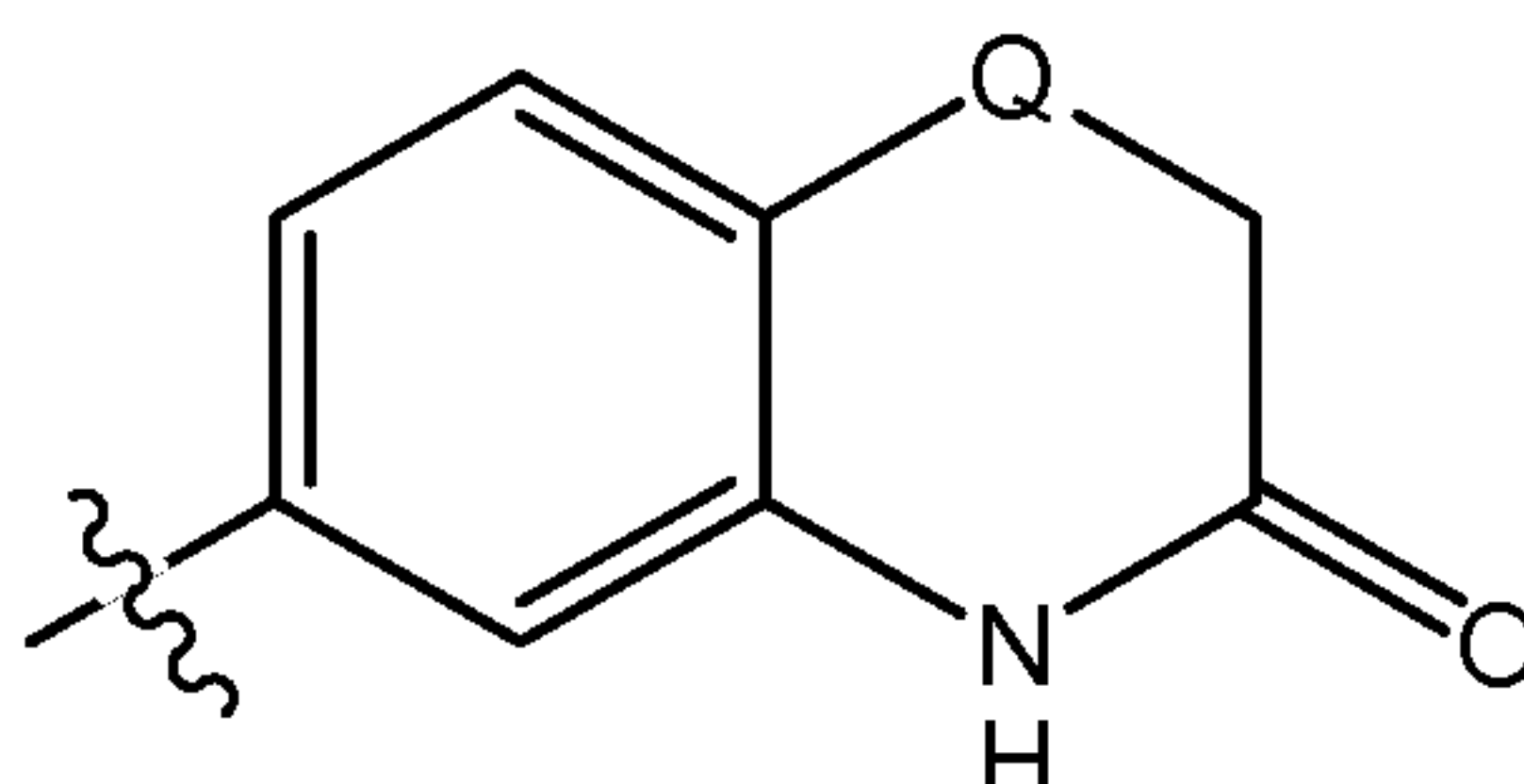
20 xvi) According to one main embodiment of this invention, the compounds of formula I as defined in embodiment i) or iii) above or in any of embodiments v) to xi) taken together with embodiment i) or iii) above, or their salts (among which the pharmaceutically acceptable salts will be preferred), will be such that B is CO.

xvii) According to another main embodiment of this invention, the compounds of formula I as defined in one of embodiments i) to xv) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that B, if present, is $(CH_2)_q$.

25 xviii) One sub-embodiment of embodiment xvii) relates to the compounds of formula I as defined in embodiment xvii) above or their salts (among which the pharmaceutically acceptable salts will be preferred) wherein q is 1 (and notably such that n is 1 and q is 1).

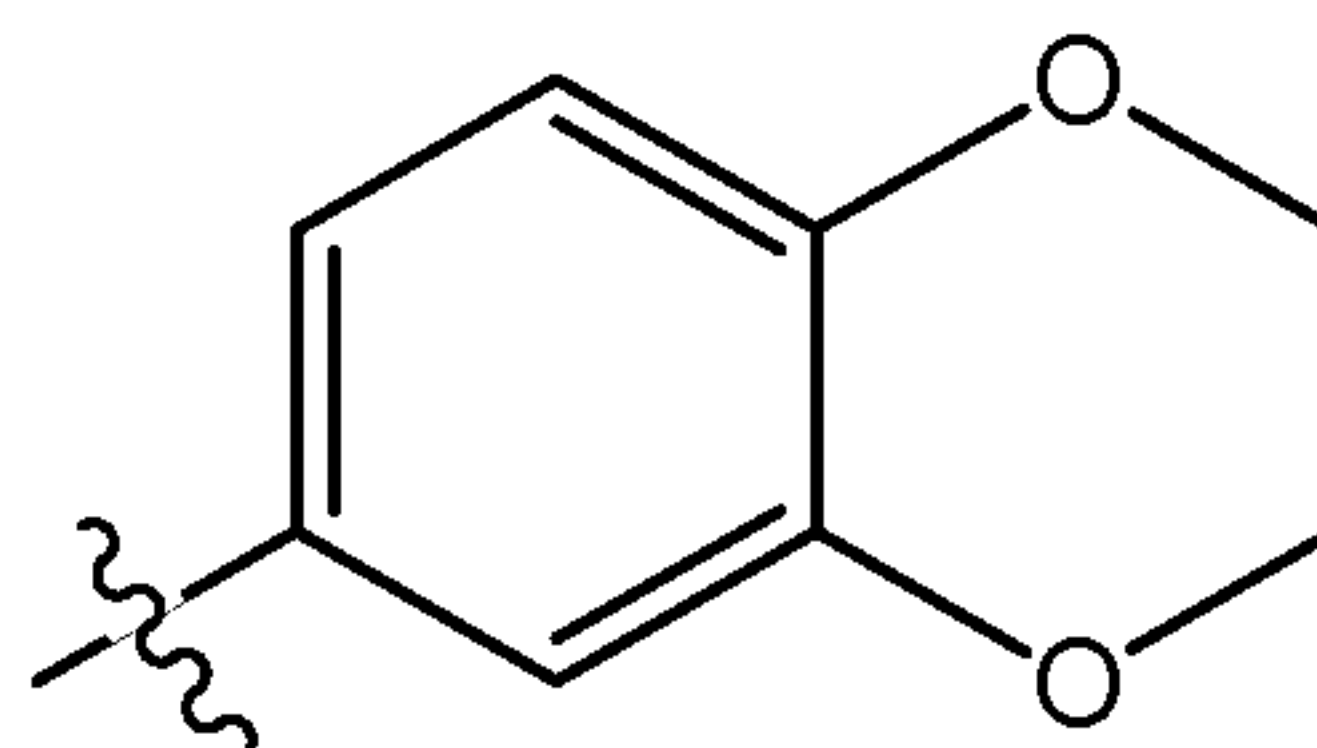
xix) The other sub-embodiment of embodiment xvii) relates to the compounds of formula I as defined in embodiment xvii) above or their salts (among which the pharmaceutically acceptable salts will be preferred) wherein q is 2.

xx) Preferably, the compounds of formula I as defined in embodiments i) to xix) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that G represents a group of the formula

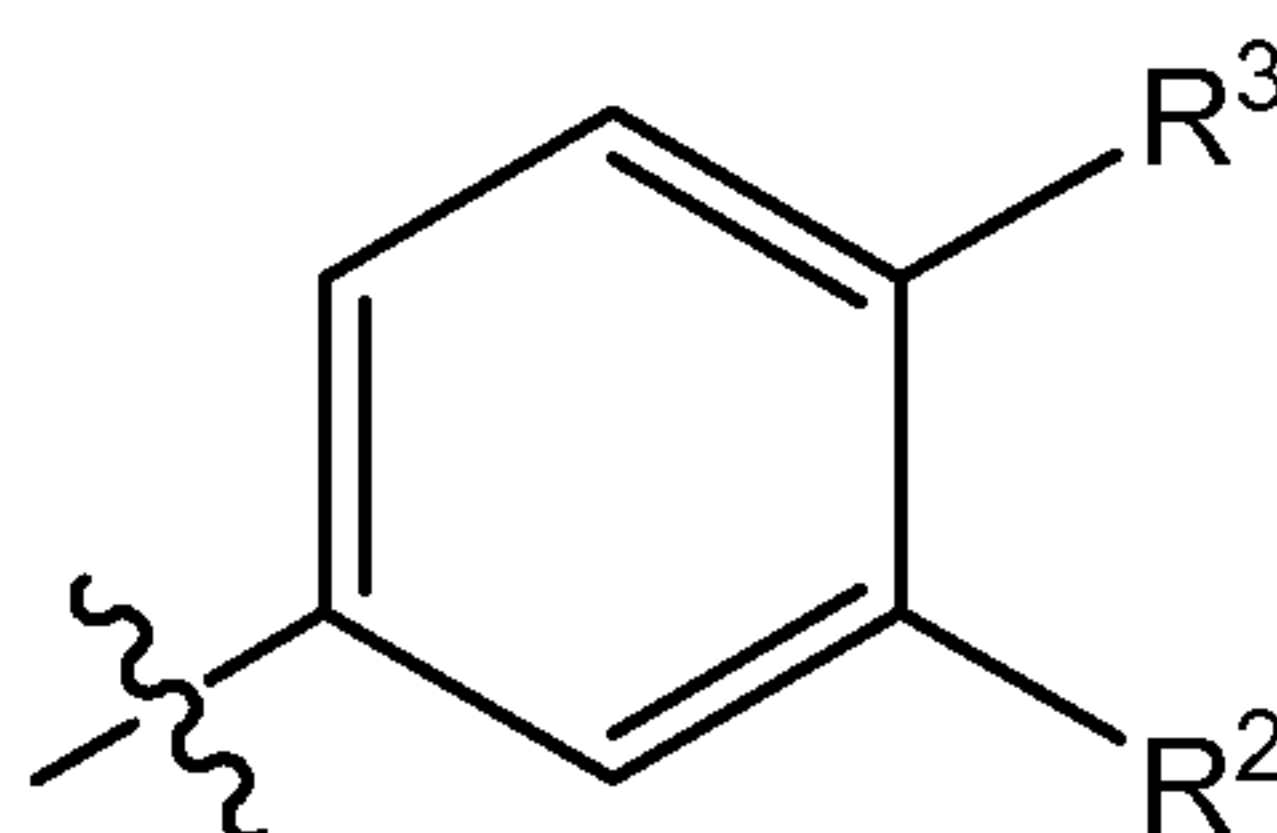


wherein Q represents O or S.

xxi) As an alternative, the compounds of formula I as defined in embodiments i) to xix) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that G represents a group of the formula

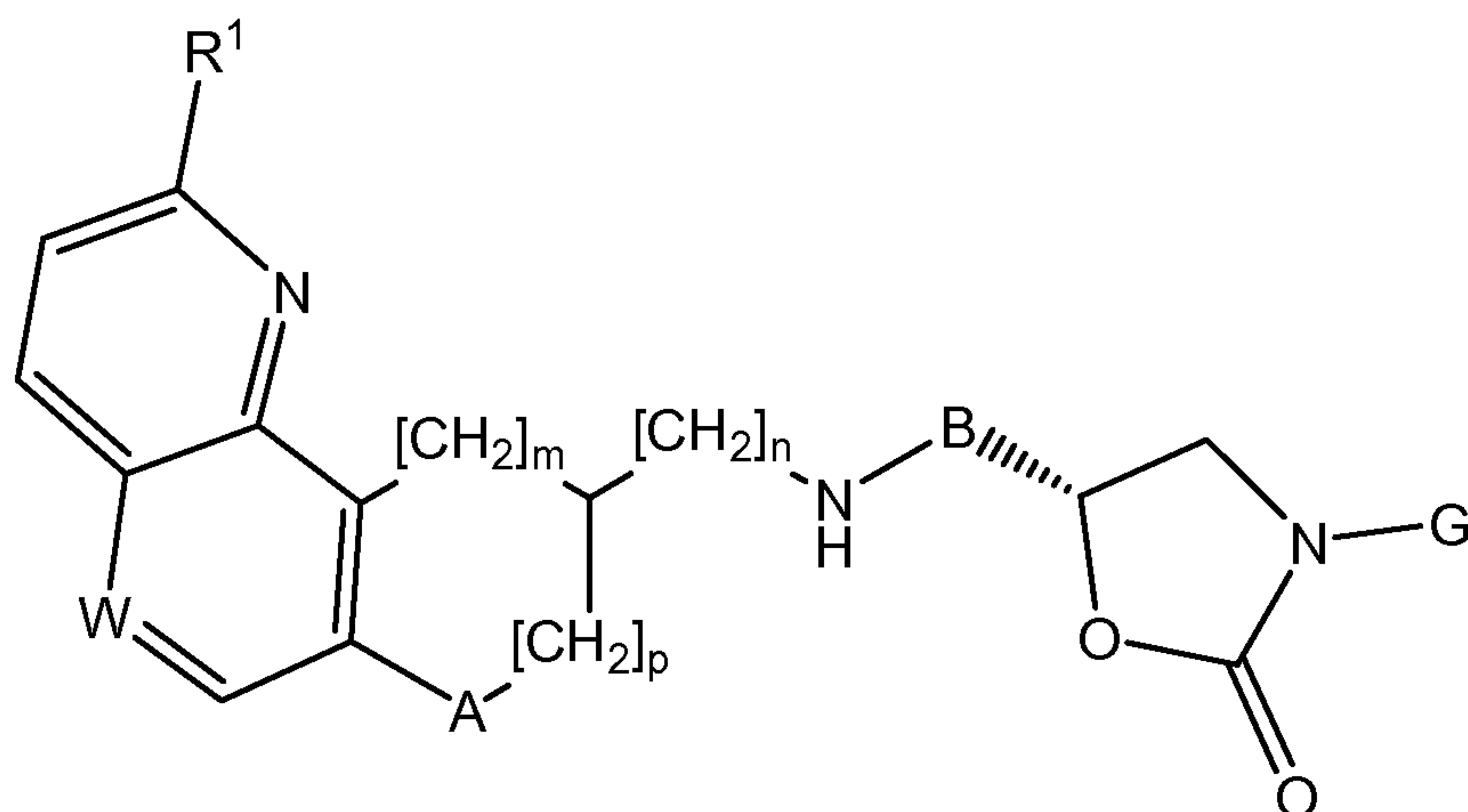


xxii) As a further alternative, the compounds of formula I as defined in embodiment i) or iii) above or in any of embodiments v) to xix) taken together with embodiment i) or iii) above, or their salts (among which the pharmaceutically acceptable salts will be preferred), will be such that G represents a group of the formula

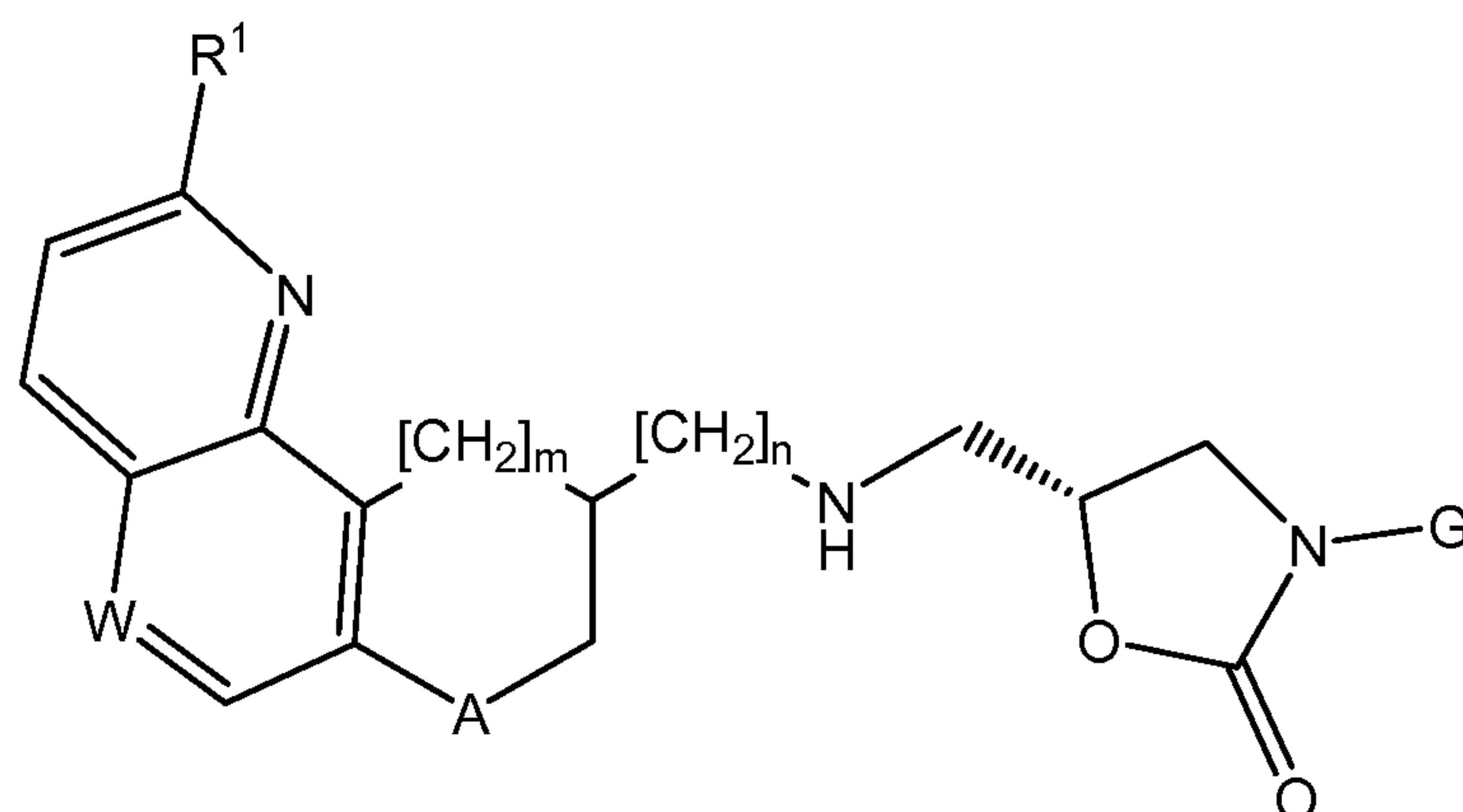


wherein R^2 represents halogen (preferably fluorine) and R^3 represents alkyl (preferably methyl).

xxiii) Preferably also, the compounds of formula I as defined in embodiments i) to xxii) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that their stereochemistry is as drawn below



or, in the particular cases of compounds of formula I_p or I_{CEP}



5 xxiv) Particularly preferred are the following compounds of formula I as defined in one of embodiments i) to iv):

- 6-((*R*)-5-{[(6-methoxy-3,4-dihydro-2*H*-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-((*R*)-5-{[(6-methoxy-3,4-dihydro-2*H*-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 10 - 6-((*R*)-5-{[(6-methoxy-3,4-dihydro-2*H*-1-oxa-5,9-diaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 6-((*R*)-5-{[(6-methoxy-3,4-dihydro-2*H*-1-oxa-5,9-diaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

- 6-((*R*)-5-{[(6-methoxy-1,2,3,4-tetrahydro-1,5,9-triaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-((*R*)-5-{[2-(2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 5 - 6-((*R*)-5-{[2-(2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 6-((*R*)-5-{[(2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

as well as the salts (in particular the pharmaceutically acceptable salts) thereof.

- 10 xxv) A further object of this invention thus relates to the following compounds of formula I as defined in one of embodiments i) to iv) :

- 6-((*R*)-5-{[(*R*)-6-methoxy-3,4-dihydro-2*H*-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-((*R*)-5-{[(*S*)-6-methoxy-3,4-dihydro-2*H*-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 15 - 6-((*R*)-5-{[(*R*)-6-methoxy-3,4-dihydro-2*H*-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 6-((*R*)-5-{[(*S*)-6-methoxy-3,4-dihydro-2*H*-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 20 - 6-((*R*)-5-{[(*R*)-6-methoxy-3,4-dihydro-2*H*-1-oxa-5,9-diaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 6-((*R*)-5-{[(*S*)-6-methoxy-3,4-dihydro-2*H*-1-oxa-5,9-diaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 6-((*R*)-5-{[(*R*)-6-methoxy-3,4-dihydro-2*H*-1-oxa-5,9-diaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 25 - 6-((*R*)-5-{[(*S*)-6-methoxy-3,4-dihydro-2*H*-1-oxa-5,9-diaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-((*R*)-5-{[(*R*)-6-methoxy-1,2,3,4-tetrahydro-1,5,9-triaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 30 - 6-((*R*)-5-{[(*S*)-6-methoxy-1,2,3,4-tetrahydro-1,5,9-triaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

- 6-((*R*)-5-{[2-((*R*)-2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

- 6-((*R*)-5-{[2-((*S*)-2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

5 - 6-((*R*)-5-{[2-((*R*)-2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;

- 6-((*R*)-5-{[2-((*S*)-2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;

10 - 6-((*R*)-5-{[2-((*R*)-2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

- 6-((*R*)-5-{[2-((*S*)-2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

as well as to the salts (in particular the pharmaceutically acceptable salts) thereof.

xxvi) Further particularly preferred compounds of formula I as defined in embodiment i)

15 or iii) are the following compounds:

- 6-((*R*)-5-{[2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

- 6-((*R*)-5-{[2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;

20 - (*R*)-3-(3-fluoro-4-methyl-phenyl)-5-{[2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-oxazolidin-2-one;

- 6-((*S*)-5-{[2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

25 - 6-((*R*)-5-{2-[2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

- 6-((*R*)-5-{2-[(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

- 6-((*S*)-5-{2-[(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

30 - (*S*)-3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-2-oxo-oxazolidine-5-carboxylic acid
[2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethyl]-amide;

- 6-((*R*)-5-{[(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-((*R*)-5-{2-[(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 5 - 6-((*R*)-5-{2-[(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-5-{[2-((*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-oxazolidin-2-one;

as well as the salts (in particular the pharmaceutically acceptable salts) thereof.

- 10 xxvii) A further object of this invention thus relates to the following compounds of formula I as defined in embodiment i) or iii):

- 6-((*R*)-5-{[2-((*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-((*R*)-5-{[2-((*S*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 15 - 6-((*R*)-5-{[2-((*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 6-((*R*)-5-{[2-((*S*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 20 - (*R*)-3-(3-fluoro-4-methyl-phenyl)-5-{[2-((*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-oxazolidin-2-one;
- (*R*)-3-(3-fluoro-4-methyl-phenyl)-5-{[2-((*S*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-oxazolidin-2-one;
- 6-((*S*)-5-{[2-((*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 25 - 6-((*S*)-5-{[2-((*S*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-((*R*)-5-{2-[2-((*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 30 - 6-((*R*)-5-{2-[2-((*S*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

- 6-((*R*)-5-{2-[(*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-((*R*)-5-{2-[(*S*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 5 - 6-((*S*)-5-{2-[(*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-((*S*)-5-{2-[(*S*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- (*S*)-3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-2-oxo-oxazolidine-5-carboxylic acid
- 10 [2-((*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethyl]-amide;
- (*S*)-3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-2-oxo-oxazolidine-5-carboxylic acid
- [2-((*S*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethyl]-amide;
- 15 - 6-((*R*)-5-{[(*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-((*R*)-5-{[(*S*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-((*R*)-5-{2-[(*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 20 - 6-((*R*)-5-{2-[(*S*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
- 6-((*R*)-5-{2-[(*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- 25 - 6-((*R*)-5-{2-[(*S*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
- (*R*)-3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-5-{[2-((*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-oxazolidin-2-one;
- (*S*)-3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-5-{[2-((*R*)-8-methoxy-1,2-dihydro-3-oxa-
- 30 5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-oxazolidin-2-one;

as well as to the salts (in particular the pharmaceutically acceptable salts) thereof.

xxxviii) The invention further relates to the compounds of formula I as defined in embodiment i) or iii) which are selected from the group consisting of the compounds listed in embodiment xxxiv) and the compounds listed in embodiment xxxvi), as well as to the salts (in particular the pharmaceutically acceptable salts) of such compounds.

- 5 xxxix) The invention moreover relates to the compounds of formula I as defined in embodiment i) or iii) which are selected from the group consisting of the compounds listed in embodiment xxxv) and the compounds listed in embodiment xxxvii), as well as to the salts (in particular the pharmaceutically acceptable salts) of such compounds.

10 The compounds of formula I according to the invention, i.e. according to one of embodiments i) to xxxix), are suitable for the use as chemotherapeutic active compounds in human and veterinary medicine and as substances for preserving inorganic and organic materials in particular all types of organic materials for example polymers, lubricants, paints, fibres, leather, paper and wood.

15 The compounds of formula I according to the invention are particularly active against bacteria and bacteria-like organisms. They are therefore particularly suitable in human and veterinary medicine for the prophylaxis and chemotherapy of local and systemic infections caused by these pathogens as well as disorders related to bacterial infections comprising pneumonia, otitis media, sinusitis, bronchitis, tonsillitis, and mastoiditis related to infection by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*,
20 *Staphylococcus aureus*, *Enterococcus faecalis*, *E. faecium*, *E. casseliflavus*, *S. epidermidis*, *S. haemolyticus*, or *Peptostreptococcus spp.*; pharyngitis, rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes*, Groups C and G streptococci, *Corynebacterium diphtheriae*, or *Actinobacillus haemolyticum*; respiratory tract infections related to infection by *Mycoplasma pneumoniae*, *Legionella pneumophila*,
25 *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Chlamydia pneumoniae*; blood and tissue infections, including endocarditis and osteomyelitis, caused by *S. aureus*, *S. haemolyticus*, *E. faecalis*, *E. faecium*, *E. durans*, including strains resistant to known antibacterials such as, but not limited to, beta-lactams, vancomycin, aminoglycosides, quinolones, chloramphenicol, tetracyclines and macrolides; uncomplicated skin and soft
30 tissue infections and abscesses, and puerperal fever related to infection by *Staphylococcus aureus*, coagulase-negative staphylococci (i.e., *S. epidermidis*, *S. haemolyticus*, etc.),

Streptococcus pyogenes, *Streptococcus agalactiae*, Streptococcal groups C-F (minute colony streptococci), viridans streptococci, *Corynebacterium minutissimum*, *Clostridium* spp., or *Bartonella henselae*; uncomplicated acute urinary tract infections related to infection by *Staphylococcus aureus*, coagulase-negative staphylococcal species, or
5 *Enterococcus* spp.; urethritis and cervicitis; sexually transmitted diseases related to infection by *Chlamydia trachomatis*, *Haemophilus ducreyi*, *Treponema pallidum*, *Ureaplasma urealyticum*, or *Neisseria gonorrhoeae*; toxin diseases related to infection by *S. aureus* (food poisoning and toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by *Helicobacter pylori*; systemic febrile syndromes related to
10 infection by *Borrelia recurrentis*; Lyme disease related to infection by *Borrelia burgdorferi*; conjunctivitis, keratitis, and dacrocystitis related to infection by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium*, or *Mycobacterium intracellulare*; infections caused by
15 *Mycobacterium tuberculosis*, *M. leprae*, *M. paratuberculosis*, *M. kansasii*, or *M. chelonae*; gastroenteritis related to infection by *Campylobacter jejuni*; intestinal protozoa related to infection by *Cryptosporidium* spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by *Bordetella pertussis*; gas gangrene related to infection by *Clostridium perfringens* or *Bacteroides* spp.; and atherosclerosis or
20 cardiovascular disease related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae*.

The compounds of formula I according to the present invention are further useful for the preparation of a medicament for the treatment of infections that are mediated by bacteria such as *E. coli*, *Klebsiella pneumoniae* and other Enterobacteriaceae, *Acinetobacter* spp.
25 including *Acinetobacter baumannii*, *Stenothrophomonas maltophilia*, *Neisseria meningitidis*, *Bacillus cereus*, *Bacillus anthracis*, *Clostridium difficile*, *Corynebacterium* spp., *Propionibacterium acnes* and bacteroides spp.

The compounds of formula I according to the present invention are further useful to treat protozoal infections caused by *Plasmodium malaria*, *Plasmodium falciparum*, *Toxoplasma*
30 *gondii*, *Pneumocystis carinii*, *Trypanosoma brucei* and *Leishmania* spp.

The present list of pathogens is to be interpreted merely as examples and in no way as limiting.

The compounds of formula I according to this invention, or the pharmaceutically acceptable salt thereof, may be used for the preparation of a medicament, and are suitable, for the prevention or treatment (and notably for the treatment) of a bacterial infection.

One aspect of this invention therefore relates to the use of a compound of formula I according to one of embodiments i) to xxxix), or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment (and notably for the treatment) of a bacterial infection. Another aspect of this invention relates to a compound of formula I according to one of embodiments i) to xxxix), or of a pharmaceutically acceptable salt thereof, for the prevention or treatment (and notably for the treatment) of a bacterial infection.

Accordingly, the compounds of formula I according to one of embodiments i) to xxxix), or the pharmaceutically acceptable salts thereof, may be used for the preparation of a medicament, and are suitable, for the prevention or treatment (and notably for the treatment) of a bacterial infection selected from the group consisting of respiratory tract infections, otitis media, meningitis, skin and soft tissue infections (whether complicated or uncomplicated), pneumonia (including hospital acquired pneumonia), bacteremia, endocarditis, intraabdominal infections, gastrointestinal infections, *Clostridium difficile* infections, urinary tract infections, sexually transmitted infections, foreign body infections, osteomyelitis, lyme disease, topical infections, ophthalmological infections, tuberculosis and tropical diseases (e.g. malaria), and notably for the prevention or treatment (especially for the treatment) of a bacterial infection selected from the group consisting of respiratory tract infections, otitis media, meningitis, skin and soft tissue infections (whether complicated or uncomplicated), pneumonia (including hospital acquired pneumonia) and bacteremia.

As well as in humans, bacterial infections can also be treated using compounds of formula I (or pharmaceutically acceptable salts thereof) in other species like pigs, ruminants, horses, dogs, cats and poultry.

The present invention also relates to pharmacologically acceptable salts and to compositions and formulations of compounds of formula I.

Any reference to a compound of formula I is to be understood as referring also to the salts (and especially the pharmaceutically acceptable salts) of such compounds, as appropriate and expedient.

5 A pharmaceutical composition according to the present invention contains at least one compound of formula I (or a pharmaceutically acceptable salt thereof) as the active agent and optionally carriers and/or diluents and/or adjuvants, and may also contain additional known antibiotics.

10 The compounds of formula I and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral or parenteral administration.

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of
15 formula I or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

20 Another aspect of the invention concerns a method for the prevention or the treatment (and notably for the treatment) of a bacterial infection in a patient comprising the administration to said patient of a pharmaceutically active amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

Besides, any preferences and (sub-)embodiments indicated for the compounds of formula I (whether for the compounds themselves, salts thereof, compositions containing the
25 compounds or salts thereof, uses of the compounds or salts thereof, etc.) apply *mutatis mutandis* to the compounds of formula I_P, the compounds of formula I_{CE} and the compounds of formula I_{CEP}.

Moreover, the compounds of formula I may also be used for cleaning purposes, e.g. to remove pathogenic microbes and bacteria from surgical instruments or to make a room or

an area aseptic. For such purposes, the compounds of formula I could be contained in a solution or in a spray formulation.

The compounds of formula I can be manufactured in accordance with the present invention using the procedures described hereafter.

5 PREPARATION OF COMPOUNDS OF FORMULA I

Abbreviations:

The following abbreviations are used throughout the specification and the examples:

	Ac	acetyl
	AcOH	acetic acid
10	AD-mix α	1,4- <i>bis</i> (dihydroquinine)phthalazine, K ₃ Fe(CN) ₆ , K ₂ CO ₃ and K ₂ OsO ₄ .2H ₂ O
	AD-mix β	1,4- <i>bis</i> (dihydroquinidine)phthalazine, K ₃ Fe(CN) ₆ , K ₂ CO ₃ and K ₂ OsO ₄ .2H ₂ O
	Alloc	allyloxycarbonyl
15	aq.	aqueous
	Boc	<i>tert</i> -butoxycarbonyl
	Cbz	benzyloxycarbonyl
	CC	column chromatography over silica gel
	CDI	1,1'-carbonyldiimidazole
20	DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
	DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
	DCE	1,2-dichloroethane
	DCM	dichloromethane
	DEAD	diethyl azodicarboxylate
25	DIAD	diisopropyl azodicarboxylate
	DIBAH	diisobutylaluminium hydride

	DIPEA	<i>N,N</i> -diisopropylethylamine
	DMAP	4-dimethylaminopyridine
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethylsulfoxide
5	DPPA	diphenyl phosphoryl azide
	EA	ethyl acetate
	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	ESI	Electron Spray Ionisation
	eq.	equivalent
10	ether	diethyl ether
	Et	ethyl
	EtOH	ethanol
	Fmoc	9-fluorenylmethoxycarbonyl
	HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium
15		hexafluorophosphate
	Hex	hexane
	Hept	heptane
	HOBT	1-hydroxybenzotriazole hydrate
	HV	high vacuum conditions
20	KHMDS	potassium hexamethyldisilazide
	LAH	lithium aluminium hydride
	LC	liquid chromatography
	LiHMDS	lithium hexamethyldisilazide
	MCPBA	<i>meta</i> -chloroperbenzoic acid
25	Me	methyl
	MeCN	acetonitrile
	MeOH	methanol
	MS	Mass Spectroscopy
	Ms	methanesulfonyl (mesyl)

	<i>n</i> -BuLi	<i>n</i> -butyl lithium
	NMO	<i>N</i> -methyl-morpholine <i>N</i> -oxide
	NMP	<i>N</i> -methylpyrrolidin-2-one
	org.	organic
5	Pd/C	palladium on carbon
	Pd(OH) ₂ /C	palladium dihydroxide on carbon
	Ph	phenyl
	Pht	phthaloyl
	Pyr	pyridine
10	rac	racemic
	rt	room temperature
	sat.	saturated
	T3P [®]	<i>n</i> -propanephosphonic acid anhydride
	TBAF	tetrabutylammonium fluoride
15	TBDMS	<i>tert</i> -butyldimethylsilyl
	TBDPS	<i>tert</i> -butyldiphenylsilyl
	tBu	<i>tert</i> -butyl
	TEA	triethylamine
	TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
20	Tf	trifluoromethanesulfonyl (triflyl)
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TLC	thin layer chromatography
	Ts	<i>para</i> -toluenesulfonyl

25 General reaction techniques:

General reaction technique 1 (amino deprotection):

The benzyl carbamates are deprotected by hydrogenolysis over a noble metal catalyst (e.g. Pd/C or Pd(OH)₂/C). The Boc group is removed under acidic conditions such as HCl

in an organic solvent such as MeOH or dioxane, or TFA neat or diluted in a solvent such as DCM. The Alloc group is removed in presence of tetrakis (triphenylphosphine)palladium(0) in presence of an allyl cation scavenger such as morpholine, dimedone or tributyltin hydride between 0°C and 50°C in a solvent such as THF.

The *N*-benzyl protected amines are deprotected by hydrogenolysis over a noble catalyst (e.g. Pd(OH)₂/C).

The *N*-acetyl protecting group is removed under basic conditions such as Na₂CO₃, LiOH or NaOH in aq. MeOH or THF, or under acidic conditions such as aq. HCl in THF.

10 The Fmoc group is removed by treatment with an organic base such as piperidine or morpholine in a solvent such as DMF or THF.

Further general methods to remove amine protecting groups have been described in *Protecting Groups in Organic Synthesis*, 3rd Ed (1999), 494-653; T.W. Greene, P.G.M. Wuts; (Publisher: John Wiley and Sons, Inc., New York, N.Y.).

15 General reaction technique 2 (activation of an alcohol and substitution with an amine or an azide):

The alcohol is reacted with MsCl, TfCl or TsCl in presence of a base such as TEA in a dry aprotic solvent such as Pyr, THF or DCM between -30°C and 50°C. In the case of the triflate or mesylate, Tf₂O or Ms₂O can also be used. These sulfonates can be reacted with sodium iodide in a ketone such as acetone or 2-butanone, in MeCN or in DMF between 40°C and 120°C delivering the corresponding iodide derivatives. Once activated (either as a sulphonate or a iodide derivative), the alcohol can be reacted with an amine or sodium azide in presence of an organic base such as DIPEA or TEA or an inorganic base such as sodium carbonate in a solvent such as DMSO or DMF between 20°C and 100°C.

25 Alternatively, the azide can also be obtained by activation of the alcohol under Mitsunobu conditions in presence of PPh₃ and DEAD or DIAD in a solvent such as THF, DMF, DCM or DME between -20°C and 60°C as reviewed by O. Mitsunobu, in *Synthesis* (1981), 1 and reaction with DPPA.

General reaction technique 3 (reductive amination):

30 The reaction between the amine and the aldehyde or ketone is performed in a solvent system allowing the removal of the formed water through physical or chemical means (e.g.

distillation of the solvent-water azeotrope or presence of drying agents such as molecular sieves, MgSO_4 or Na_2SO_4). Such a solvent system consists typically in toluene, Hex, THF, DCM or DCE or in a mixture of solvents such as MeOH-DCE. The reaction can be catalyzed by traces of acid (usually AcOH). The intermediate imine is reduced with a suitable reducing agent (e.g. NaBH_4 , NaBH_3CN , or $\text{NaBH}(\text{OAc})_3$) or through hydrogenation over a noble catalyst such as Pd/C. The reaction is carried out between -10°C and 110°C , preferably between 0°C and 60°C . The reaction can also be carried out in one pot. It can also be performed in protic solvents such as MeOH or water in presence of a picoline-borane complex (*Tetrahedron* (2004), **60**, 7899-7906).

10 General reaction technique 4 (alkylation of an amine):

The amine derivative is reacted with an alkyl or alkenyl halide such as allyl iodide in presence of an inorganic base such as K_2CO_3 or an organic base such as TEA in a solvent such as THF between 0°C and 80°C . In the particular case of a carbamate, the reaction is performed in presence of NaH between 0°C and rt. Further details can be found in
15 *Comprehensive Organic Transformations. A guide to Functional Group Preparations; 2nd Edition*, R. C. Larock, Wiley-VC; New York, Chichester, Weinheim, Brisbane, Singapore, Toronto, 1999. Section Amines p.779.

General reaction technique 5 (cis dihydroxylation):

The diol is obtained by dihydroxylation of the corresponding alkenyl derivative using a
20 catalytic amount of osmium tetroxide in the presence a co-oxidant such as NMO in aq. solvent such as an acetone-water or DCM-water mixture (see Cha, J.K. *Chem. Rev.* (1995), **95**, 1761-1795). The chiral cis-diols are obtained by using AD-mix α or AD-mix β in presence of methanesulfonamide in a water/2-methyl-2-propanol mixture as described in *Chem. Rev.* (1994), 94, 2483. The sense of induction relies on the chiral ligand contained
25 in the AD mixture, either a dihydroquinine-based ligand in AD-mix α or a dihydroquinidine-based ligand in AD-mix β .

General reaction technique 6 (oxazolidinone formation):

The 1,2-aminoalcohol derivative is reacted with phosgene, diphosgene or triphosgene. This reaction is preferably carried out in a dry aprotic solvent such as DCM or THF in presence
30 of an organic base such as TEA or Pyr and at a temperature between -30° and $+40^\circ\text{C}$.

Alternatively, the 1,2-aminoalcohol derivative is reacted with CDI or *N,N'*-disuccinimidyl carbonate in a dry aprotic solvent such as DCM or THF in presence of an organic base such as TEA or Pyr and at a temperature between -30° and $+80^{\circ}\text{C}$.

General reaction technique 7 (amine protection):

- 5 Amines are usually protected as carbamates such as Alloc, Cbz, Boc or Fmoc. They are obtained by reacting the amine with allyl or benzyl chloroformate, di-*tert*-butyl dicarbonate or Fmoc chloride in presence of a base such as NaOH, TEA, DMAP or imidazole. They can also be protected as *N*-benzyl derivatives by reaction with benzyl bromide or chloride in presence of a base such as Na_2CO_3 or TEA. Alternatively, *N*-benzyl derivatives
10 can be obtained through reductive amination in presence of benzaldehyde (see general reaction technique 3).

Further strategies to introduce other amine protecting groups have been described in *Protecting Groups in Organic Synthesis*, 3rd Ed (1999), 494-653; T.W. Greene, P.G.M. Wuts; (Publisher: John Wiley and Sons, Inc., New York, N.Y.).

15 General reaction technique 8 (reduction of carboxylates into alcohols):

- The ester is reduced with a boron or aluminium hydride reducing agent such as LiBH_4 or LiAlH_4 in a solvent such as THF between -20°C and 40°C . Alternatively, the ester function is hydrolyzed into its corresponding acid using an alkali hydroxide such as NaOH, KOH or LiOH in water or in a mixture of water with polar protic or aprotic organic solvent
20 such as THF or MeOH between -10°C and 50°C . The resulting carboxylic acid is further reduced into the corresponding alcohol using a borane derivative such as a $\text{BH}_3\cdot\text{THF}$ complex in a solvent such as THF between -10°C and 40°C .

General reaction technique 9 (formation of aldehydes):

- The primary alcohols can be transformed into their corresponding aldehydes through
25 oxidation under Swern (see D. Swern et al., *J. Org. Chem.* (1978), **43**, 2480–2482) or Dess Martin (see D.B. Dess and J.C. Martin, *J. Org. Chem.* (1983), **48**, 4155) conditions, respectively. Alternatively, the esters can be transformed into their corresponding aldehydes by controlled reduction with a bulky hydride reagent such as DIBAL.

General reaction technique 10 (ring closure):

The alcohol derivative is dissolved in THF or DMF and treated with tBuOK and the solution is heated between 60°C to 100°C for one hour. The reaction mixture is quenched with a sat. NH₄Cl solution.

5 General reaction technique 10a (ring closure):

The amine derivative is dissolved in NMP or DMF and treated with DIPEA or K₂CO₃ and the solution is heated between 60°C to 100°C for one hour. The reaction mixture is quenched with a sat. NH₄Cl solution.

General reaction technique 11 (hydroxy deprotection):

- 10 The silyl ether groups are removed either using fluoride anion sources such as TBAF in THF between 0°C and 40°C or HF in MeCN between 0°C and 40°C or using acidic conditions such as AcOH in THF/MeOH or HCl in MeOH. Further methods to remove the TBDMS and TBDPS groups are given in *Protecting Groups in Organic Synthesis*, 3rd Ed (1999), 133-139 and 142-143 respectively; T.W.Greene, P.G.M. Wuts; (Publisher: John Wiley and Sons, Inc., New York, N.Y.).
- 15 Further general methods to remove alcohol protecting groups are described in *Protecting Groups in Organic Synthesis*, 3rd Ed (1999), 23-147; T.W.Greene, P.G.M. Wuts; (Publisher: John Wiley and Sons, Inc., New York, N.Y.).

General reaction technique 12 (oxazolidine ring formation using glycidyl esters):

- 20 The aniline carbamate is reacted in a dry solvent such as THF with a strong organic base such as *n*-BuLi between -100°C and -30°C or with tBuOLi, tBuOK or KHMDS between -100°C and -30°C. The anion is reacted at these temperatures with the required glycidyl esters and allowed to reach rt.

General reaction technique 13 (reduction of azides into amines):

- 25 The azides are hydrogenated over a noble metal catalyst such as Pd/C in solvent such as MeOH or EA. In case the molecule is containing an unsaturated double or triple bond, the reduction can be performed using PPh₃ in presence of water as described in *J. Med. Chem.* (1993), **36**, 2558-68.

General reaction technique 14 (Wittig):

The required phosphonium salt is treated in a solvent such as water with an inorganic base such as NaOH. The corresponding phosphorane is collected by filtration and dried *in vacuo*. It is reacted with the required aldehyde in an aprotic solvent such as THF, DCM or toluene between 0°C and 90°C. Alternatively the Wittig-Horner variant of the reaction can be used wherein the phosphono ester (generated from the corresponding bromide and triethylphosphite) is reacted with the aldehyde in presence of a base such as NaH or NaOMe in a solvent such as ether or THF between 0°C and 50°C.

General reaction technique 15 (protection of alcohols):

- 10 The alcohols are protected as silyl ether (usually TBDMS or TBDPS). The alcohol is reacted with the required silyl chloride reagent (TBDMSCl or TBDPSCl) in presence of a base such as imidazole or TEA in a solvent such as DCM, THF or DMF between 10°C and 40°C.

Further strategies to introduce other alcohol protecting groups have been described in
15 *Protecting Groups in Organic Synthesis* 3rd Ed (1999), 23-147; T.W.Greene, P.G.M. Wuts; (Publisher: John Wiley and Sons, Inc., New York, N.Y.).

General reaction technique 16 (intramolecular ring closure according to Buchwald):

- In the case wherein an alcohol is ring closed, the aromatic halide (Cl, Br, I) is reacted in presence of a palladium catalyst such as palladium (II) acetate, in presence of a
20 dialkylphosphinobiphenyl ligand such as [1,1']binaphthalenyl-2-yl-di-*tert*-butyl-phosphane and in presence of a base such as K₂CO₃ or Cs₂CO₃ between +20°C and +100°C, as described in *J. Am. Chem. Soc.* (2001), **123**, 12202-12206.

- In the case wherein an amine is ring closed, the aromatic halide (Cl, Br, I) is reacted in presence of CuI, in presence of Cs₂CO₃ between +20°C and +100°C, as described in *J. Am.*
25 *Chem. Soc.* (2006), **128**, 8742-8743.

General reaction technique 17 (amide coupling):

- The carboxylic acid is reacted with the amine in presence of an activating agent such as DCC, EDC, *n*-propylphosphonic cyclic anhydride, HATU or di-(*N*-succinimidyl)-carbonate, in a dry aprotic solvent such as DCM, MeCN or DMF between -20°C and
30 +60°C (see G. Benz in *Comprehensive Organic Synthesis*, B.M. Trost, I. Fleming, Eds;

Pergamon Press: New York (1991), vol. 6, p. 381). Alternatively, the carboxylic acid can be activated by conversion into its corresponding acid chloride by reaction with oxalyl chloride or thionyl chloride neat or in a solvent like DCM between -20° and +60°C. Further activating agents can be found in *Comprehensive Organic Transformations. A guide to Functional Group Preparations*; 2nd Edition, R. C. Larock, Wiley-VC; New York, Chichester, Weinheim, Brisbane, Singapore, Toronto, 1999. Section nitriles, carboxylic acids and derivatives, p. 1941-1949.

General reaction technique 18 (oxidation of alcohols into acids):

Alcohols can be directly oxidized into their corresponding acids by a variety of methods as described in *Comprehensive Organic Transformations. A guide to Functional Group Preparations*; 2nd Edition, R. C. Larock, Wiley-VC; New York, Chichester, Weinheim, Brisbane, Singapore, Toronto, 1999. Section nitriles, carboxylic acids and derivatives, p. 1646-1648. Among them, [*bis*(acetoxy)iodo]benzene in presence of TEMPO, the Jones reagents (CrO₃/H₂SO₄), NaIO₄ in presence of RuCl₃, KMnO₄ or pyridine H₂Cr₂O₇ are frequently used.

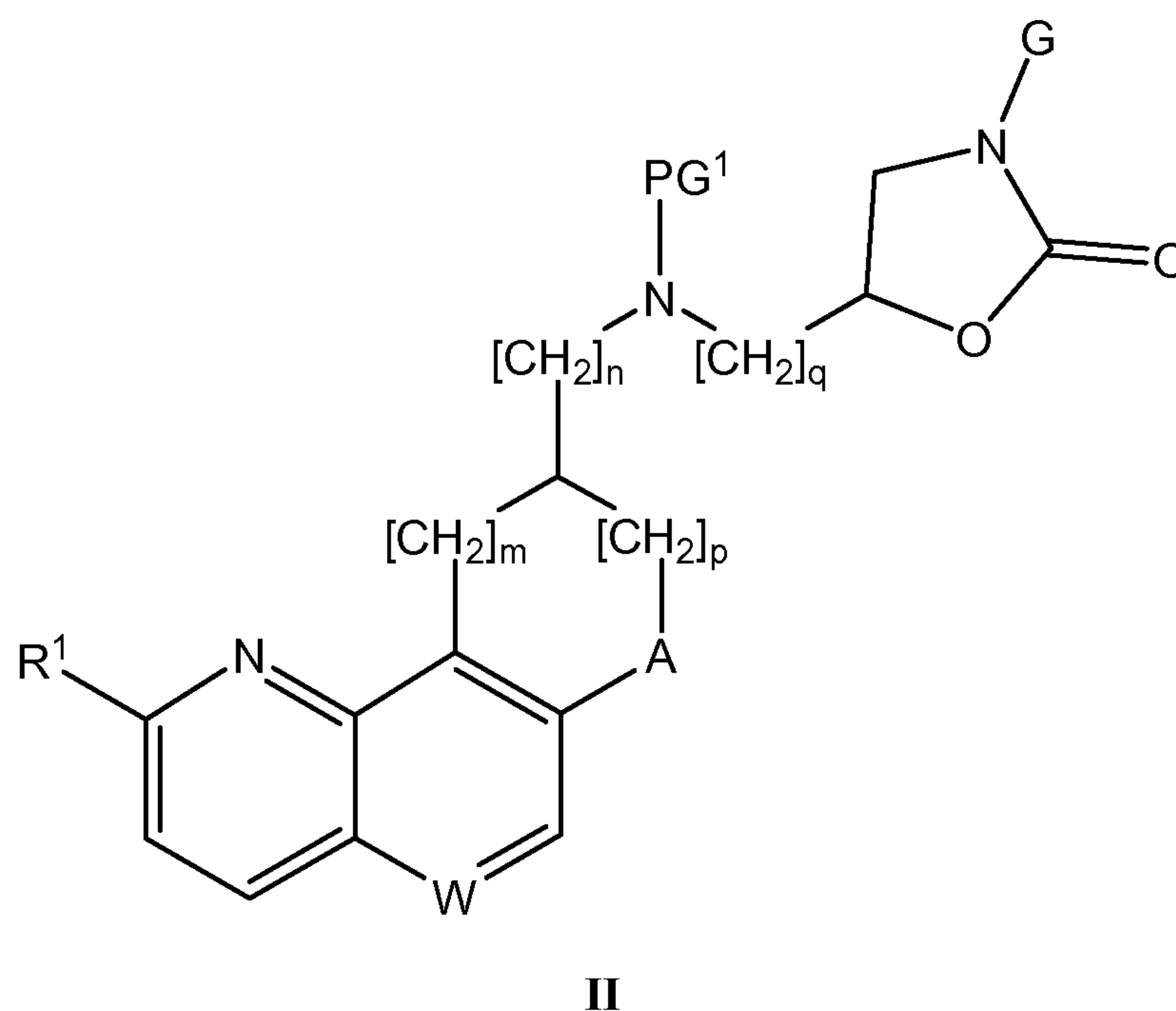
General preparation methods:

Preparation of the compounds of formula I:

The compounds of formula I can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by a person skilled in the art by routine optimisation procedures.

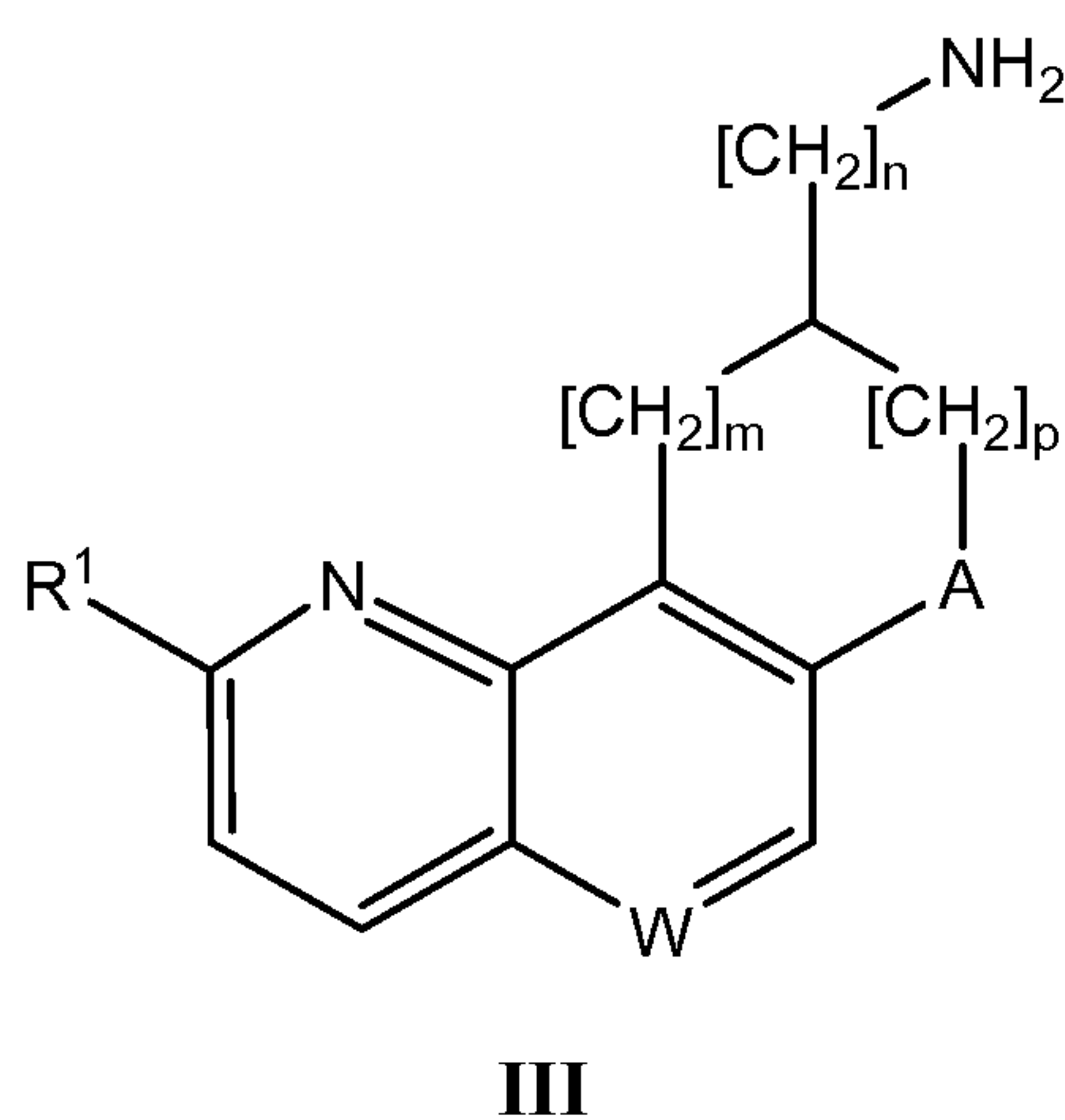
Sections a) to g) hereafter describe general methods for preparing compounds of formula I. In these sections, the symbols A, R¹, W, B, G, m, n, p and q have the same meanings as in formula I unless mentioned otherwise.

- a) The compounds of formula I and B is $(\text{CH}_2)_q$ can be obtained by deprotecting the compounds of formula II

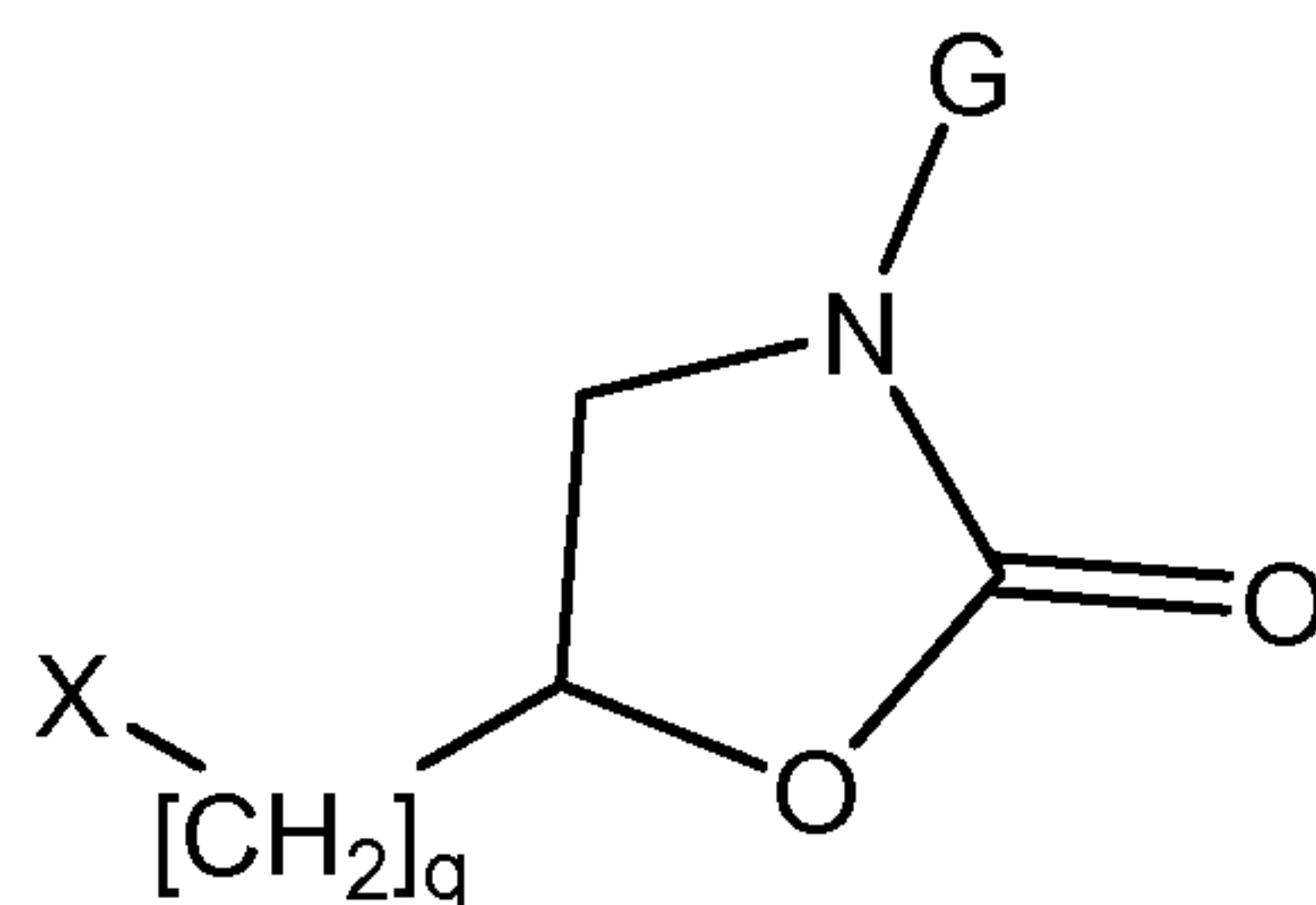


wherein A is O, NH or N-PG⁰ and PG⁰ and PG¹ each represent an amino protecting group such as Boc, Cbz, Fmoc or benzyl, following general reaction technique 1.

- 5 b) The compounds of formula I wherein B is $(\text{CH}_2)_q$ can be obtained by reacting the compounds of formula III



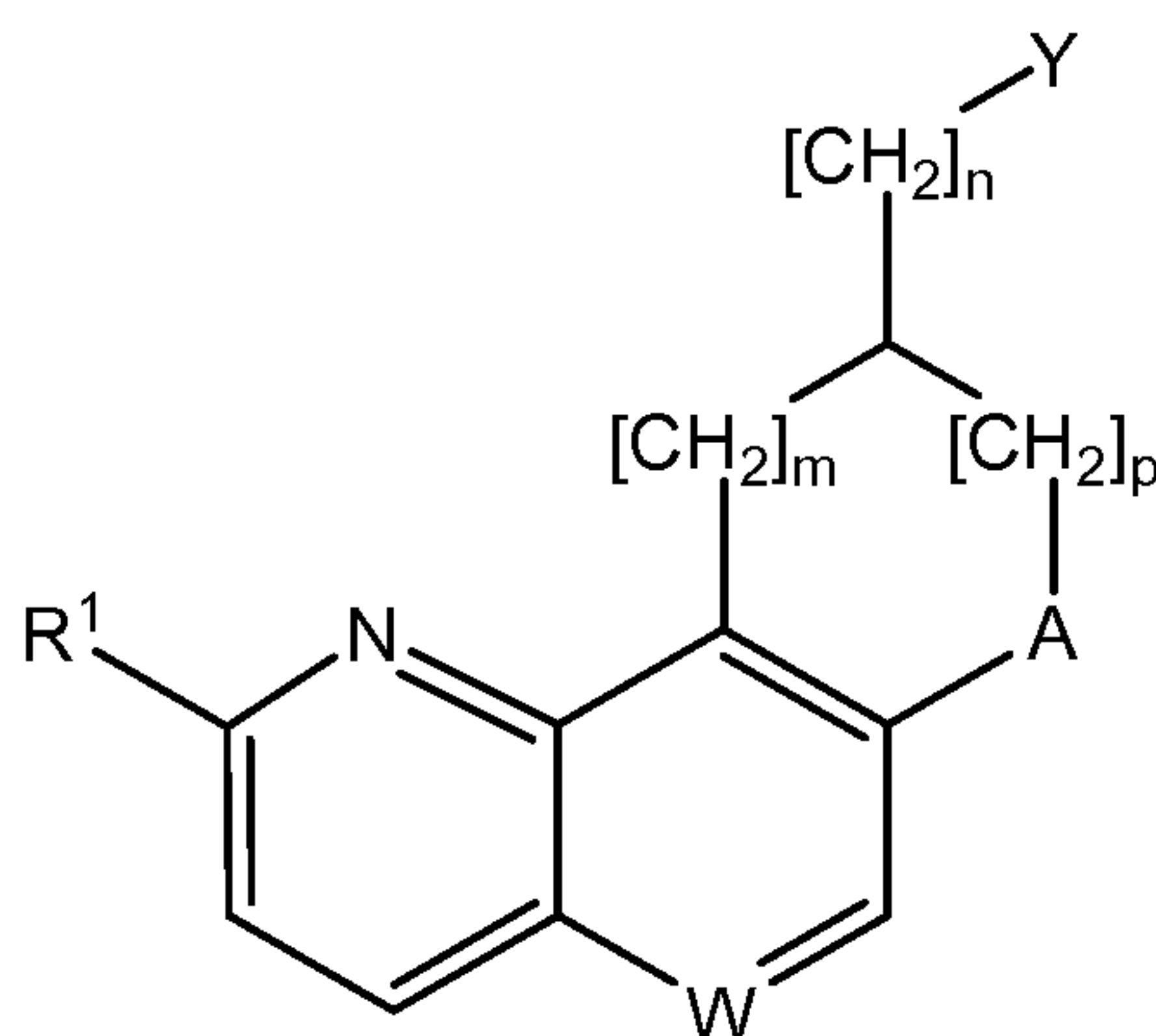
wherein A is O or NPG⁰, wherein PG⁰ is an amino protecting group such as Cbz, Boc, Fmoc or benzyl, with the compounds of formula IV



IV

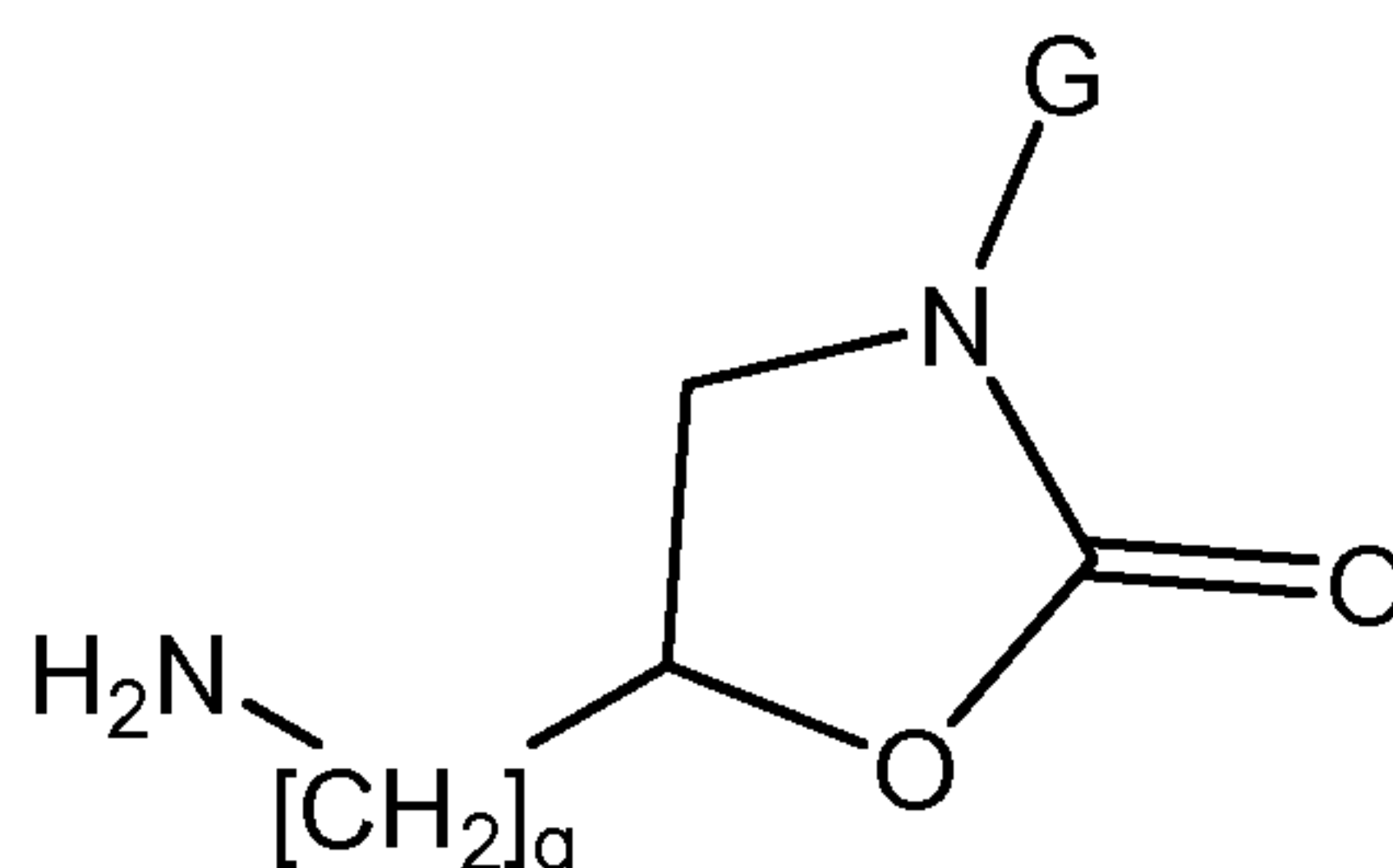
wherein X represents a halogen such as iodine or bromine, or a group of the formula OSO₂R^a wherein R^a represents methyl, trifluoromethyl or tolyl, following general reaction technique 2. In the cases wherein A is N-PG⁰, the protecting group can be removed following general reaction technique 1.

- c) The compounds of formula I wherein B is (CH₂)_q can also be obtained by reacting the compounds of formula V



V

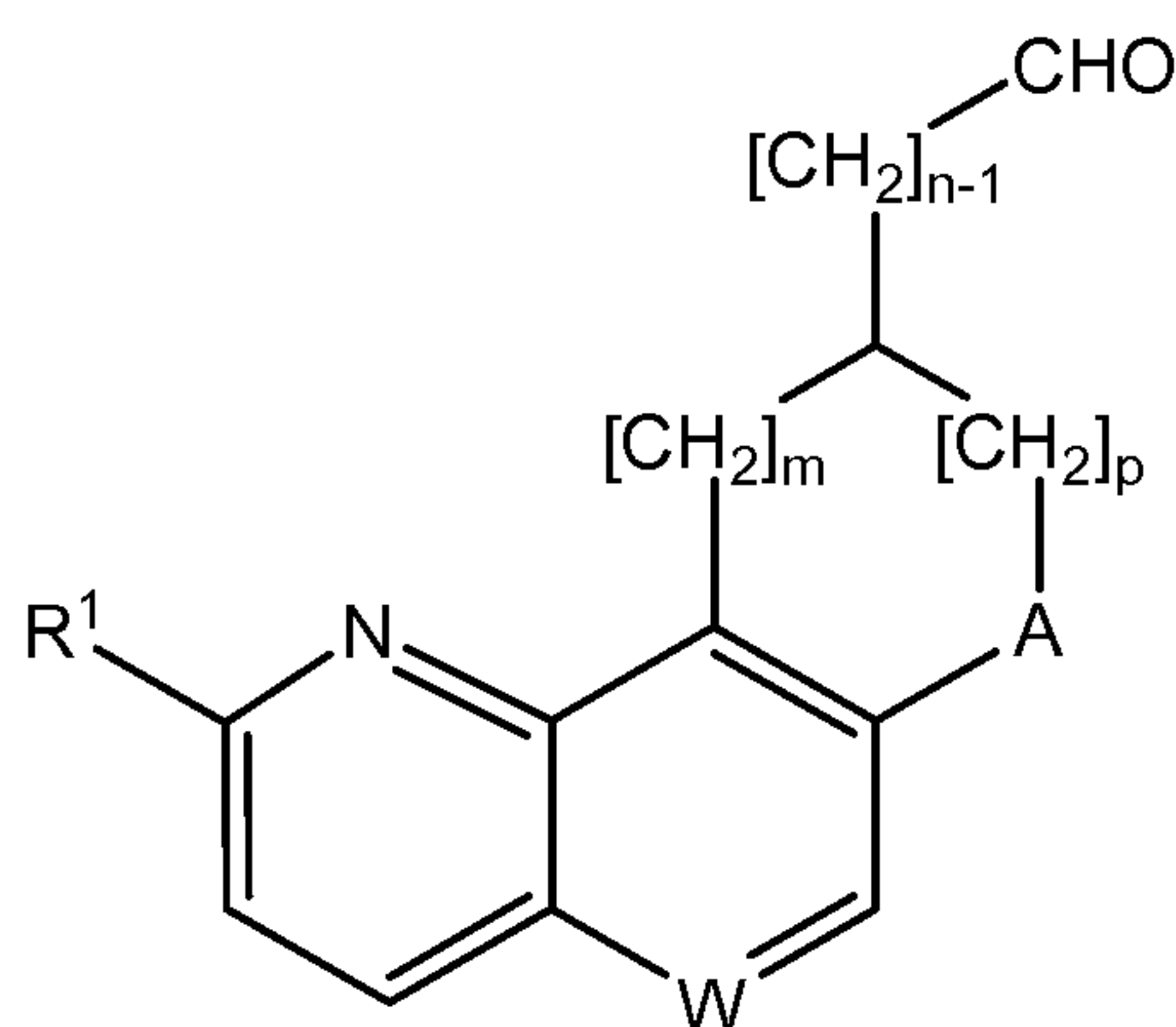
wherein A is O or N-PG⁰, PG⁰ is an amino protecting group such as Boc, Cbz, Fmoc or benzyl and Y represents a halogen such as iodine or bromine, or a group of the formula OSO₂R^a wherein R^a represents methyl, trifluoromethyl or tolyl, following general reaction technique 2, with the compounds of formula VI



VI

5 In the cases wherein A is N-PG⁰, the protecting group can be removed following general reaction technique 1.

d) The compounds of formula I wherein B is (CH₂)_q can furthermore be obtained by reacting the compounds of formula VII

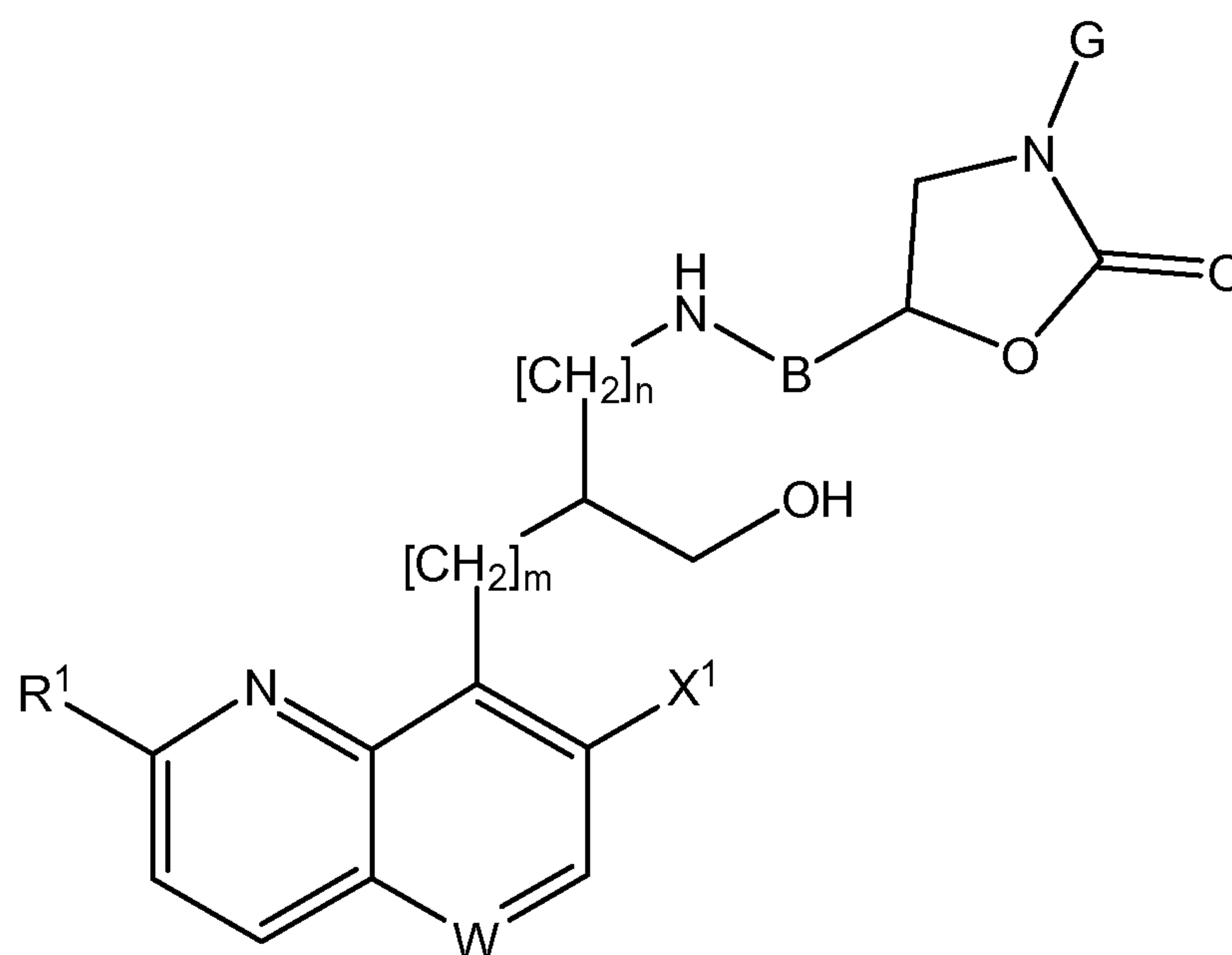


VII

10 wherein A is O or N-PG⁰, PG⁰ being an amino protecting group such as Boc, Cbz, Fmoc or benzyl, with the previously mentioned compounds of formula VI following general reaction technique 3.

- 32 -

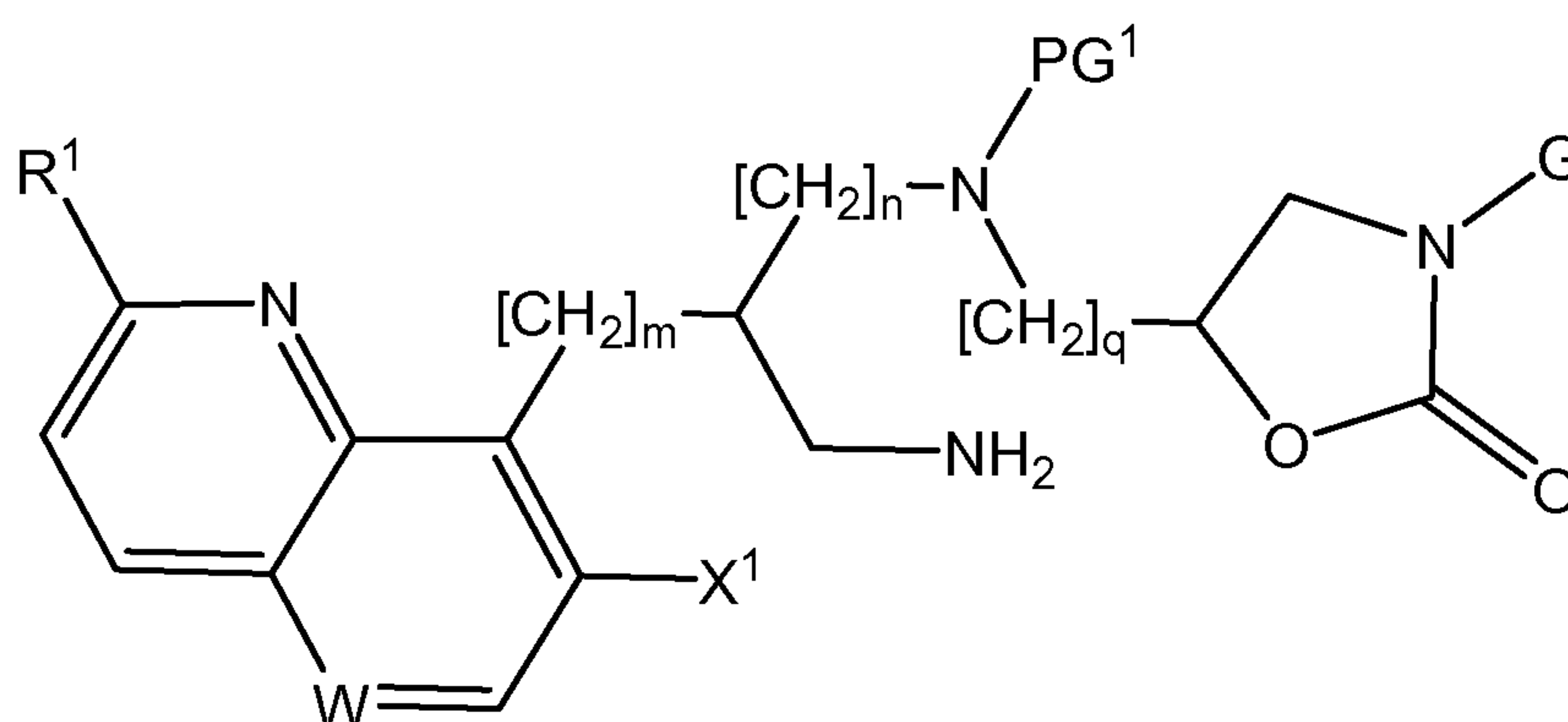
e) The compounds of formula I wherein A is O and p is 1 can be obtained by cyclising the compounds of formula VIII



VIII

wherein X¹ represents halogen such as fluorine or bromine according to general reaction technique 10. Alternatively, the compounds of formula VIII can be *N*-protected according to general reaction technique 7, ring closed under Buchwald conditions according to general reaction technique 16 and finally *N*-deprotected according to general reaction technique 1.

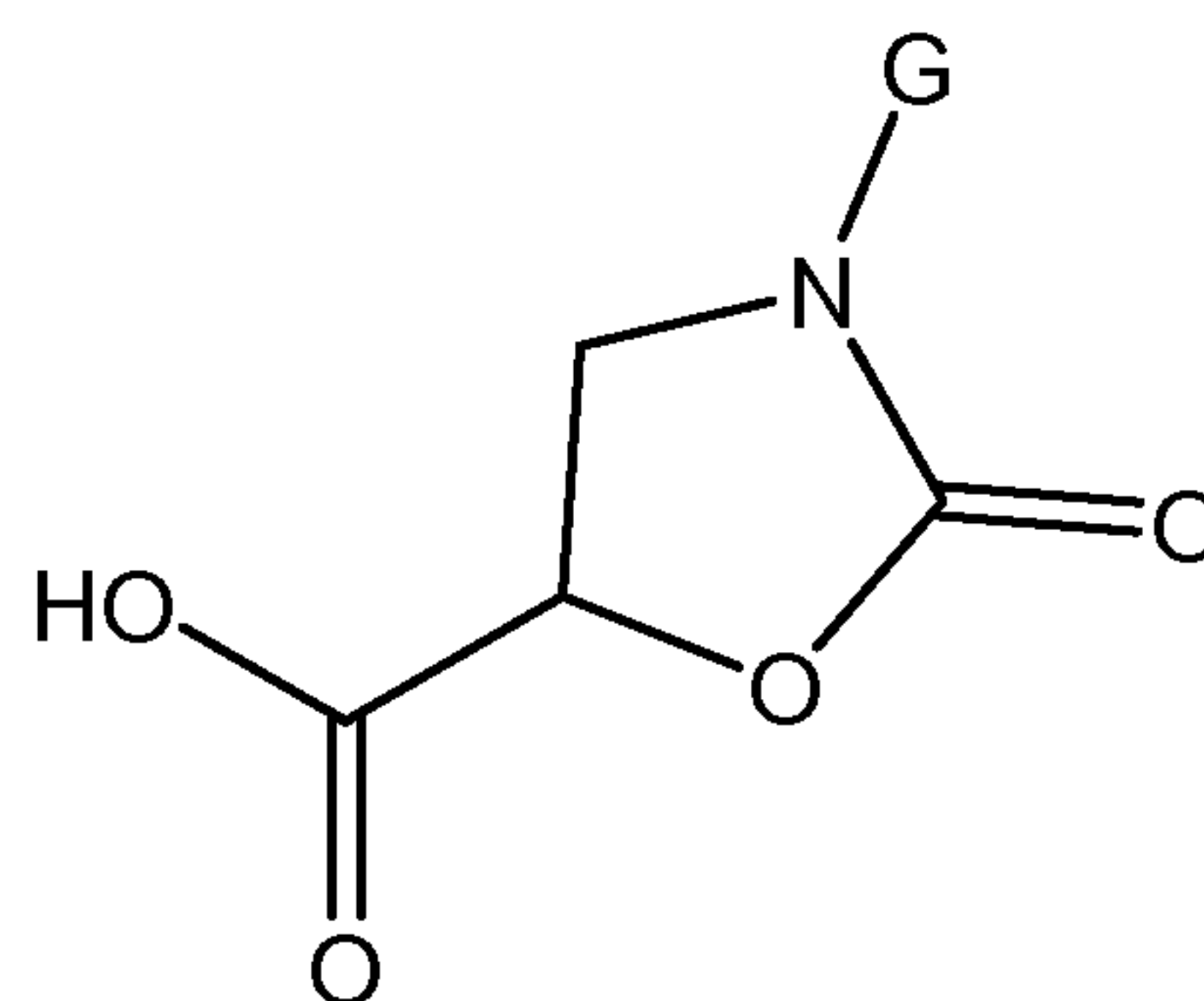
f) The compounds of formula I wherein A is NH, p is 1 and B is (CH₂)_q can be obtained by cyclising the compounds of formula IX



IX

wherein X^1 represents halogen such as fluorine or bromine and PG^1 is an amino protecting group such as Boc, Cbz, Fmoc or benzyl according to general reaction technique 10 followed by removal of the amino protecting group according to general reaction technique 1.

- 5 g) The compounds of formula I wherein B is CO can be obtained by reacting the derivatives of formula III described previously with the derivatives of formula X



X

according to general reaction technique 17. In the cases wherein A is $N-PG^0$, the protecting group can be removed following general reaction technique 1.

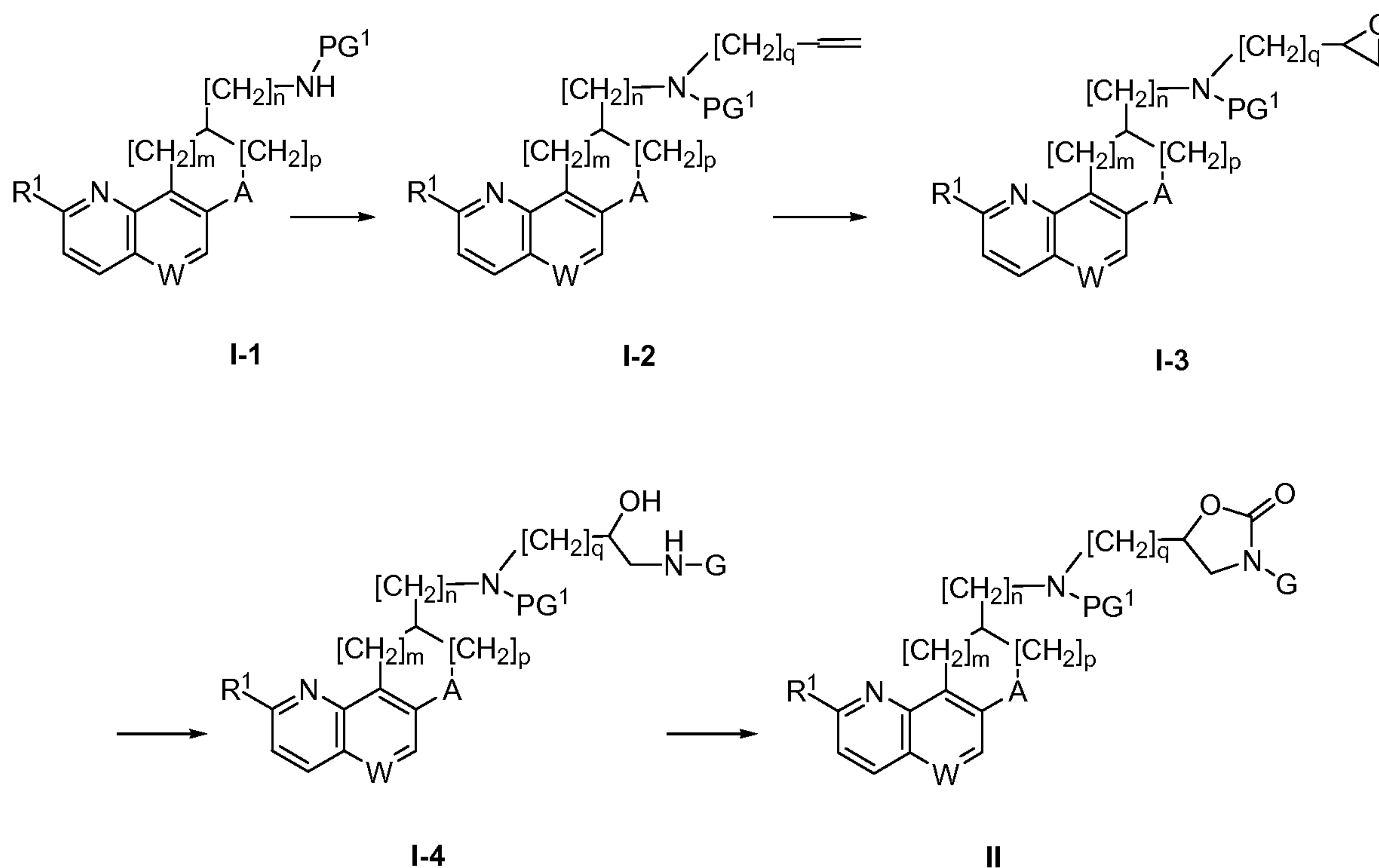
10 The compounds of formula I thus obtained may, if desired, be converted into their salts, and notably into their pharmaceutically acceptable salts.

Besides, whenever the compounds of formula I are obtained in the form of mixtures of enantiomers, the enantiomers can be separated using methods known to one skilled in the art, e.g. by formation and separation of diastereomeric salts or by HPLC over a chiral stationary phase such as a Regis Whelk-O1(R,R) (10 μ m) column, a Daicel ChiralCel OD-H (5-10 μ m) column, or a Daicel ChiralPak IA (10 μ m) or AD-H (5 μ m) column. Typical conditions of chiral HPLC are an isocratic mixture of eluent A (EtOH, in presence or absence of an amine such as triethylamine, diethylamine) and eluent B (hexane), at a flow rate of 0.8 to 150 mL/min. Whenever the compounds of formula I are obtained in the form of mixtures of diastereomers they may be separated by an appropriate combination of

20 silica gel chromatography, HPLC and crystallization techniques.

Preparation of the compounds of formulae II to X:

The compounds of formula II can be prepared as described in Scheme 1 hereafter.

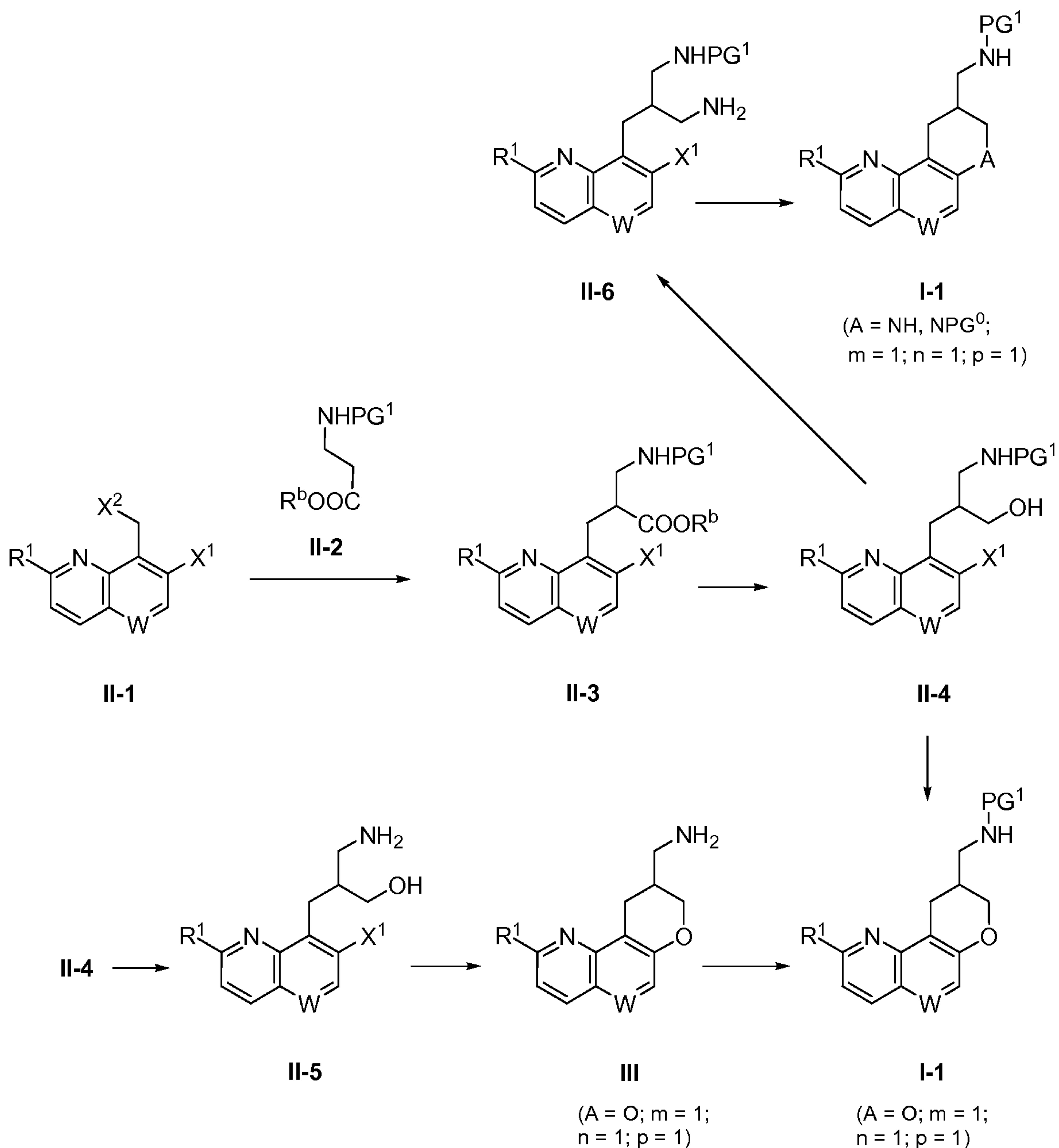


Scheme 1

In Scheme 1, A represents O, NH or NPG⁰ and PG⁰ and PG¹ represent independently from each other an amino protecting group such as Boc, Fmoc, Cbz or benzyl.

- 5 The compounds of formula I-1 wherein A is O or N-PG⁰ can be transformed into the compounds of formula I-3 by reaction with allyl bromide or 4-bromo-1-butene according to general reaction technique 4, followed by *cis*-dihydroxylation according to general reaction technique 5, followed by activation of the primary alcohol function as a mesylate according to general reaction technique 2 and ring closure into the epoxide in presence of a
- 10 base such as Na₂CO₃ or TEA. Alternatively the compounds of formula I-3 wherein q is 1 might be obtained by reacting intermediates of formula I-1 with epichlorhydrin. The epoxides of formula I-3 can be further reacted with an aniline of formula G-NH₂ and the resulting amino alcohols of formula I-4 can be transformed into the compounds of formula II wherein A is O or N-PG⁰ according to general reaction technique 6. If A is N-PG⁰, the
- 15 amino protecting group can be removed according to general reaction technique 1.

The compounds of formula III and I-1 wherein m is 1, n is 1 and p is 1 can be prepared as described in Scheme 2 hereafter.

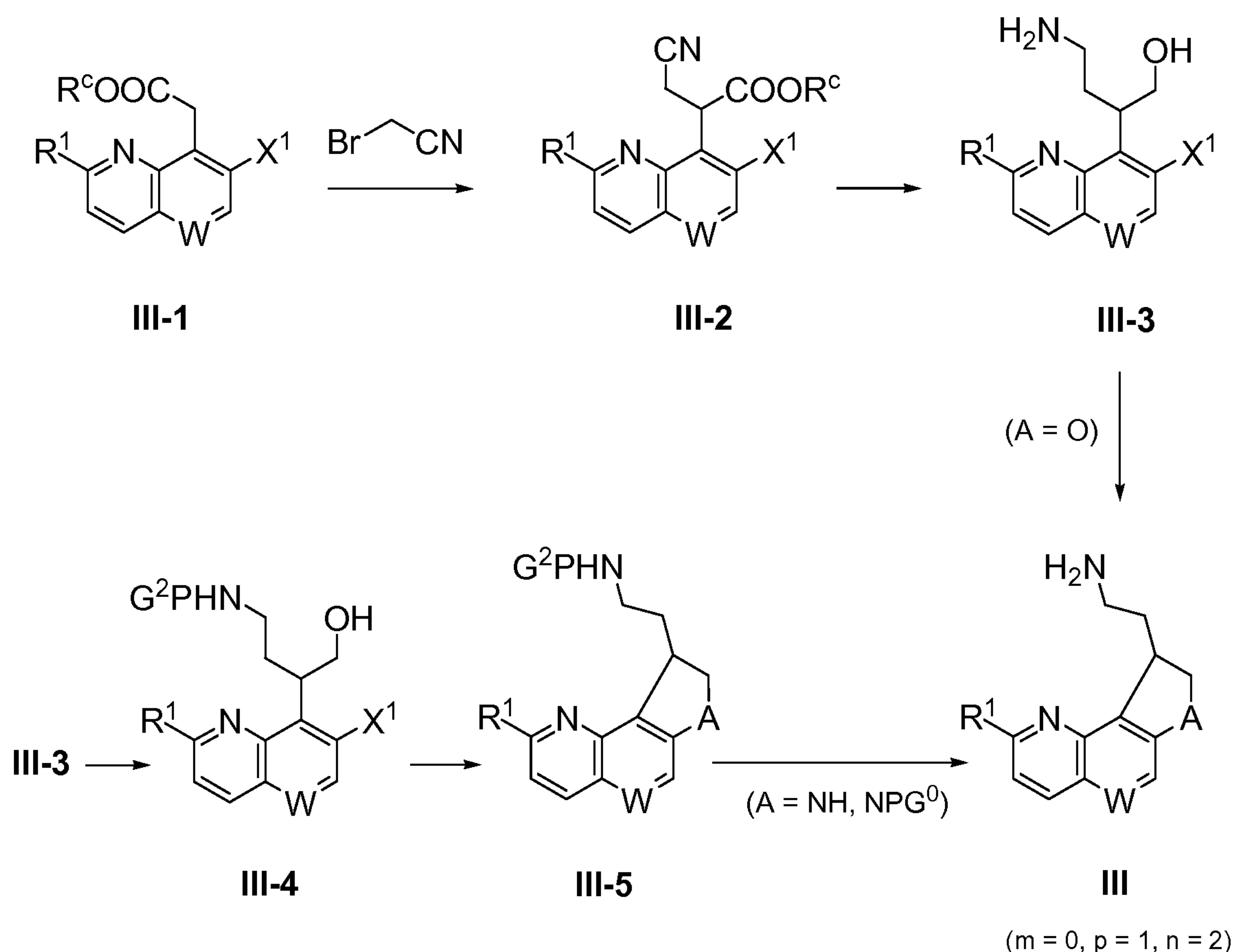


Scheme 2

In Scheme 2, X¹ and X² represent independently from each other halogen such as fluorine (e.g. for X¹) or bromine (e.g. for X²), R^b represents alkyl or benzyl and PG¹ represents an amino protecting group such as Cbz, Boc, Fmoc or benzyl.

The intermediates of formula II-1 can be reacted with the β -alanine derivatives of formula II-2 (e.g. *N*-(*tert*-butoxycarbonyl)- β -alanine methyl ester; commercial) in the presence of a strong base such as LiHDMS below -50°C in a dry solvent such as THF. The resulting amino ester derivatives of formula II-3 can be reduced into the corresponding
5 alcohol derivatives of formula II-4 according to general reaction technique 8. The amino protecting group can be removed according to general reaction technique 1 and the resulting amino alcohols of formula II-5 can then be cyclised according to general reaction techniques 10*a* or 16. The compounds of formula I-1 can be obtained by protection of the compounds of formula III according to general reaction technique 7. Alternatively they can
10 be obtained by cyclising the intermediates of formula II-4 in presence of a base such as K₂CO₃ or NaH. The compounds of formula I-1 wherein A is NH or NPG⁰ can be obtained by transforming the compounds of formula II-4 into their corresponding mesylates and amines of formula II-6 according to general reaction techniques 2 and 13. These latter intermediates can be cyclised according to general reaction technique 10 or 10*a*, affording
15 the compounds of formula I-1 wherein A is NH. The compounds of formula I-1 wherein A is NPG⁰ can be obtained by subsequent protection according to general reaction technique 7.

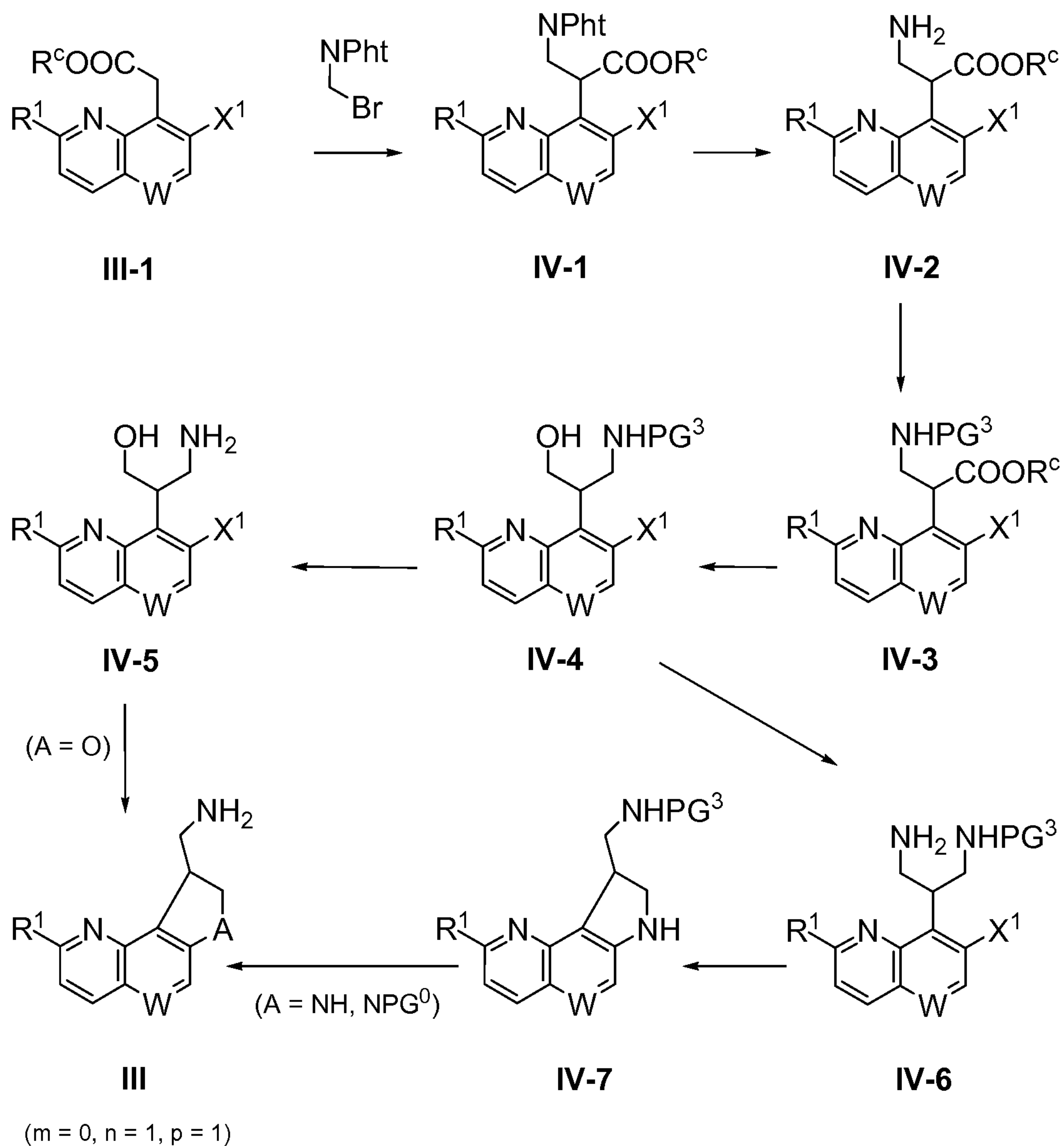
The compounds of formula III wherein m is 0, p is 1 and n is 2 can be prepared as described in Scheme 3 hereafter.

**Scheme 3**

In Scheme 3, R^c represents alkyl, X^1 represents halogen such as fluorine, chlorine or bromine and PG^0 and PG^2 each represent an amino protecting group such as Cbz, Boc, Fmoc or benzyl.

The esters of formula III-1 can be reacted with bromoacetonitrile in presence of a strong base such as LiHDMS below -50°C in a dry solvent such as THF. The resulting nitrile derivatives of formula III-2 can be reduced with LAH in presence of AlCl_3 affording the amino alcohols of formula III-3 which can then be cyclised into the derivatives of formula III according to general reaction technique 10. The amine function of the compounds of formula III-3 can be protected according to general reaction technique 7 and the alcohol function can be transformed into the corresponding amine according to general reaction techniques 2 and 13 and further be cyclised according to general reaction techniques 10a or 16. The resulting derivatives of formula III-5 wherein A is NH can optionally be protected according to general reaction technique 7 and finally the protecting group on the primary amine is removed according to general reaction technique 1.

The compounds of formula III wherein m is 0 and n and p are each 1 can be prepared as described in Scheme 4 hereafter.



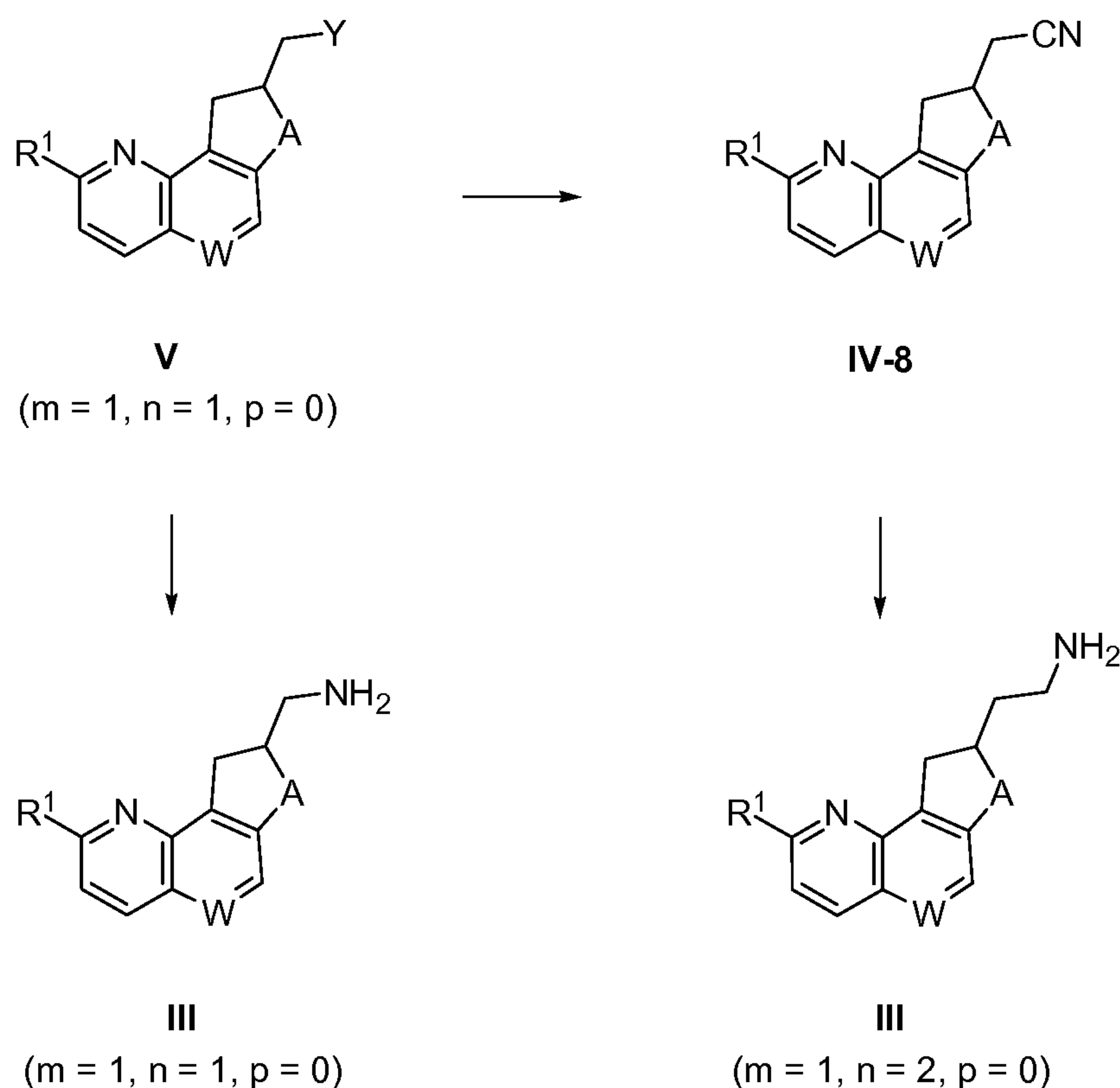
Scheme 4

In Scheme 4, R^c represents alkyl, X¹ represents halogen such as fluorine, bromine or chlorine and PG³ represents an amino protecting group such as Cbz, Boc, Fmoc or benzyl.

- 5 The intermediates of formula III-1 can be reacted with *N*-(bromomethyl)phthalimide (commercial) in presence of a strong base such as LiHDMS below -50°C in a dry solvent such as THF. The resulting phthalimido derivatives of formula IV-1 can be reacted with a hydrazine derivative such as hydrazine hydrate or *N*-methyl hydrazine in a solvent such as ethanol or DCE between 40°C and 80°C affording the corresponding amino derivatives of

formula IV-2, which can be protected following general reaction technique 7. The intermediates of formula IV-3 can be reduced following general reaction technique 8, the protecting group can be removed following general reaction technique 1, and the compounds can then be ring closed using general reaction technique 10 to yield the desired compounds of formula III wherein A is O. The compounds of formula III wherein A is NH or NPG⁰ can be obtained by transforming the alcohol derivatives of formula IV-4 into the corresponding amino derivatives of formula IV-6 according to general reaction techniques 2 and 13 followed by cyclisation according general reaction technique 10. The resulting derivatives of formula IV-7 wherein A is NH can optionally be protected according to general reaction technique 2 and finally the protecting group on the primary amine can be removed according to general reaction technique 1.

The compounds of formula III wherein p is 0, m is 1 and n is 1 or 2 can be prepared as described in Scheme 4a hereafter.

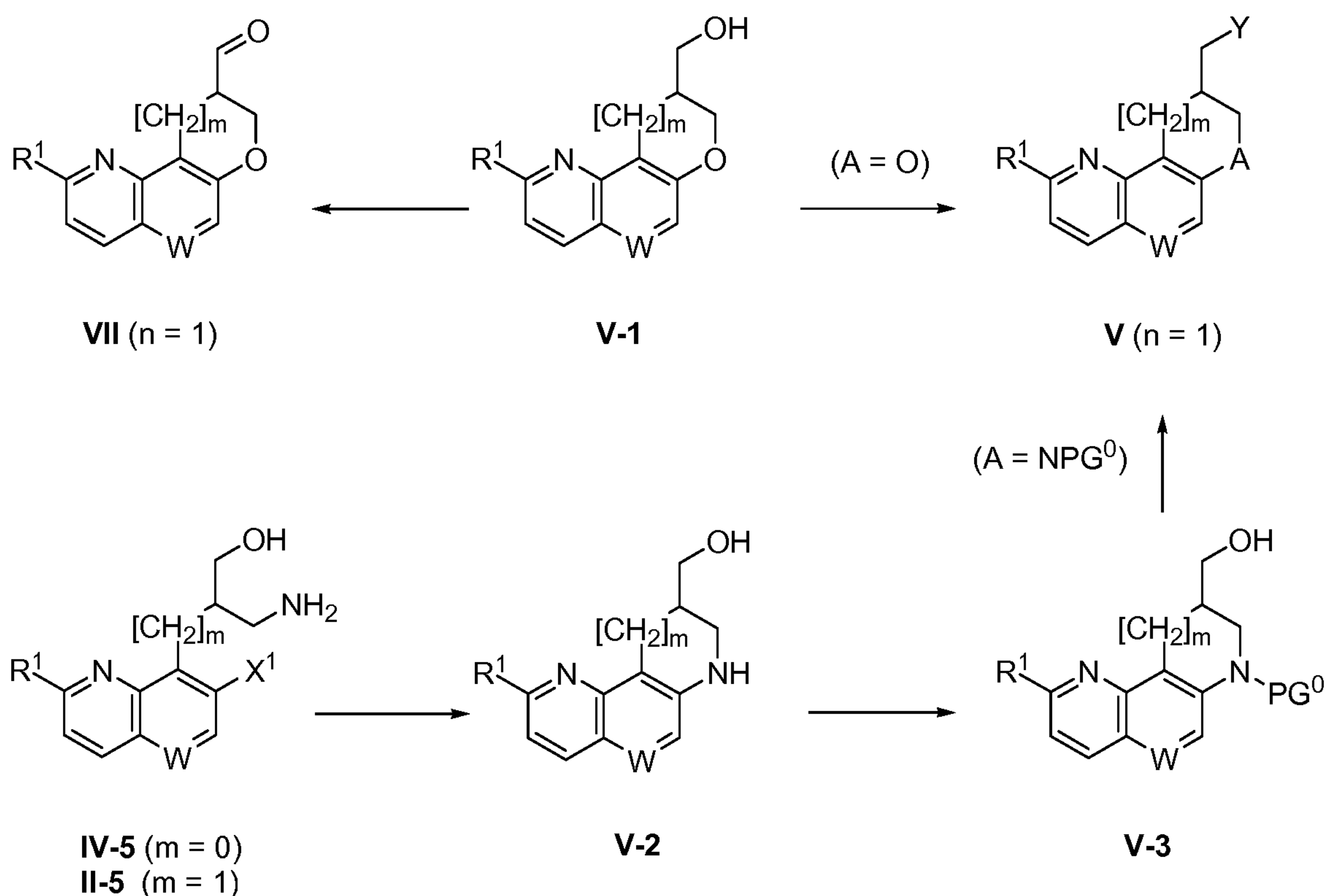


Scheme 4a

The compounds of formula V wherein m is 1, n is 1, p is 0, Y is OSO₂R^a wherein R^a represents methyl, trifluoromethyl or tolyl, A is O or NPG⁰ wherein PG⁰ is an amino protecting group such as Cbz, Boc, Fmoc or benzyl can be reacted with an alkali metal

cyanide, affording the corresponding nitrile derivatives of formula IV-8 which can further be transformed into the corresponding amine derivatives of formula III wherein m is 1, n is 2 and p is 0 by reaction with an hydride reagent such as LAH. The compounds of formula V can also be transformed into the corresponding amine derivatives of formula III wherein m and n are each 1 and p is 0 according to general reaction techniques 2 and 13.

The compounds of formulae V and VII wherein n is 1 and p is 1 can be prepared as described in Scheme 5 hereafter.



Scheme 5

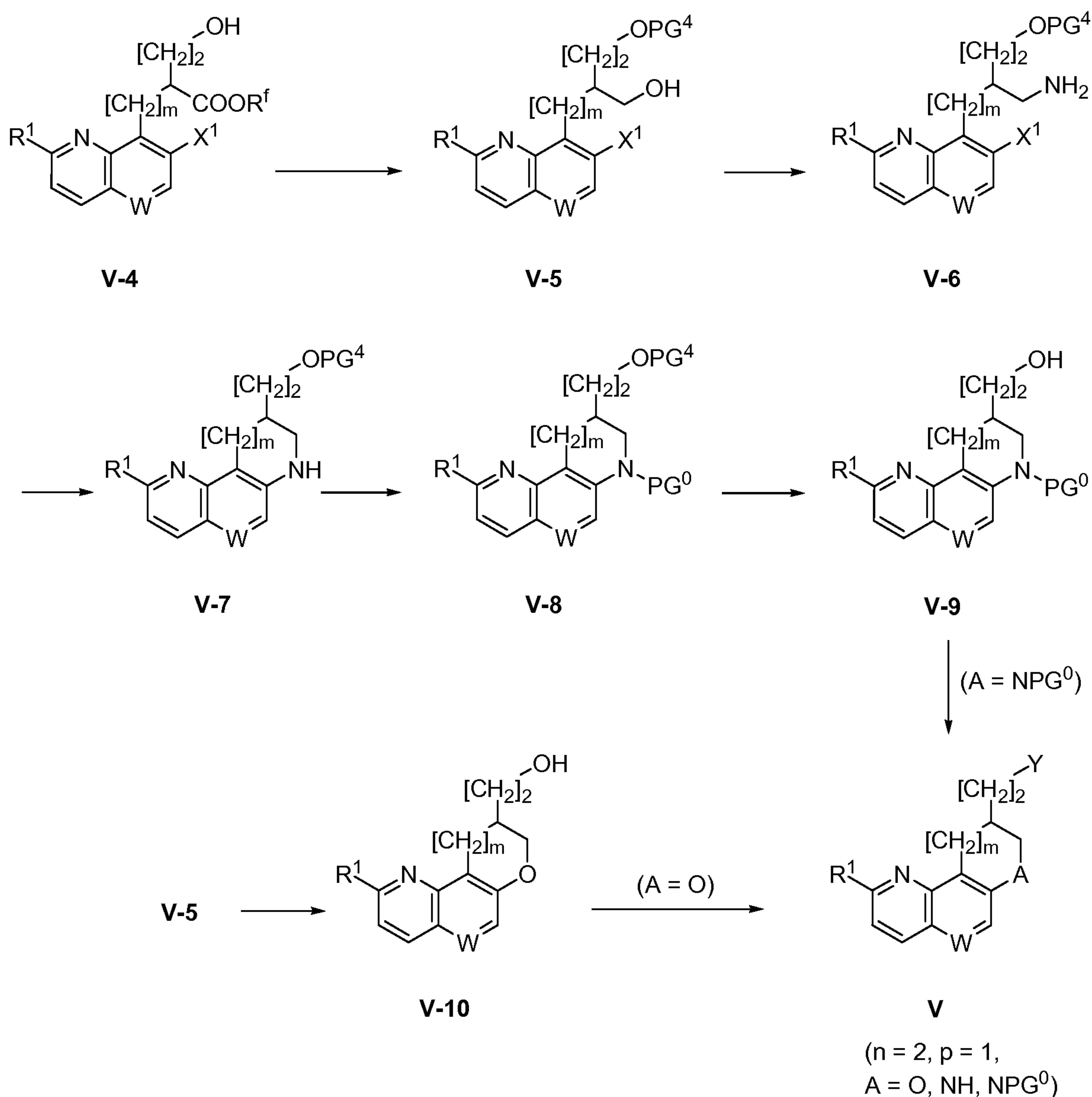
In Scheme 5, PG^0 represents an amino protecting group such as Boc, Fmoc, Cbz or benzyl and X^1 represents halogen such as fluorine or bromine.

10 The compounds of formula V wherein A is O, m is 0 or 1 and n is 1 and the compounds of formula VII wherein m is 0 or 1 and n is 1 can be obtained from the corresponding alcohol derivatives of formula V-1 by either activation of the alcohol function or oxidation into the corresponding aldehydes, following general reaction techniques 2 and 9 respectively.

15 The compounds of formula V wherein A is $N-PG^0$, m is 0 or 1 and n is 1 can be obtained by activation of the alcohol function of the derivatives of formula V-3 following general reaction technique 2. The starting alcohols of formula V-3 can be obtained from the

precursors of formula V-2 according to the general reaction technique 7. The compounds of formula V-2 can be obtained from compounds of formula II-5 or IV-5 by cyclisation using general reaction technique 10a or 16. The compounds of formula V-2 can also be obtained from the corresponding protected alcohols, obtained from the compounds of formula II-5 or IV-6 following general reaction technique 15, by intramolecular cyclisation according to the general reaction technique 16, followed by removal of the alcohol protection following general reaction technique 11.

Besides, the compounds of formula V wherein n is 2 and p is 1 can be prepared as described in Scheme 5a hereafter.

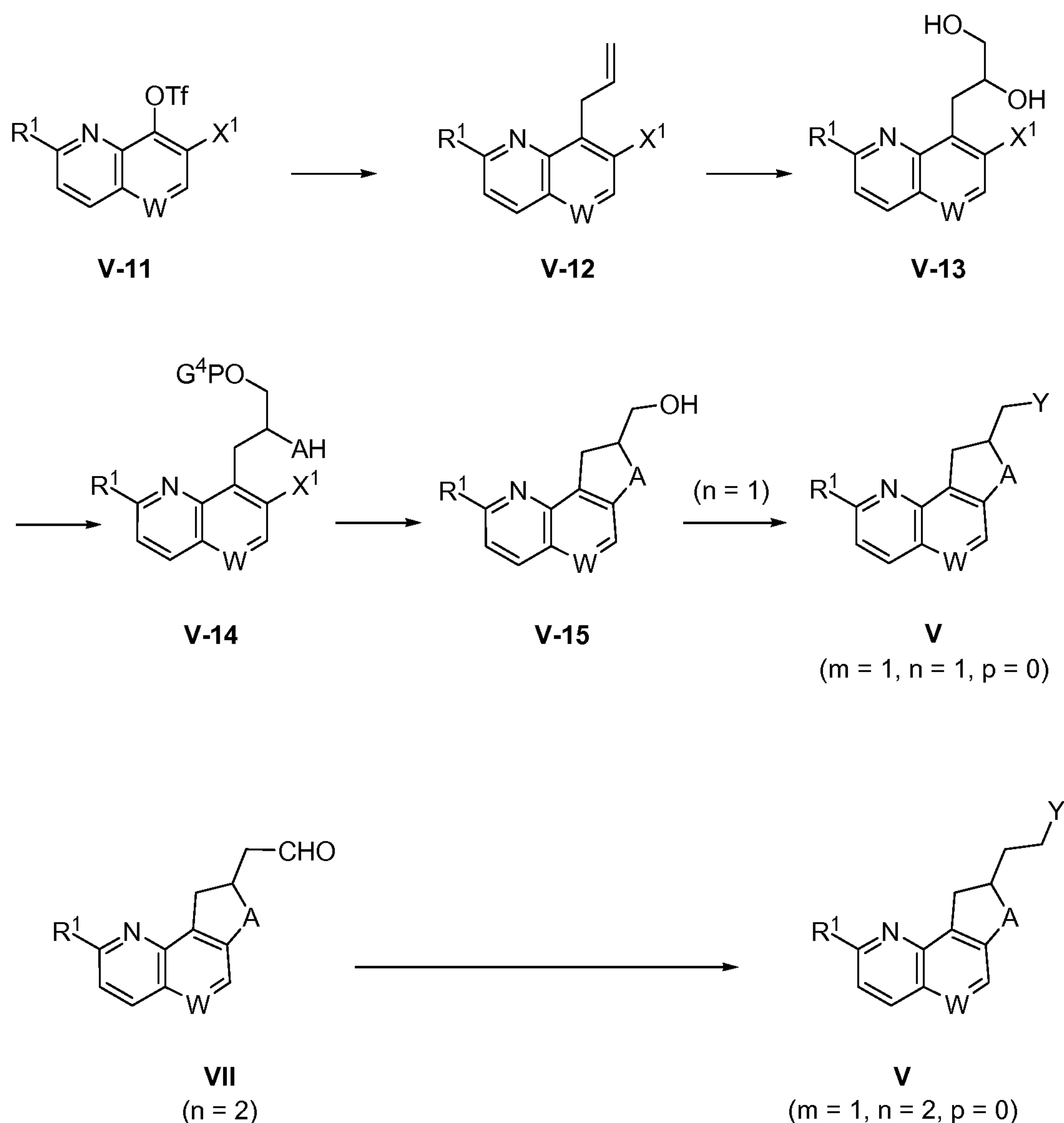


Scheme 5a

In Scheme 5a, PG⁰ represents an amino protecting group such as Boc, Fmoc, Cbz or benzyl, PG⁴ represents a hydroxy protecting group such as TBDMS or OCOR^g wherein R^g is alkyl, R^f represents alkyl or benzyl and X¹ represents halogen such as fluorine.

The compounds of formula V wherein A is N-PG⁰ can be obtained from the alcohol derivatives of formula V-4 after sequential protection of the alcohol function following general reaction technique 15 and reduction of the ester function following general reaction technique 8. The resulting alcohols derivatives of formula V-5 can be transformed into the corresponding amine derivatives of formula V-6 following general reaction techniques 2 and 13. The amine derivatives of formula V-6 can be cyclised into the derivatives of formula V-7 by treatment with a base such as DIPEA or K₂CO₃ (if W is N), or following general reaction technique 16 (if W is CH). The tricyclic derivatives of formula V-7 can be transformed into the compounds of formula V-8 following general reaction technique 7 and the alcohol protecting group can be removed following general reaction technique 11. The resulting alcohol derivatives of formula V-9 can then be transformed into the desired derivatives of formula V wherein A is NPG⁰ following general reaction technique 2. The derivatives of formula V-5 can also be directly cyclised using general reaction technique 10a or 16, affording, after removal of the alcohol protecting group following general reaction technique 11, the intermediate derivatives of formula V-10 which can be further transformed into the derivatives of formula V wherein A is O using general reaction technique 2.

The compounds of formula V wherein m is 1, n is 1 or 2 and p is 0 can be prepared as described in Scheme 5b hereafter.

**Scheme 5b**

In Scheme 5b, A represents O, NH or N-PG⁰ wherein PG⁰ represents an amino protecting group such as Boc, Cbz, Fmoc or benzyl, PG⁴ represents a hydroxy protecting group such as TBDMS or OCOR^g wherein R^g is alkyl and X¹ represents halogen such as chlorine.

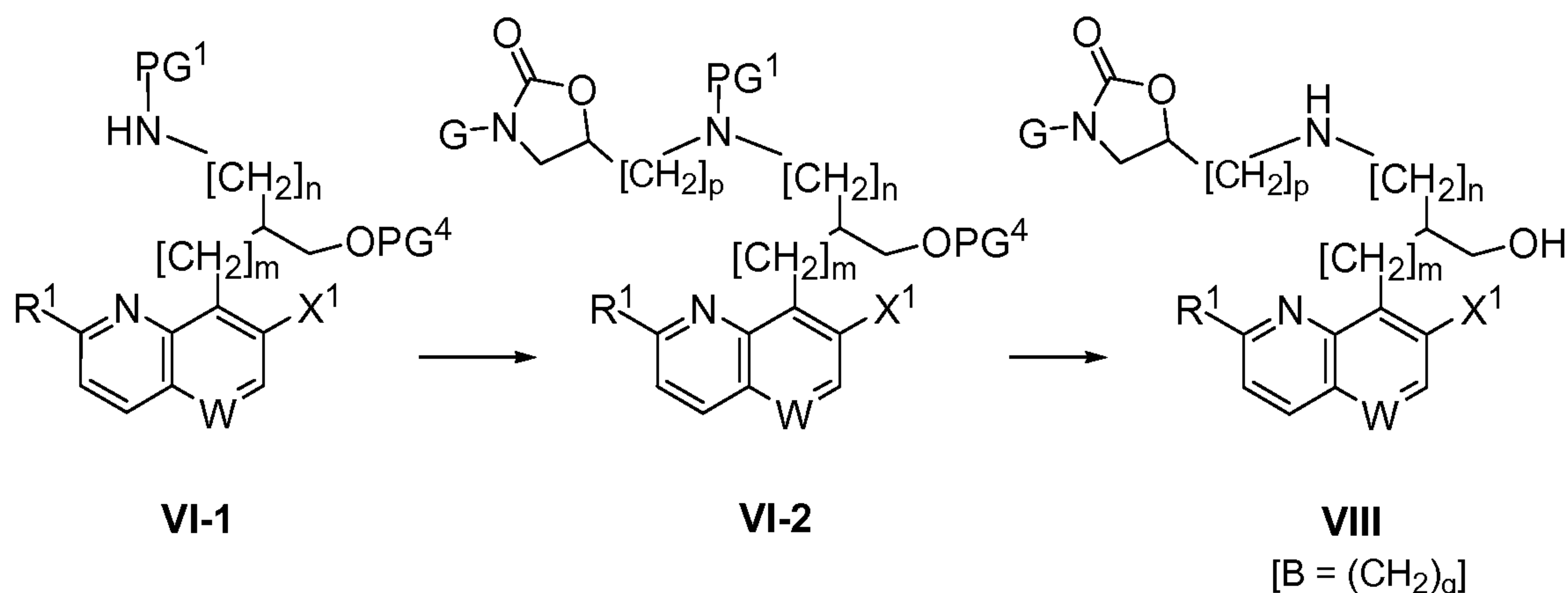
- 5 The triflate derivatives of formula V-11 (e.g. trifluoromethanesulfonic acid 3-chloro-6-methoxy-[1,5]naphthyridin-4-yl ester; prepared according to WO 2004/058144) can be transformed into the corresponding allyl derivatives of formula V-12 after reaction with allyltributyltin in presence of a cross coupling palladium catalyst such as Pd(PPh₃)₄. These intermediates can be transformed into the corresponding diols of formula V-13 using
- 10 general reaction technique 5. The primary alcohol function of the latter can be protected using general reaction technique 15, affording the intermediates of formula V-14 wherein

A is O. These derivatives can be transformed into the corresponding intermediates of formula V-14 wherein A is NH using general reaction techniques 2 and 13. The intermediates of formula V-14 can be cyclised into the derivatives of formula V-15 using general reaction technique 10 if A is O, or general reaction technique 10a or 16 if A is NH.

- 5 In the case wherein A is NH, an amino protecting group (PG^0) should be introduced using general reaction technique 7. The alcohol function of the intermediates of formula V-15 can be activated using general reaction technique 2, affording the intermediates of formula V wherein n is 1. The intermediates of formula V wherein n is 2 can be obtained by reduction of the corresponding aldehydes of formula VII wherein n is 2 using general
10 reaction technique 8 followed by activation of the alcohol using general reaction technique 2.

The compounds of formula VII can be obtained by oxidation of the corresponding alcohol derivatives of formulae V-1, V-3, V-9, V-10 and V-15 using general reaction technique 9 or, in the case of compounds of formula VII wherein m is 1, n is 2 and p is 0, by reduction
15 of the nitrile derivatives of formula IV-8 with DIBAH.

The compounds of formula VIII wherein B is $(CH_2)_q$ can be prepared as described in Scheme 6 hereafter.



Scheme 6

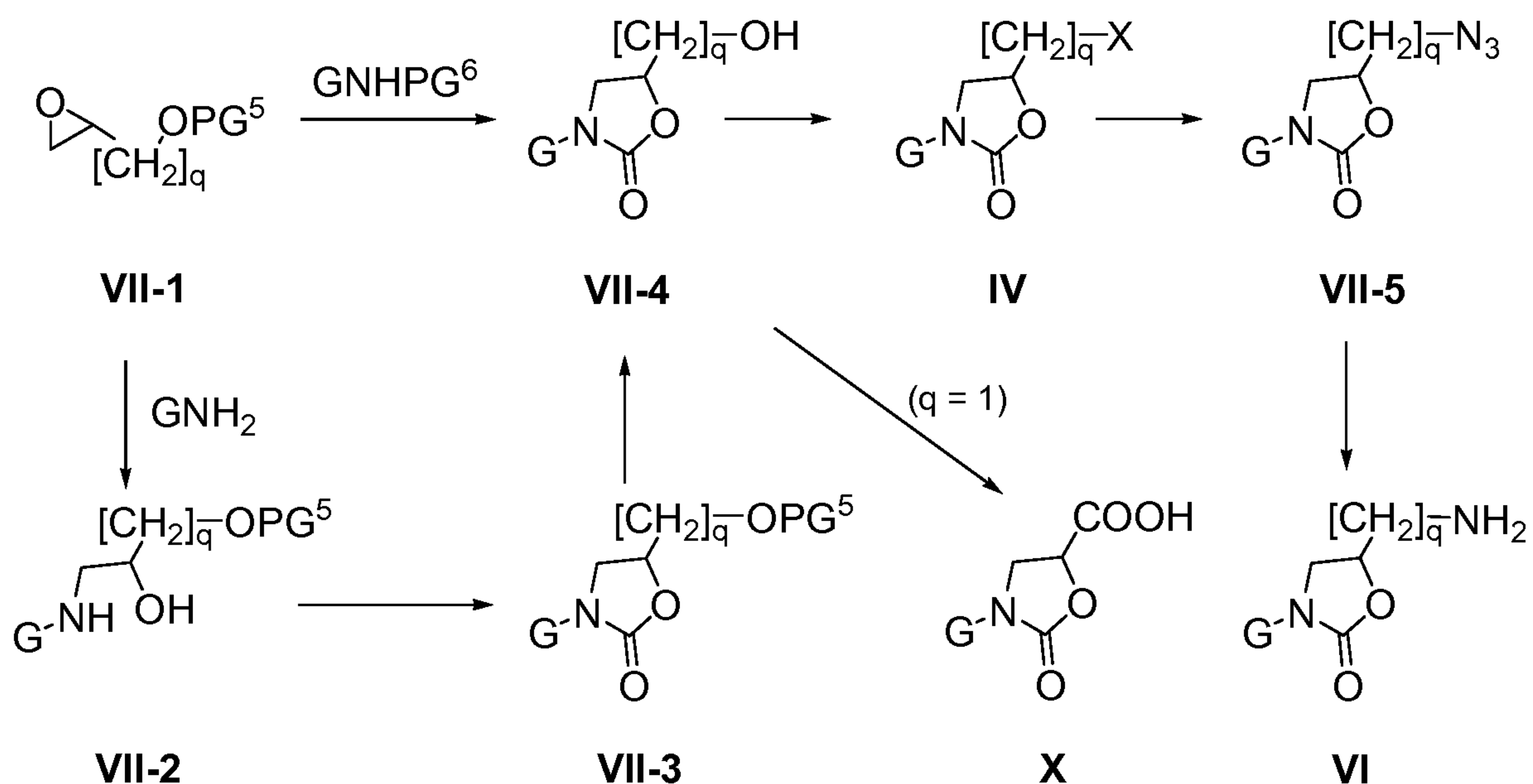
In Scheme 6, X^1 is a halogen such as fluorine, chlorine or bromine, PG^1 is an amino protecting group such as Boc or Cbz and PG^4 is a hydroxy protecting group such as
20 TBDMS.

The derivatives of formula VI-1 can be transformed into the corresponding derivatives of formula VI-2 following the same methods as described in Scheme 1 for the preparation of

compounds of formula II. The compounds of formula VIII wherein B is $(\text{CH}_2)_q$ can then be obtained by deprotection of compounds of formula VI-2 using general reaction techniques 1 and 11.

The compounds of formula VIII wherein B is CO can be obtained by removing the amino protecting group from the abovementioned compounds of formula VI-1 using general reaction technique 1 followed by formation of the corresponding amide by reaction with the compounds of formula X according to general reaction technique 17. The compounds of formula VIII can then be obtained by deprotection of compounds of formula VI-2 using general reaction technique 11.

The compounds of formulae IV, VI and X can be prepared as described in Scheme 7 hereafter.



Scheme 7

In Scheme 7, PG^5 represents a hydroxy protecting group such as TBDMS or OCOR^g wherein R^g is alkyl, PG^6 is COOR^h wherein R^h is alkyl or benzyl and X represents a halogen such as iodine or bromine, or a group of the formula OSO_2R^a wherein R^a represents methyl, trifluoromethyl or tolyl.

The epoxides of formula VII-1 wherein PG^5 is OCOR^g (e.g. glycidyl butyrate, commercial; or 3,4-epoxybutyl butyrate, prepared according to *J. Am. Chem. Soc.* (2005), 127(32), 11426-11435) can be reacted with the carbamates of formula GNHPG^6 (wherein PG^6

represents COOMe, Cbz or Boc) according to general reaction technique 12, affording the oxazolidinones of formula VII-4. Alternatively, the epoxides of formula VII-1 wherein PG⁵ is a silyl protecting group (e.g. glycidyl *tert*-butyldimethylsilyl ether; commercial) can be reacted with the aniline derivatives of formula GNH₂ affording the amino alcohol derivatives of formula VII-2. These aminoalcohols can be transformed into the oxazolidinones of formula VII-3 according to general reaction technique 6 and the hydroxy protecting group can then be removed according to general reaction technique 11 to afford the compounds of formula VII-4. The alcohols can be sequentially transformed into the corresponding derivatives of formula IV wherein X is OMs, OTs, OTf or I and into the corresponding azide derivatives of formula VII-5 using general technique 2. The amine derivatives of formula VI can then be obtained after reduction of azide derivatives of formula VII-5 according to general reaction technique 13. Besides, the acids of formula X can be obtained by oxidation of the corresponding alcohols of formula VII-4 wherein q is 1 using general reaction technique 18.

The compounds of formula IX can be obtained by protecting the amine function of compounds of formula VIII wherein B is (CH₂)_q according to general reaction technique 7, activation of the alcohol function and transformation into the corresponding azide according to general reaction technique 2 and transformation of the azide into the corresponding amine according to general reaction technique 13.

Preparation of the starting compounds:

The compounds of formula I-1 wherein A is O can be made from compounds of formula III by protection of the primary amine according to general reaction technique 7.

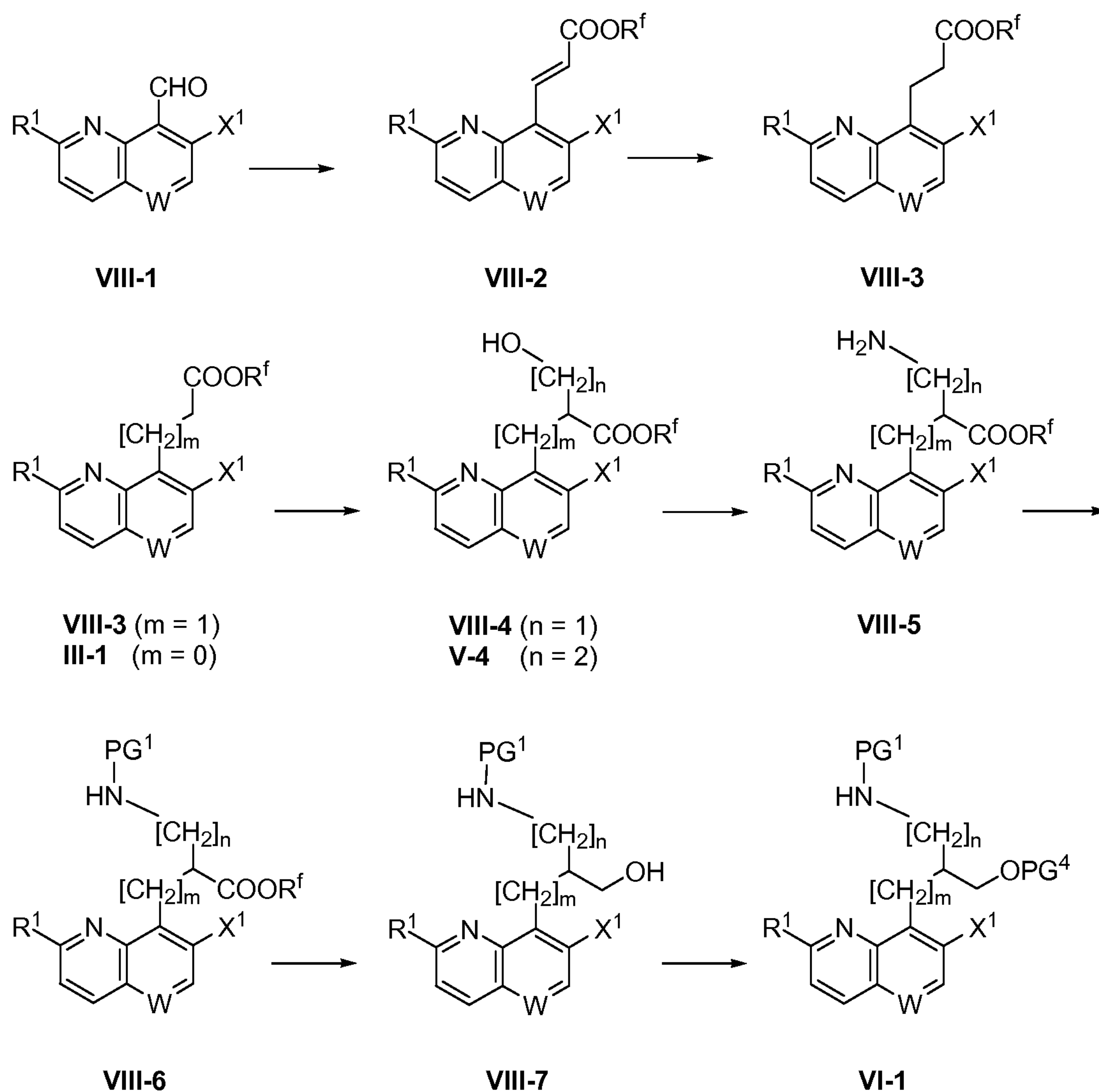
The compounds of formula I-1 wherein A is N-PG⁰, PG⁰ being Boc, Cbz or Fmoc, can be made from the compounds of formula V following sequential formation of the corresponding azide (using general reaction technique 2) and the corresponding amine (using general reaction technique 13) followed by protection of the primary amine (using general reaction technique 7).

The compounds of formula II-1 wherein W is CH, R¹ is OMe and X¹ is F can be prepared according to WO 2008/003690. The compounds of formula II-1 wherein W is N, R¹ is OMe and X¹ is F can be prepared by reduction of the corresponding formyl derivatives

(obtained according to WO 2006/032466) through reduction with NaBH_4 followed by reaction of the intermediate benzyl alcohols with PBr_3 .

The compounds of formula III-1 wherein W is CH or N, R^1 is OMe and X^1 is F can be prepared according to WO 2007/081597 and WO 2007/122258.

- 5 The compounds of formulae V-4 and VI-1 can be obtained as described in Scheme 8 hereafter.



Scheme 8

In Scheme 8, R^f is alkyl, X^1 is halogen such as fluorine, chlorine or bromine, PG^1 is an amino protecting group such as Boc, Cbz, Fmoc or benzyl and PG^4 is a hydroxy protecting group such as TBDMS.

The compounds of formula VIII-3 can be obtained by reacting the aldehydes of formula VIII-1 (e.g. $R^1 = \text{OMe}$, $X^1 = \text{F}$ and $W = \text{N}$, prepared according to WO 2006/032466) with an alkoxycarbonylmethylene triphenylphosphorane according to general reaction technique 14, followed by hydrogenation over a noble metal catalyst such as Pd/C. The intermediates of formula VIII-4 or the compounds of formula V-4 wherein m is 0 or 1 can then be obtained by reacting the corresponding compounds of formula III-1 or VIII-3 with either an aqueous formaldehyde solution or oxirane.

The alcohol derivatives of formula V-4 or VIII-4 can be activated according to general reaction technique 2 and transformed into the corresponding amines of formula VIII-5 after reaction with sodium azide and conversion into the amine according to general reaction technique 13. The amine derivatives of formula VIII-5 can be protected using general reaction technique 7 and the resulting esters of formula VIII-6 can be reduced into the corresponding alcohols of formula VIII-7 using general reaction technique 8. The primary alcohol of the compounds of formula VIII-7 can be protected according to general reaction technique 15, affording the compounds of formula VI-1.

Finally, the compounds of formula GNHPG⁶ can be obtained from the corresponding commercially available derivatives of formula GNH₂ according to general reaction technique 7.

Particular embodiments of the invention are described in the following Examples, which serve to illustrate the invention in more detail without limiting its scope in any way.

EXAMPLES

All temperatures are stated in °C. Compounds are characterized by ¹H-NMR (300 MHz) (Varian Oxford); or by ¹H-NMR (400 MHz) (Bruker Advance 400). Chemical shifts δ are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet, q = quadruplet, p = pentuplet, hex = hexet, hept = heptet, m = multiplet, br. = broad, coupling constants are given in Hz. Alternatively compounds are characterized by LC-MS (Sciex API 2000 with Agilent 1100 Binary Pump and DAD, using RP-C18 based columns); by TLC (TLC-plates from Merck, Silica gel 60 F₂₅₄); or by melting point.

Compounds are purified by chromatography on Silica gel 60A. NH_4OH as used for CC is 25% aq. Racemates can be separated into their enantiomers as described before. Preferred conditions of chiral HPLC are: ChiralPak AD (4.6x250mm, 5 μm) column, using an isocratic mixture (eg. at a ratio of 10/90) of eluent A (EtOH, in presence of diethylamine in an amount of eg. 0.1%) and eluent B (Hex), at rt, at a flow rate of eg. 0.8 mL/min.

General procedures:

Procedure A: LAH ester reduction:

To a solution of ester (1 mmol) in THF (15 mL), cooled to 0°C, is added in one portion LAH (3.5 eq.). The mixture is stirred at the same temperature for 15 to 60 min. Water (0.46 mL) is carefully added, followed by 2M NaOH (0.80 mL) and water (0.80 mL). After stirring 5 min, Na_2SO_4 (1.2 g) is added and the mixture is stirred 15 min. The solids are filtered off and thoroughly washed with EA. The filtrate is concentrated to dryness under reduced pressure. The residue is then purified by CC.

Procedure B: Boc deprotection:

The Boc protected amine (1 mmol) is dissolved in DCM (5 mL) and treated with Et_3SiH (optional; 0.2 mL, 1.1 eq.) and TFA (2 mL). The mixture is stirred at rt for 1 h, concentrated *in vacuo* and taken up in DCM/aq. NH_4OH . The org. layer is washed with water, dried over MgSO_4 and concentrated under reduced pressure.

Procedure C: intramolecular cyclisation:

To a solution of alcohol in THF (6 mL) is added KOtBu (2-4 eq.). The mixture is stirred in a sealed glass vial at 65°C until completion of the reaction (ca. 1 h). After cooling to rt, water is added and the mixture is extracted with DCM. The aq. layer is basified with NH_4OH and extracted with DCM. The combined org. layers are concentrated to dryness under reduced pressure. The residue is then purified by CC.

Procedure D: alkylation of amines with iodides:

A solution of amine (1 mmol), iodide (1 mmol) and DIPEA (1.1 mmol) in dry DMSO is heated to 70°C until completion of the reaction (1-3 days). After cooling, water and EA are added and the phases are separated. The aq. layer is extracted two more times with EA and

the combined org. layers are washed with water (3 x) and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue is then purified by CC.

Procedure E: alkylation of amines with mesylates:

5 A solution of the amine (1.0-2.3 mmol), the mesylate (1 mmol) and DIPEA (1.1 mmol) in dry DMSO is heated to 70°C until completion of the reaction (2-5 days). After cooling, water and EA are added and the phases are separated. The aq. layer is extracted two more times with EA and the combined org. layers are washed with water (3x) and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue is then purified by CC.

Procedure F: Boc protection:

10 To a solution of amine in DCM or THF are added TEA (1.5 eq.) and Boc₂O (1.05 eq.). The reaction is stirred at rt until completion of the reaction. The reaction mixture is then concentrated under reduced pressure.

Example 1: 6-((R)-5-{[[(RS)-6-methoxy-3,4-dihydro-2H-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

15 *1.i. rac-2-(tert-butoxycarbonylamino-methyl)-3-(7-fluoro-2-methoxy-quinolin-8-yl)-propionic acid ethyl ester:*

To a solution of LiHMDS (1M, 20 mL), cooled to -78°C, was added dropwise a solution of 3-tert-butoxycarbonylamino-propionic acid ethyl ester (2.01 g, 9.26 mmol; prepared according to *Tetrahedron Lett.* (2003), **44**(14), 2807) in THF (20 mL). The solution was stirred at the same temperature for 90 min. A solution of 8-bromomethyl-7-fluoro-2-methoxy-quinoline (2.5 g, 1 eq., prepared according to WO 2007/081597) in THF (10 mL) was quickly added and the reaction proceeded 2 h, keeping the internal temperature below -50°C. Water (100 mL) and EA (200 mL) were added. The two layers were separated and the aq. layer was extracted with EA. The combined org. layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was purified by CC (Hept-EA 2-1) to afford the title intermediate as a pale yellow oil which solidified after standing at rt for one day (2.83 g, 75% yield).

25 MS (ESI, m/z): 407.3 [M+H⁺].

1.ii. *rac*-[3-(7-fluoro-2-methoxy-quinolin-8-yl)-2-hydroxymethyl-propyl]-carbamic acid *tert*-butyl ester:

Starting from intermediate 1.i and using procedure A, the title intermediate was obtained as a colourless oil (534 mg, 93% yield).

5 MS (ESI, *m/z*): 365.1 [M+H⁺].

1.iii. *rac*-2-aminomethyl-3-(7-fluoro-2-methoxy-quinolin-8-yl)-propan-1-ol:

Starting from intermediate 1.ii and using procedure B, the title intermediate was obtained as a colourless oil (311 mg, 52% yield).

MS (ESI, *m/z*): 265.3 [M+H⁺].

10 1.iv. *rac*-C-(6-methoxy-3,4-dihydro-2H-1-oxa-5-aza-phenanthren-3-yl)-methylamine:

Starting from intermediate 1.iii and using procedure C, the title intermediate was obtained as a colourless oil (120 mg, 47% yield).

MS (ESI, *m/z*): 245.3 [M+H⁺].

1.v. 6-((*S*)-3-chloro-2-hydroxy-propylamino)-4H-benzo[1,4]thiazin-3-one:

15 A suspension of 6-amino-4H-benzo[1,4]thiazin-3-one (18.0 g, 100 mmol; commercial) and Ca(OTf)₂ (0.5 eq.) in MeCN (800 mL) was heated at 50° for 1 h. (*S*)-epichlorohydrin (18.5 g, 200 mmol) was added and the mixture was stirred at rt for 72 h and at 45°C for 24 h. The volatiles were removed under reduced pressure. After aqueous workup and extraction with EA, the title intermediate crystallized from EA to afford a beige solid
20 (17.38 g, 64% yield).

MS (ESI, *m/z*): 273.2 [M+H⁺].

1.vi. 6-((*S*)-5-chloromethyl-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

A solution of intermediate 1.v (17.38 g, 63.7 mmol) in THF (300 mL) was treated with CDI (1.2 eq.) and stirred at rt for 30 min and at 50°C for 5 h. The mixture was
25 concentrated, diluted with EA and washed with water and brine, dried over MgSO₄ and concentrated. The residue was purified by CC (EA/Hept 2:1, EA) to afford the title intermediate as a pale yellow solid (14.0 g, 74% yield).

MS (ESI, *m/z*): 299.1 [M+H⁺].

1.vii. 6-((S)-5-iodomethyl-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

A mixture of intermediate 1.vi (14.0 g, 46.9 mmol) and NaI (3 eq.) in 2-butanone (150 mL) was heated at 85°C for 2 days. After cooling to rt, the mixture was diluted with 10% Na₂S₂O₃ (300 mL) and ether/EA (100 mL). The mixture was vigorously stirred for 10 min and filtered. The solids were thoroughly washed with water and ether and dried at HV to afford a pale beige solid. The phases of the combined filtrates were separated and the org. phase washed with brine, dried over MgSO₄ and concentrated to afford a pale beige solid. The solids of both processes were combined to afford the title intermediate as a pale beige solid (15.0 g, 82% yield).

10 MS (ESI, m/z): 391.4 [M+H⁺].

1.viii. 6-((R)-5-{[((RS)-6-methoxy-3,4-dihydro-2H-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

Starting from intermediates 1.iv and 1.vii and using procedure D, the title compound was obtained as a colourless solid (40 mg, 36% yield).

15 ¹H NMR (CDCl₃) δ: 8.39 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.43 (m, 2H), 7.27 (m, 1H), 6.93 (m, 2H), 6.74 (d, J = 8.8 Hz, 1H), 4.77 (m, 1H), 4.34 (m, 1H), 3.95 (m, 6H), 3.60-3.30 (m, 5H), 2.91 (m, 4H), 2.26 (m, 1H).

MS (ESI, m/z): 506.9 [M+H⁺].

Example 2: 6-((R)-5-{[((RS)-6-methoxy-3,4-dihydro-2H-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]oxazin-3-one:*2.i. 6-[(S)-3-(tert-butyl-dimethyl-silanyloxy)-2-hydroxy-propylamino]-4H-benzo[1,4]oxazin-3-one:*

To a solution of *tert*-butyl-dimethyl-((S)-1-oxiranylmethoxy)-silane (commercial; 13.0 g, 69 mmol) in MeCN (220 mL) was added LiClO₄ (22 g, 207 mmol). 6-amino-4H-benzo[1,4]oxazin-3-one (commercial; 11.45 g, 64 mmol) was added and the mixture was stirred at 50°C for 6 h. The solvent was removed *in vacuo* and the residue was purified by CC (DCM/MeOH/NH₄OH 1000/25/2 to 1000/100/2) to afford the title intermediate as a pale brown foam (11.16 g, 44% yield).

25 MS (ESI, m/z): 353.3 [M+H⁺].

2.ii. 6-[(S)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2-oxo-oxazolidin-3-yl]-4H-benzo[1,4]oxazin-3-one:

A solution of intermediate 2.i (11.16 g, 30 mmol) and CDI (5.57 g, 33 mmol) in THF (130 mL) was heated at 50°C for 2 h; the mixture was concentrated *in vacuo* and partitioned between EA and water. Some crystallized product was filtered and washed with H₂O and EA to afford 5.21 g of solid. The org. layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by purified by CC (DCM/MeOH 1000:50:4) to give additional 2.28 g of product as a colourless solid (total: 7.49 g, 63% yield).

MS (ESI, m/z): 379.2 [M+H⁺].

2.iii. 6-((S)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]oxazin-3-one:

A suspension of intermediate 2.ii (11.49 g, 29.1 mmol) in THF (30 mL) was treated with TBAF (1M in THF, 29.1 mL). The yellow solution was stirred at 0°C for 3 h and then partitioned between water and EA. Some crystallized product was filtered and washed with H₂O and EA to give 6.49 g of an off-white solid. The aq. phase was extracted with EA (3x). The combined org. layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was triturated with EA to give 1.23 g of an off-white solid (total: 7.72 g, 95% yield).

MS (ESI, m/z): 265.5 [M+H⁺].

2.iv. Methanesulfonic acid (S)-2-oxo-3-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-oxazolidin-5-ylmethyl ester:

A suspension of intermediate 2.iii (5.45 g, 20.6 mmol) in anhydrous DCM (110 mL) was treated with DIPEA (3.5 eq.) and the mixture was cooled to 0°C. Ms₂O (1.5 eq.) was added dropwise. The resulting mixture was stirred at 0°C for 15 min. Water was added and stirring was continued for 15 min at rt. The precipitated product was filtered, washed with water and DCM, and triturated with DCM/MeOH/NH₄OH (1000/25/2) to give the title intermediate as a colourless solid (3.75 g, 53% yield).

¹H NMR (DMSO-d₆) δ: 10.72 (s, 1H), 7.29 (dd, J = 2.1, 0.6 Hz, 1H), 6.94 (m, 2H), 4.95 (m, 1H), 4.52 (s, 2H), 4.49 (m, 2H), 4.11 (t, J = 9.1 Hz, 1H), 3.73 (m, 2H), 3.23 (s, 3H).

MS (ESI, m/z): 343.3 [M+H⁺].

2.v. 6-((R)-5-[[((RS)-6-methoxy-3,4-dihydro-2H-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-methyl]-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]oxazin-3-one:

Starting from intermediates 1.iv and 2.iv and using procedure E, the title compound was obtained as a colourless solid (9 mg, 11% yield).

5 MS (ESI, m/z): 490.9 [M+H⁺].

Example 3: 6-((R)-5-[[((RS)-6-methoxy-3,4-dihydro-2H-1-oxa-5,9-diaza-phenanthren-3-ylmethyl)-amino]-methyl]-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]oxazin-3-one:

3.i. (3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-methanol:

10 To an ice-chilled suspension of 3-fluoro-6-methoxy-[1,5]naphthyridine-4-carbaldehyde (5 g, 24.25 mmol; prepared as in WO 2006/032466) in MeOH (180 mL) was added NaBH₄ (1.03 g, 26.68 mmol, 1.1 eq.) in one portion. After 30 min, the reaction mixture was warmed to rt. Water (180 mL) was added and the volatiles were removed under reduced pressure. The residue was filtered off and washed with water. The aq. filtrate was extracted
15 twice with EA (2 x 100 mL). The combined org. layers were washed with brine (120 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure to afford a yellow solid. The residue was purified by CC (Hept-EA 1:1) to give the title intermediate as a pale yellow solid (4.01 g, 79% yield).

MS (ESI, m/z): 209.4 [M+H⁺].

20 3.ii. 8-bromomethyl-7-fluoro-2-methoxy-[1,5]naphthyridine:

To a solution of intermediate 3.i (4.01 g, 19.2 mmol) in DMF (28.5 mL) was added at rt PBr₃ (2 mL). After stirring the reaction at rt for 80 min, water (95 mL) and sat. NaHCO₃ (ca. 45 mL) were added until no gas evolution was observed any longer. The solid that formed was filtered off and washed with water. The solid was taken up in EA (250 mL),
25 dried over MgSO₄, and the solution was directly filtered through a pad of silica gel. The filtrate was concentrated to dryness to give the title intermediate as a pale yellow solid (4.60 g, 88% yield).

MS (ESI, m/z): 270.9 [M+H⁺].

3.iii. *rac*-2-(*tert*-butoxycarbonylamino-methyl)-3-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-propionic acid ethyl ester:

To a solution of LiHMDS (1M, 17 mL), cooled to -78°C, was added dropwise a solution of 3-*tert*-butoxycarbonylamino-propionic acid ethyl ester (1.7 g, 7.8 mmol; prepared according to *Tetrahedron Lett.* (2003), **44**(14), 2807) in THF (20 mL). The solution was stirred at the same temperature for 90 min. A solution of intermediate 3.ii (2.1 g, 7.8 mmol) in THF (10 mL) was quickly added and the reaction proceeded 2 h, keeping the internal temperature below -50°C. Water (100 mL) and EA (200 mL) were added. The two layers were decanted and the aq. layer was extracted with EA. The combined org. layers were washed with brine, dried over MgSO₄, filtered and concentrated to dryness. The residue was purified by CC (Hept-EA 2:1) to afford the title intermediate as a pale yellow oil (2.38 g, 75% yield).

MS (ESI, m/z): 408.6 [M+H⁺].

3.iv. *rac*-[3-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-2-hydroxymethyl-propyl]-carbamic acid *tert*-butyl ester:

Starting from intermediate 3.iii and using procedure A, the title compound was obtained as a pale yellow oil (1.59 g, 74% yield).

MS (ESI, m/z): 366.2 [M+H⁺].

3.v. *rac*-aminomethyl-3-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-propan-1-ol:

Starting from intermediate 3.iv and using procedure B, the title compound was obtained as a yellow oil (688 mg, 100% yield).

MS (ESI, m/z): 266.2 [M+H⁺].

3.vi. *rac*-C-(6-methoxy-3,4-dihydro-2H-1-oxa-5,9-diaza-phenanthren-3-yl)-methylamine:

Starting from intermediate 3.v and using procedure C, the title compound was obtained as a yellow oil (150 mg, 52% yield).

MS (ESI, m/z): 246.3 [M+H⁺].

3.vii. 6-((*R*)-5-{[*((R)*)-6-methoxy-3,4-dihydro-2*H*-1-oxa-5,9-diaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one:

Starting from intermediates 3.vi and 2.iv and using procedure E, the title compound was obtained as a colourless solid (47 mg, 26% yield).

5 MS (ESI, *m/z*): 492.0 [*M*+*H*⁺].

Example 4: 6-((*R*)-5-{[*((R)*)-6-methoxy-3,4-dihydro-2*H*-1-oxa-5,9-diaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one:

Starting from intermediates 3.vi and 1.vii and using procedure D, the title compound was
10 obtained as a pale yellow foam (31 mg, 25% yield).

¹H NMR (CDCl₃) δ: 8.40 (s, 1H), 8.24 (s, 1H), 8.10 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.28 (m, 1H), 6.93 (m, 2H), 4.78 (m, 1H), 4.38 (m, 1H), 4.06 (m, 5H), 3.86 (m, 1H), 3.42 (s, 2H), 3.32 (m, 1H), 3.08 (m, 1H), 2.84 (m, 4H), 2.29 (m, 1H).

MS (ESI, *m/z*): 508.0 [*M*+*H*⁺].

15 **Example 5: 6-((*R*)-5-{[*((R)*)-6-methoxy-1,2,3,4-tetrahydro-1,5,9-triaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one:**

5.i. *rac*-(6-methoxy-1,2,3,4-tetrahydro-1,5,9-triaza-phenanthren-3-yl)-methanol:

To a solution of intermediate 3.v (298 mg, 1.12 mmol) in NMP (8 mL) was added DIPEA (1.2 eq.). The mixture was stirred in a sealed glass vial at 90°C for 6 h. After cooling to rt,
20 water was added and the mixture was extracted with EA (2 x). The org. layer was washed several times with water and once with brine, dried over MgSO₄ and concentrated. The residue was purified by CC (DCM-MeOH-NH₄OH 1000:100:8) to afford the title intermediate as a colourless foam (84 mg, 30% yield).

MS (ESI, *m/z*): 246.1 [*M*+*H*⁺].

25 5.ii. *rac*-*C*-(6-methoxy-1,2,3,4-tetrahydro-1,5,9-triaza-phenanthren-3-yl)-methylamine:

PPh₃ (143 mg, 0.54 mmol) was dissolved in THF (2 mL) and then cooled to 0°C. DIAD (116 mg, 0.54 mmol) was then added via a syringe at 0°C. After the solution was stirred for 15 min (yellow suspension), a solution of intermediate 5.i (88 mg, 0.36 mmol) in THF (1 mL) was slowly added, followed immediately by the addition of DPPA (151 mg,

0.54 mmol). The reaction mixture was allowed to warm to rt and stirred for 4 h. The mixture was concentrated and the residue was filtered over a short pad of silica gel using EA as eluent. The solution was concentrated and the resulting crude azide intermediate was dissolved in THF (1.5 mL). To this solution was added PPh₃ (194 mg, 0.74 mmol) and water (0.67 mL, 10 eq.). The mixture was heated at 50°C for 1 h. The reaction mixture was concentrated and the residue was taken in DCM and extracted with 10% citric acid (2x). The comb. aq. layers were basified with NH₄OH and then extracted with 9:1 DCM-MeOH (3x). The comb. org. layers were concentrated and the residue was purified by CC (DCM-MeOH-NH₄OH 1000:100:8 to 1000:200:16) to afford the title intermediate as a yellow solid (31 mg, 35% yield).

MS (ESI, m/z): 245.2 [M+H⁺].

5.iii. 6-((R)-5-{[((RS)-6-methoxy-1,2,3,4-tetrahydro-1,5,9-triaza-phenanthren-3-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

Starting from intermediates 5.ii and 1.vii and using procedure D, the title compound was obtained as a pale yellow foam (14 mg, 21% yield).

MS (ESI, m/z): 507.1 [M+H⁺].

Example 6: 6-((R)-5-{[2-((RS)-2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

6.i. rac-3-cyano-2-(7-fluoro-2-methoxy-quinolin-8-yl)-propionic acid methyl ester:

To a solution of (7-fluoro-2-methoxy-quinolin-8-yl)-acetic acid methyl ester (1.0 g, 4.0 mmol; prepared as in WO 2007/081597) in THF (10 mL) cooled to -78°C was added LiHMDS (1M, 4.43 mL, 1.2 eq.) dropwise over 15 min. The resulting orange mixture was stirred at -78°C for 2 h. Bromoacetonitrile (1.5 eq.) was added dropwise over 20 min and stirring was continued at -78°C for an additional 2 h. The reaction was quenched with water and extracted with EA (3x). The combined org. phases were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by CC (Hept/EA 2:1 to 1:1) to afford the title intermediate as a colourless solid (953 mg, 82% yield).

MS (ESI, m/z): 289.4 [M+H⁺].

6.ii. *rac*-4-amino-2-(7-fluoro-2-methoxy-quinolin-8-yl)-butan-1-ol:

To a solution of AlCl_3 (967 mg, 7.25 mmol) in Et_2O (50 mL) cooled to -78°C was added LAH (1M in THF, 7.25 mL) within 10 min. After stirring for 15 min at -78°C , a suspension of intermediate 6.i (950 mg, 3.30 mmol) in Et_2O (40 mL) was added within 5 15 min. The resulting suspension was then stirred at rt for 4 h, cooled to 0°C , and quenched with sat. Na_2SO_4 . The mixture was basified with NH_4OH and extracted with EA (3x). The combined org. phases were dried over Na_2SO_4 , filtered and concentrated to afford the title intermediate as a yellow oil (870 mg, 100% yield).

MS (ESI, m/z): 265.3 $[\text{M}+\text{H}^+]$.

10 6.iii. *rac*-2-(2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamine:

Starting from intermediate 6.ii and using procedure C, the title compound was obtained as a yellow foam (236 mg, 96% yield).

MS (ESI, m/z): 245.1 $[\text{M}+\text{H}^+]$.

15 6.iv. 6-((*R*)-5-{[2-((*RS*)-2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one:

Starting from intermediates 6.iii and 1.vii and using procedure D, the title compound was obtained as an off-white foam (18 mg, 8% yield).

MS (ESI, m/z): 507.0 $[\text{M}+\text{H}^+]$.

20 **Example 7: 6-((*R*)-5-{[2-((*RS*)-2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one:**

Starting from intermediates 6.iii and 2.iv and using procedure E, the title compound was obtained as a pale yellow foam (14 mg, 6% yield).

MS (ESI, m/z): 490.9 $[\text{M}+\text{H}^+]$.

Example 8: 6-((R)-5-[[[(RS)-2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-ylmethyl)-amino]-methyl]-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one:

8.i. rac-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-(7-fluoro-2-methoxy-quinolin-8-yl)-propionic acid methyl ester:

- 5 To a solution of LiHMDS (1*M* in THF, 9.6 mL) was added at -78°C a solution of (7-fluoro-2-methoxy-quinolin-8-yl)-acetic acid methyl ester (2.0 g, 8.0 mmol; prepared as in WO 2007/081597) in THF (16 mL) over 10 min. After stirring the resulting orange mixture for 1 h at -78°C, a solution of *N*-(bromomethyl)phthalimide (1.2 eq.) in THF (16 mL) was added dropwise over 10 min. The mixture was stirred 1 h at -78°C and then at
10 rt overnight. The yellow solution was quenched with 1*N* HCl (80 mL) and then extracted with DCM. The combined org layers were washed with water, dried over MgSO₄, concentrated and purified by CC (Hept/EA 1:1) to give 1.89 g of a yellow solid which was recrystallized from EA/MeOH/NH₄OH (90:10:1) to afford the title intermediate as a colourless solid (924 mg, 28% yield).
15 MS (ESI, *m/z*): 409.3 [M+H⁺].

8.ii. rac-3-tert-butoxycarbonylamino-2-(7-fluoro-2-methoxy-quinolin-8-yl)-propionic acid methyl ester:

- To a suspension of intermediate 8.i (774 mg, 1.90 mmol) in EtOH (10 mL) was added dropwise hydrazine monohydrate (0.46 mL, 5 eq.) at rt. The mixture was stirred for 2 h at
20 rt. The solvent was removed under reduced pressure and the colourless residue taken up in EA and citric acid 10%. The layers were separated and the aq. phase was washed with EA. The org. layers were discarded. The product containing aq. phase was rebaseified with NH₄OH and extracted twice with DCM. The combined DCM phases were dried over MgSO₄ and concentrated to afford a pale yellow solid (526 mg). The thus obtained free
25 amine was Boc protected according to procedure F to afford the title intermediate as a pale yellow foam (656 mg, 92% yield).

MS (ESI, *m/z*): 379.1 [M+H⁺].

8.iii. *rac*-[2-(7-fluoro-2-methoxy-quinolin-8-yl)-3-hydroxy-propyl]-carbamic acid *tert*-butyl ester:

Starting from intermediate 8.ii and using procedure A, the title compound was obtained as a pale yellow foam (675 mg, 81% yield).

5 MS (ESI, *m/z*): 351.3 [M+H⁺].

8.iv. *rac*-3-amino-2-(7-fluoro-2-methoxy-quinolin-8-yl)-propan-1-ol:

Starting from intermediate 8.iii and using procedure B, the title compound was obtained as a pale yellow oil (266 mg, 92% yield).

MS (ESI, *m/z*): 251.1 [M+H⁺].

10 8.v. *rac*-C-(2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-methylamine:

Starting from intermediate 8.iv and using procedure C, the title compound was obtained as a yellow oil (59 mg, 24% yield).

MS (ESI, *m/z*): 231.4 [M+H⁺].

15 8.vi. 6-((*R*)-5-{[(*RS*)-2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one:

Starting from intermediates 8.v and 1.vii and using procedure D, the title compound was obtained as an off-white foam (9 mg, 15% yield).

MS (ESI, *m/z*): 492.9 [M+H⁺].

20 **Example 9: 6-((*R*)-5-{[2-((*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one:**

9.i. *rac*-3-cyano-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-propionic acid ethyl ester:

25 LiHMDS in THF (1*M*; 12.5 mL) was added at -78°C during 15 min to a solution of (3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-acetic acid ethyl ester (3.00 g; prepared in analogy to the corresponding methyl ester described in WO 2007/122258) in THF (30 mL). The resulting orange mixture was stirred at -78°C for 2 h. Bromoacetonitrile (1.13 mL) was added dropwise and the reaction mixture was further stirred at -78°C for 2 h. The reaction mixture was treated with water and extracted with EA. The combined

org. phases were washed with brine, dried over MgSO_4 , filtered and concentrated. The crude product was purified by CC (Hept/EA 2:1 to 1:1) affording a yellow oil (3.09 g; 89.7% yield).

MS (ESI, m/z): 304.4 $[\text{M}+\text{H}^+]$.

5 *9.ii. rac-4-amino-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-butan-1-ol:*

A solution of LAH in THF (1M; 22 mL) was added dropwise at -78°C to a solution of AlCl_3 in Et_2O (100 mL). After stirring for 15 min a solution of intermediate 9.i (3.0 g) in Et_2O (140 mL) was added dropwise. After further stirring at -78°C for 1 h, the suspension was allowed to reach 0°C over 5 h. The reaction mixture was sequentially treated with a
10 sat. aq. Na_2SO_4 solution, water and aq. NH_4OH before extraction with EA. The org. phase was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by CC (DCM/MeOH/ NH_4OH 1000:100:8 to 1000:200:16), affording a yellow oil (1.0 g; 38% yield).

MS (ESI, m/z): 266.3 $[\text{M}+\text{H}^+]$.

15 *9.iii. rac-2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[a]naphthalen-1-yl)-ethylamine:*

$t\text{BuOK}$ (840 mg) was added to a solution of intermediate 9.ii (994 mg) in THF (16 mL). The mixture was stirred in a sealed glass vial at 70°C for 10 min. After cooling to rt, water was added and the mixture was extracted with DCM (3x). The combined org. layers were
20 dried over MgSO_4 and concentrated to dryness. The residue was purified by CC (DCM/MeOH/ NH_4OH 1000:100:8), affording a yellow oil (330 mg; 36.4% yield).

MS (ESI, m/z): 246.3 $[\text{M}+\text{H}^+]$.

9.iv. 6-((R)-5-{[2-((RS)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[a]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

25 Starting from intermediates 1.vii (74.2 mg) and 9.iii (45 mg) and using procedure D, the title compound was obtained as a yellow foam (18 mg; 21% yield).

MS (ESI, m/z): 508.2 $[\text{M}+\text{H}^+]$.

Example 10: 6-((*R*)-5-{[2-((*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one:

Starting from intermediates 2.iv (55.8 mg) and 9.iii (40 mg) and using procedure D, the title compound was obtained as a light brown foam (3 mg; 2% yield).

MS (ESI, *m/z*): 492.0 [*M*+*H*⁺].

Example 11: (*R*)-3-(3-fluoro-4-methyl-phenyl)-5-{[2-((*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-oxazolidin-2-one:

Starting from intermediate 9.iii (40 mg) and (5*S*)-3-(3-fluoro-4-methylphenyl)-5-(iodomethyl)-2-oxazolidinone (56 mg; prepared according to WO 2008/126034) and proceeding in analogy to Example 10, the title compound was obtained as a yellow oil (1 mg; 1% yield).

MS (ESI, *m/z*): 453.1 [*M*+*H*⁺].

Example 12: 6-((*S*)-5-{[2-((*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one:

Starting from intermediate 9.iii (40 mg) and 6-((*R*)-5-iodomethyl-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one (63 mg; prepared according to WO 2008/126034) and proceeding in analogy to Example 10, the title compound was obtained as a light yellow solid (12 mg; 15% yield).

MS (ESI, *m/z*): 508.0 [*M*+*H*⁺].

Example 13: 6-((*R*)-5-{2-[2-((*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[*a*]naphthalen-1-yl)-ethylamino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one:

13.i. 6-[(*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-2-hydroxy-butylamino]-4*H*-benzo[1,4]thiazin-3-one:

A solution of (2*R*)-2-[2-[[*tert*-butyldimethylsilyl]oxy]ethyl]-oxirane (12.0 g; prepared according to WO 2007/144423) and 6-amino-4*H*-benzo[1,4]thiazin-3-one (10.7 g;

commercial) in EtOH/water (9:1) was heated to 80°C for 2 days. The solvents were removed under reduced pressure and the residue was triturated in ether/MeOH and filtered. The filtrate was evaporated under reduced pressure, affording a brown oil (18.8 g; 83% yield).

5 MS (ESI, m/z): 383.2 [M+H⁺].

13.ii. 6-{(R)-5-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-2-oxo-oxazolidin-3-yl}-4H-benzo[1,4]thiazin-3-one:

Starting from intermediate 13.i (23.5 g) and CDI (7.97 g) and proceeding in analogy to Example 1, step 1.vi, the title compound was obtained as a colourless solid (8.40 g; 42%
10 yield).

MS (ESI, m/z): 409.3 [M+H⁺].

13.iii. 6-[(R)-5-(2-hydroxy-ethyl)-2-oxo-oxazolidin-3-yl]-4H-benzo[1,4]thiazin-3-one:

Starting from intermediate 13.ii (8.4 g) and proceeding in analogy to Example 2, step 2.iii, the title compound was obtained as a colourless solid (4.79 g; 79% yield).

15 MS (ESI, m/z): 295.5 [M+H⁺].

13.iv. Methanesulfonic acid 2-[(R)-2-oxo-3-(3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl)-oxazolidin-5-yl]-ethyl ester:

Starting from intermediate 13.iii (4.7 g) and proceeding in analogy to Example 2, step 2.iv, the title compound was obtained as a colourless solid (5.80 g; 98% yield).

20 MS (ESI, m/z): 373.4 [M+H⁺].

13.v. 6-((R)-5-{2-[2-((RS)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[a]naphthalen-1-yl)-ethylamino]-ethyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

Starting from intermediates 13.iv and 9.iii and using procedure E, the title compound was
25 obtained as a light yellow solid (19 mg, 22% yield).

¹H NMR (CDCl₃) δ: 8.80 (s, 1H), 8.44 (s, 1H), 8.07 (d, J = 9.1 Hz, 1H), 7.38 (m, 1H), 7.27 (m, 1H), 6.98 (m, 1H), 6.87 (d, J = 8.8 Hz, 1H), 5.09 (m, 1H), 4.80 (m, 1H), 4.14 (m, 1H), 4.03 (m, 3H), 3.67 (m, 1H), 3.48 (m, 1H), 3.38 (m, 1H), 3.23 (d, J = 9.7 Hz, 1H), 2.95 (m, 2H), 2.49 (m, 4H), 2.13 (m, 2H), 1.90 (m, 1H).

MS (ESI, m/z): 522.2 [M+H⁺].

Example 14: 6-((R)-5-{2-(((RS)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[a]naphthalen-1-ylmethyl)-amino)-ethyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

5 14.i. *rac*-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-propionic acid ethyl ester:

A solution of (3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-acetic acid ethyl ester (6.78 g; prepared in analogy to the corresponding methyl ester described in WO 2007/122258) in THF (30 mL) was added dropwise at -78°C to a solution of LiHMDS (31 mL; 1M in THF) 10 diluted in THF (20 mL). After stirring for 1 h at -78°C a solution of *N*-(bromomethyl)phthalimide (7.40 g) in THF (30 mL) was added dropwise and the mixture was stirred for an additional 1 h at -78°C and then overnight at rt. The yellow solution was quenched with 1N HCl (280 mL) and extracted with DCM. The combined org. layers were washed with H₂O, dried over MgSO₄, concentrated and purified by CC 15 (Hept/EA 1:1), affording a light yellow foam (5.49 g; 51% yield).

MS (ESI, m/z): 424.2 [M+H⁺].

14.ii. *rac*-3-amino-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-propionic acid ethyl ester:

Hydrazine monohydrate (3.15 mL) was added dropwise at rt to a suspension of the 20 intermediate 14.i (5.5 g) in EtOH (90 mL) and the mixture was further stirred for 2 h at rt. The solvent was removed under reduced pressure and the residue was taken up in EA and aq. citric acid (10%). The aq. layer was washed with EA, treated with aq. NH₄OH (28%) and extracted twice with DCM. The combined DCM phases were dried over MgSO₄ and concentrated under reduced pressure, affording a yellow oil (2.59 g; 68% yield).

25 MS (ESI, m/z): 294.2 [M+H⁺].

14.iii. *rac*-3-*tert*-butoxycarbonylamino-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-propionic acid ethyl ester:

Starting from intermediate 14.ii (2.59 g) using procedure F, the title compound was obtained as an orange oil (2.91 g, 97% yield).

MS (ESI, m/z): 394.2 [M+H⁺].

14.iv. rac-[2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-3-hydroxy-propyl]-carbamic acid tert-butyl ester:

Starting from intermediate 14.iii (2.23 g) using procedure A, the title compound was
5 obtained as a yellow foam (2.3 g, quantitative yield).

MS (ESI, m/z): 352.2 [M+H⁺].

14.v. rac-3-amino-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-propan-1-ol:

Starting from intermediate 14.iv (850 mg) using procedure B, the title compound was
obtained as an orange gum (644 mg; quantitative yield).

10 MS (ESI, m/z): 252.2 [M+H⁺].

14.vi. rac-C-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[a]naphthalen-1-yl)-methylamine:

Starting from intermediate 14.v (200 mg) and using procedure C, the title compound was
obtained as a yellow solid (61 mg, 33% yield).

15 MS (ESI, m/z): 232.3 [M+H⁺].

14.vii. 6-((R)-5-{2-[(RS)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[a]naphthalen-1-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

Starting from intermediates 14.vi (20 mg) and 13.iv (32 mg) and using procedure E, the
20 title compound was obtained as a light yellow solid (10 mg, 23% yield).

MS (ESI, m/z): 508.0 [M+H⁺].

Example 15: 6-((S)-5-{2-[(RS)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[a]naphthalen-1-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

25 *15.i. Methanesulfonic acid 2-[(S)-2-oxo-3-(3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl)-oxazolidin-5-yl]-ethyl ester:*

Starting from (2S)-2-[2-[[*tert*-butyldimethylsilyl]oxy]ethyl]-oxirane (prepared according to *J. Org. Chem.* (1992), **57**, 353-358) and proceeding in analogy to Example 13, steps 13.i to

13.iv, the title compound was obtained as an off-white solid. The yields for the preparation were similar and the analytical data (^1H NMR and MS) were identical.

15.ii. 6-((*S*)-5-{2-[(*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[*a*]naphthalen-1-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one:

Starting from intermediates 14.vi (20 mg) and 15.i (32 mg) and using procedure E, the title compound was obtained as a light yellow foam (12 mg, 27% yield).

MS (ESI, m/z): 508.0 [$\text{M}+\text{H}^+$].

Example 16: (*S*)-3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-2-oxo-oxazolidine-5-carboxylic acid [2-((*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[*a*]naphthalen-1-yl)-ethyl]-amide:

T3P[®] (114 mg; 0.11 mL; 50% in EA) was added at 0 °C to a solution of (*5S*)-3-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-oxo-5-oxazolidinecarboxylic acid (43 mg; prepared according to WO 2008/126024), intermediate 9.iii (40 mg) and DIPEA (56 μL) in DMF (1 mL). The mixture was allowed to reach rt and was further stirred at rt temperature for 2 h. Water was added and the mixture was twice extracted with EA. The org. layers were washed with water and aq. citric acid (10%). The aq. layer was basified with NaHCO_3 and extracted with EA. The combined org. layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The product was purified by CC (DCM/MeOH/ NH_4OH 1000:50:4), affording a light yellow foam (10 mg; 12% yield).

MS (ESI, m/z): 492.9 [$\text{M}+\text{H}^+$].

Example 17: 6-((*R*)-5-{[(*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one:

17.i. 8-allyl-7-chloro-2-methoxy-[1,5]naphthyridine:

A flask charged with trifluoromethanesulfonic acid 3-chloro-6-methoxy-[1,5]naphthyridin-4-yl ester (1.50 g; prepared according to WO 2004/058144), allyltributylstannane (1.68 g) and DMF was degassed with N_2 . The reaction mixture was treated with LiCl (695 mg) and $\text{Pd}(\text{PPh}_3)_4$ (126 mg) and further stirred at 100 °C for 4 h. After cooling, the mixture was

poured into 10% aq. NH_4OH and EA, the aq. layer was extracted with EA and the combined org. layers were washed with water (2x) and brine, dried over MgSO_4 and concentrated. The residue was purified by CC (Hept/EA 4:1), affording a yellow oil (795 mg; 77% yield).

5 MS (ESI, m/z): 235.1 $[\text{M}+\text{H}^+]$.

17.ii. rac-3-(3-chloro-6-methoxy-[1,5]naphthyridin-4-yl)-propane-1,2-diol:

A solution of intermediate 17.i (790 mg) in DCM (12 mL) was treated with water (1.7 mL), NMO (500 mg) and $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (12 mg). The resulting mixture was vigorously stirred at rt overnight. The phases were separated, the aq. layer was extracted
10 several times with DCM/MeOH (9:1) and the combined org. layers were washed with aq. $\text{Na}_2\text{S}_2\text{O}_3$ (10%). The residue was by CC (DCM/MeOH/ NH_4OH ; 1000:50:4), affording a beige solid (674 mg; 75% yield).

MS (ESI, m/z): 269.2 $[\text{M}+\text{H}^+]$.

17.iii. rac-1-(tert-butyl-dimethyl-silanyloxy)-3-(3-chloro-6-methoxy-[1,5]naphthyridin-4-yl)-propan-2-ol:

A solution of intermediate 17.ii (670 mg) in DCM (1 mL) was treated with imidazole (171 mg), DMAP (30 mg) and TBDMSCl (396 mg). The mixture was stirred at rt for 4 days. Water was added and the mixture was extracted with DCM. The org. layer was dried over MgSO_4 concentrated under reduced pressure and purified by CC
20 (DCM/MeOH/ NH_4OH ; 1000:25:2 to 1000:100:8), affording a light yellow oil (533 mg; 56% yield).

MS (ESI, m/z): 383.1 $[\text{M}+\text{H}^+]$.

17.iv. rac-2-(tert-butyl-dimethyl-silanyloxymethyl)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[a]naphthalene:

A suspension of intermediate 17.iii (530 mg), Cs_2CO_3 (676 mg), $\text{Pd}(\text{OAc})_2$ (31 mg) and *rac*-2-(di-*tert*-butylphosphino)-1,1'-binaphthyl (66 mg) in toluene (3 mL) was heated to 70°C under N_2 for 4 h. The reaction mixture was partitioned between water and EA and the org. layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated to dryness. The residue was purified by CC (EA/Hept 1:1), affording a brown oil (390 mg; 81% yield).

30 MS (ESI, m/z): 347.1 $[\text{M}+\text{H}^+]$.

17.v. *rac*-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-yl)-methanol:

A solution of intermediate 17.iv (390 mg) in THF (15 mL) was treated with a TBAF solution (1M in THF; 1.13 mL). The solution was stirred at rt overnight, partitioned
5 between water and DCM. The org. layer was concentrated under reduced pressure and purified by CC (EA /Hept 1:2 to 2:1), affording a yellow solid (226 mg; 86% yield).

MS (ESI, *m/z*): 233.4 [*M*+*H*⁺].

17.vi. *rac*-C-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-yl)-methylamine:

10 DIAD (0.31 mL) was added at 0°C to a solution of PPh₃ in THF (7 mL). After stirring for 15 min at 0°C, a solution of intermediate 17.v (226 mg) in THF (4 mL) was added dropwise, followed by DPPA (0.32 mL). The reaction mixture was allowed to reach rt and further stirred for 4 h. The mixture was concentrated under reduced pressure and the residue was purified by CC (EA) affording the intermediate *rac*-2-azidomethyl-8-methoxy-
15 1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalene as a yellow oil (870 mg).

MS (ESI, *m/z*): 258.2 [*M*+*H*⁺].

A solution of this intermediate azide in THF (10 mL) was treated with PPh₃ (514 mg) and water (0.18 mL). The mixture was heated at 50°C for 1 h. The reaction mixture was concentrated and the residue was taken in DCM and extracted with 10% citric acid (2x).

20 The combined aq. layers were basified with NH₄OH and then extracted with DCM/MeOH (9:1). The combined org. phases were dried over MgSO₄, concentrated under reduced pressure and purified by CC (DCM/MeOH/NH₄OH 1000:50:4 to 1000:100:8), affording the title compound as a light yellow solid (88 mg; 39% yield).

MS (ESI, *m/z*): 232.4 [*M*+*H*⁺].

25 17.vii. 6-((*R*)-5-{[((*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one:

Starting from intermediates 17.vi (28 mg) and 1.vii (52 mg) and using procedure D, the title compound was obtained as a light yellow foam (15 mg, 24% yield).

MS (ESI, *m/z*): 494.2 [*M*+*H*⁺].

Example 18: 6-((*R*)-5-{2-[(*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one:

18.i. (*2R*)-*tert*-butyl-dimethyl-(2-oxiranyl-ethoxy)-silane and (*2S*)-4-(*tert*-butyl-dimethyl-silanyloxy)-butane-1,2-diol:

The title intermediates were prepared in analogy to Kishi et al., *Org. Lett.* (2005), 7, 3997, (intermediate S2-3) *via* hydrolytic kinetic resolution of (*RS*)-*tert*-butyl-dimethyl-(2-oxiranyl-ethoxy)-silane (prepared according to *J. Org. Chem.* (2008), 73, 1093). Two compounds were isolated after CC (Hept/EA 2:1).

10 First eluting compound: (*2R*)-*tert*-butyl-dimethyl-(2-oxiranyl-ethoxy)-silane (colourless oil, 25.3 g, 48% yield):

¹H NMR (CDCl₃) δ: 3.77 (t, *J* = 6.4 Hz, 2H), 3.04 (m, 1H), 2.78 (m, 1H), 2.51 (dd, *J* = 5.0, 2.9 Hz, 1H), 1.74 (m, 2H), 0.90 (d, *J* = 0.6 Hz, 9H), 0.06 (s, 6H).

Second eluting compound: (*2S*)-4-(*tert*-butyl-dimethyl-silanyloxy)-butane-1,2-diol
15 (colourless oil, 24.9 g, 43% yield):

¹H NMR (CDCl₃) δ: 3.89 (m, 3H), 3.62 (s, 1H), 3.53 (m, 1H), 3.42 (br. s, 1H), 2.29 (m, 1H), 1.70 (m, 2H), 0.90 (s, 9H), 0.09 (s, 6H).

18.ii. 6-[(*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-2-hydroxy-butylamino]-4*H*-benzo[1,4]oxazin-3-one:

20 A solution of 6-amino-4*H*-benzo[1,4]oxazin-3-one (commercial; 6.49 g, 39.5 mmol) and (*2R*)-*tert*-butyl-dimethyl-(2-oxiranyl-ethoxy)-silane (first eluting compound of step 18.i, 8.0 g, 39.5 mmol) in 9-1 EtOH/H₂O (240 mL) was heated at 80°C for 2 days. The mixture was concentrated under reduced pressure. Residual starting aniline could be removed by addition of Et₂O/MeOH followed by filtration. The filtrate was concentrated under reduced
25 pressure and the residue was purified by CC (DCM/MeOH/NH₄OH 1000:50:4) to afford the title intermediate as a brown oil (5.82 g, 40% yield).

MS (ESI, *m/z*): 367.3 [M+H⁺].

18.iii. 6-{(R)-5-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-2-oxo-oxazolidin-3-yl}-4H-benzo[1,4]oxazin-3-one:

A solution of intermediate 18.ii (5.8 g, 15.8 mmol) and CDI (3.07 g, 1.2 eq.) in THF (50 mL) was heated at 50°C overnight. The mixture was concentrated under reduced pressure and partitioned between EA and water. The aq. layer was extracted once more with EA and the combined org. layers were dried over MgSO₄ and concentrated. The residue was triturated with Et₂O/EA/MeOH to afford the title compound as a beige solid (2.7 g, 43% yield).

MS (ESI, m/z): 393.5 [M+H⁺].

10 18.iv. 6-[(R)-5-(2-hydroxy-ethyl)-2-oxo-oxazolidin-3-yl]-4H-benzo[1,4]oxazin-3-one:

A solution of intermediate 18.iii (2.70 g, 6.88 mmol) in THF (15 mL) was treated with TBAF (1M solution in THF, 8.3 mL, 1.2 eq.) at 0°C. The solution was stirred at 0°C for 2 h. The mixture was partitioned between water and EA and the aq. phase was extracted with EA (3x). The combined org. layers were washed with water and brine, dried over MgSO₄ and concentrated. The residue was triturated with Et₂O/MeOH to afford the title compound as an off-white solid (1.25 g, 65% yield).

MS (ESI, m/z): 279.5 [M+H⁺].

18.v. Methanesulfonic acid 2-[(R)-2-oxo-3-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-oxazolidin-5-yl]-ethyl ester:

20 A solution of intermediate 18.iv (2.1 g, 7.55 mmol) and DIPEA (3.57 mL, 2.9 eq.) in anhydrous DCM (40 mL) was cooled to 0°C and treated dropwise with MsCl (0.71 mL, 1.2 eq.). The resulting mixture was stirred at 0°C for 1 h. Water and DCM were added and the phases separated. The org. layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was triturated with MeOH to afford the title compound as an off-white solid (1.16 g, 43% yield).

¹H NMR (DMSO-d₆) δ: 10.72 (s, 1H), 7.30 (d, J = 2.1 Hz, 1H), 6.93 (m, 2H), 4.76 (m, 1H), 4.52 (s, 2H), 4.34 (m, 2H), 4.11 (t, J = 8.8 Hz, 1H), 3.72 (m, 1H), 3.20 (s, 3H), 2.17 (m, 2H).

MS (ESI, m/z): 357.2 [M+H⁺].

18.vi. 6-[(R)-5-(2-iodo-ethyl)-2-oxo-oxazolidin-3-yl]-4H-benzo[1,4]oxazin-3-one:

A suspension of intermediate 18.v (1.16 g, 3.26 mmol) and NaI (1.46 g, 3 eq.) in 2-butanone (10 mL) was heated at 85°C overnight. After cooling, the mixture was diluted with ether/EA (10 mL) and treated with 10% aq. Na₂S₂O₃ (30 mL). After stirring for 10 min the phases were separated and the aq. layer was washed with EA. The combined org. layers were washed with water (2x), dried over MgSO₄ and concentrated under reduced pressure to afford the title compound as an off-white solid (0.91 g, 72% yield).

¹H NMR (CDCl₃) δ: 8.24 (s, 1H), 7.42 (d, J = 2.3 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 6.79 (dd, J = 8.8, 2.6 Hz, 1H), 4.80 (m, 1H), 4.59 (s, 2H), 4.14 (t, J = 8.8 Hz, 1H), 3.65 (dd, J = 8.8, 6.7 Hz, 1H), 3.33 (m, 2H), 2.30 (m, 2H).

18.vii. 6-((R)-5-{2-[(*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]oxazin-3-one:

Starting from intermediates 17.vi (28 mg) and 18.vi (49 mg) and using procedure D, the title compound was obtained as a light brown foam (27 mg, 43% yield).

¹H NMR (CDCl₃) δ: 8.41 (d, J = 2.3 Hz, 1H), 8.12 (m, 1H), 7.27 (m, 1H), 6.91 (m, 2H), 6.79 (m, 1H), 5.18 (m, 1H), 4.75 (m, 1H), 4.56 (s, 2H), 4.03 (s, 3H), 3.90 (m, 1H), 3.62 (m, 2H), 3.32 (m, 2H), 2.95 (m, 4H), 2.04 (m, 1H), 1.91 (m, 1H).

MS (ESI, m/z): 492.2 [M+H⁺].

Example 19: 6-((R)-5-{2-[(*RS*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diazacyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4H-benzo[1,4]thiazin-3-one:

Starting from intermediates 17.vi (30 mg) and 13.iv (51 mg) and using procedure E, the title compound was obtained as a light yellow foam (19 mg, 27% yield).

MS (ESI, m/z): 508.0 [M+H⁺].

Example 20: (RS)-3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-5-{[2-((R)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-oxazolidin-2-one:

Starting from intermediate 9.iii (40 mg) and (5*S*)-3-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-[[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone (54 mg; prepared according to WO 2008/126034) and using procedure E, the title compound was obtained as a light yellow foam (6 mg, 8% yield).

¹H NMR (CDCl₃) δ: 8.46 (d, J = 4.7 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.10 (dd, J = 4.4, 2.6 Hz, 1H), 7.00 (m, 1H), 6.88 (m, 2H), 5.11 (m, 1H), 4.90 (m, 1H), 4.25 (m, 4H), 4.16 (m, 1H), 4.05 (s, 3H), 3.78 (m, 1H), 3.70-2.75 (m, 6H), 2.52 (m, 2H).

MS (ESI, m/z): 479.1 [M+H⁺].

Pharmacological properties of the invention compounds

***In vitro* assays**

Experimental methods:

- 15 Minimal inhibitory concentrations (MICs; mg/l) were determined in cation-adjusted Mueller–Hinton Broth by a microdilution method following the description given in “Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically”, Approved standard, 7th ed., Clinical and Laboratory Standards Institute (CLSI) Document M7-A7, Wayne, PA, USA, 2006.

20 Results:

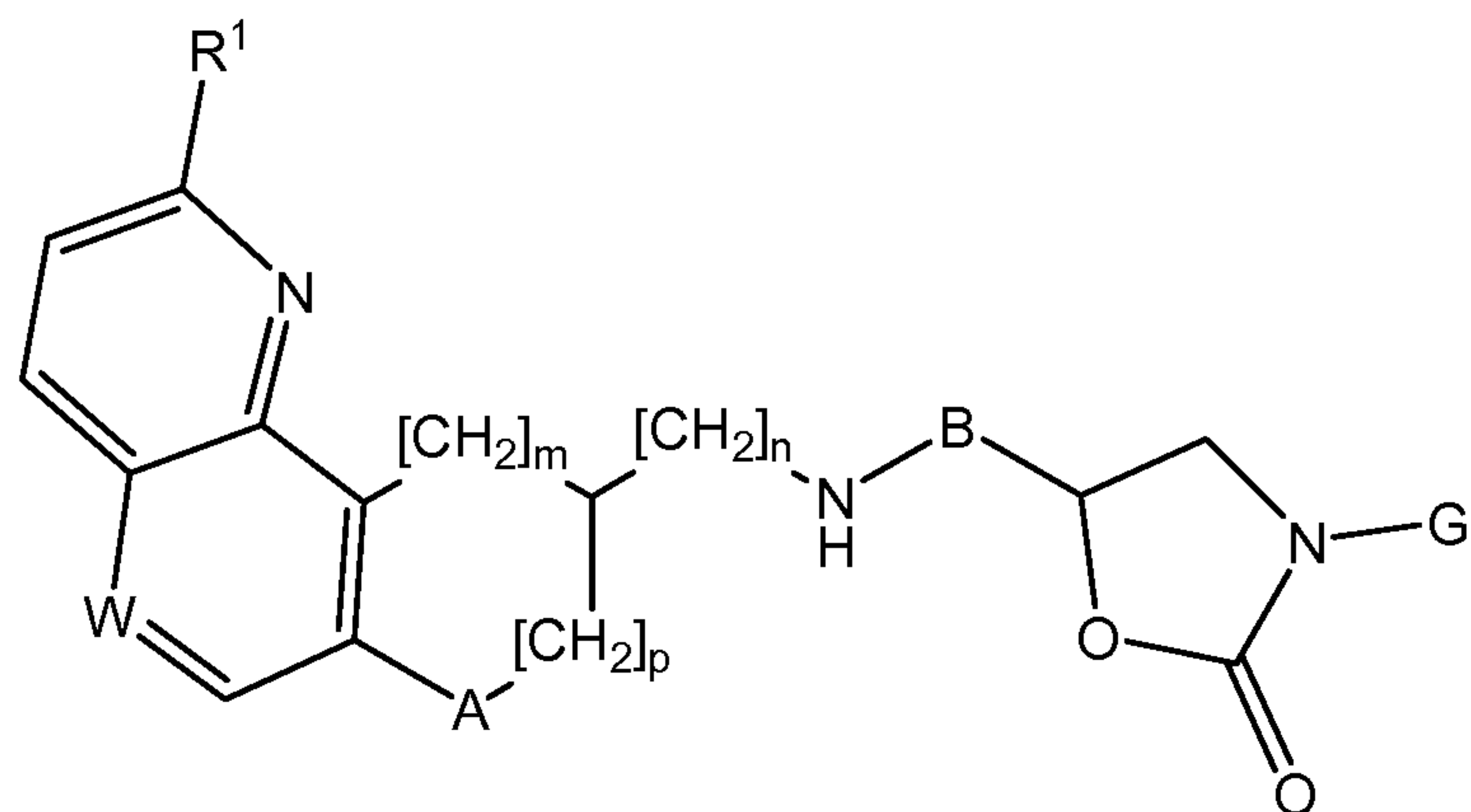
All Example compounds were tested against several Gram positive and Gram negative bacteria such as *S. aureus*, *E. faecalis*, *S. pneumoniae*, *M. catarrhalis*, *A. baumannii*, *E.coli* or *P. aeruginosa*.

Typical antibacterial test results are given in the table hereafter (MIC in mg/l).

Example No.	MIC for <i>S. aureus</i> A798	Example No	MIC for <i>S. aureus</i> A798
1	≤ 0.031	2	≤ 0.031
3	≤ 0.031	4	≤ 0.031
5	≤ 0.031	6	≤ 0.031
7	≤ 0.031	8	≤ 0.031
9	≤ 0.031	10	≤ 0.031
11	0.25	12	≤ 0.031
13	≤ 0.031	14	≤ 0.031
15	≤ 0.031	16	≤ 0.031
17	≤ 0.031	18	≤ 0.031
19	≤ 0.031	20	1

Claims

1. A compound of formula I



I

wherein

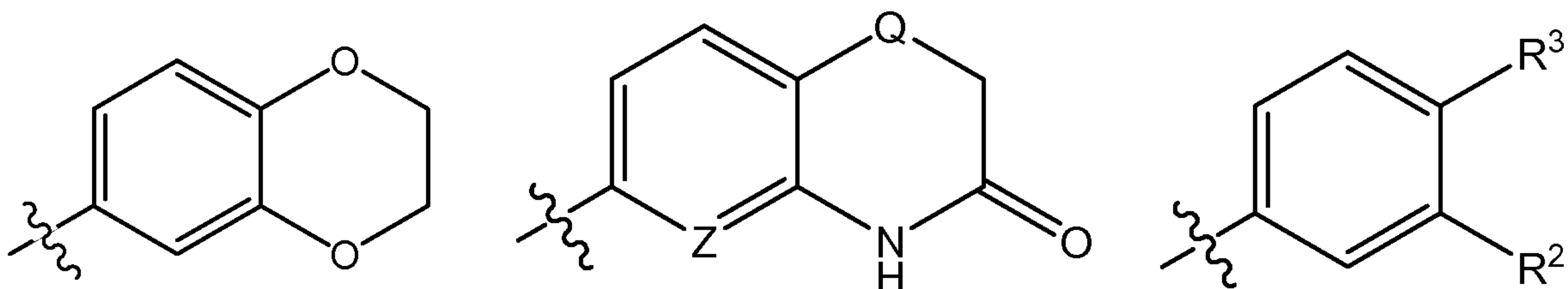
R¹ is alkoxy or halogen;

W is CH or N;

5 A is O or NH;

B is CO or (CH₂)ₑ;

G is a group having one of the three formulae below



wherein Q represents O or S, Z represents CH or N, R² represents halogen and R³ represents alkyl;

10 m is 0 or 1;

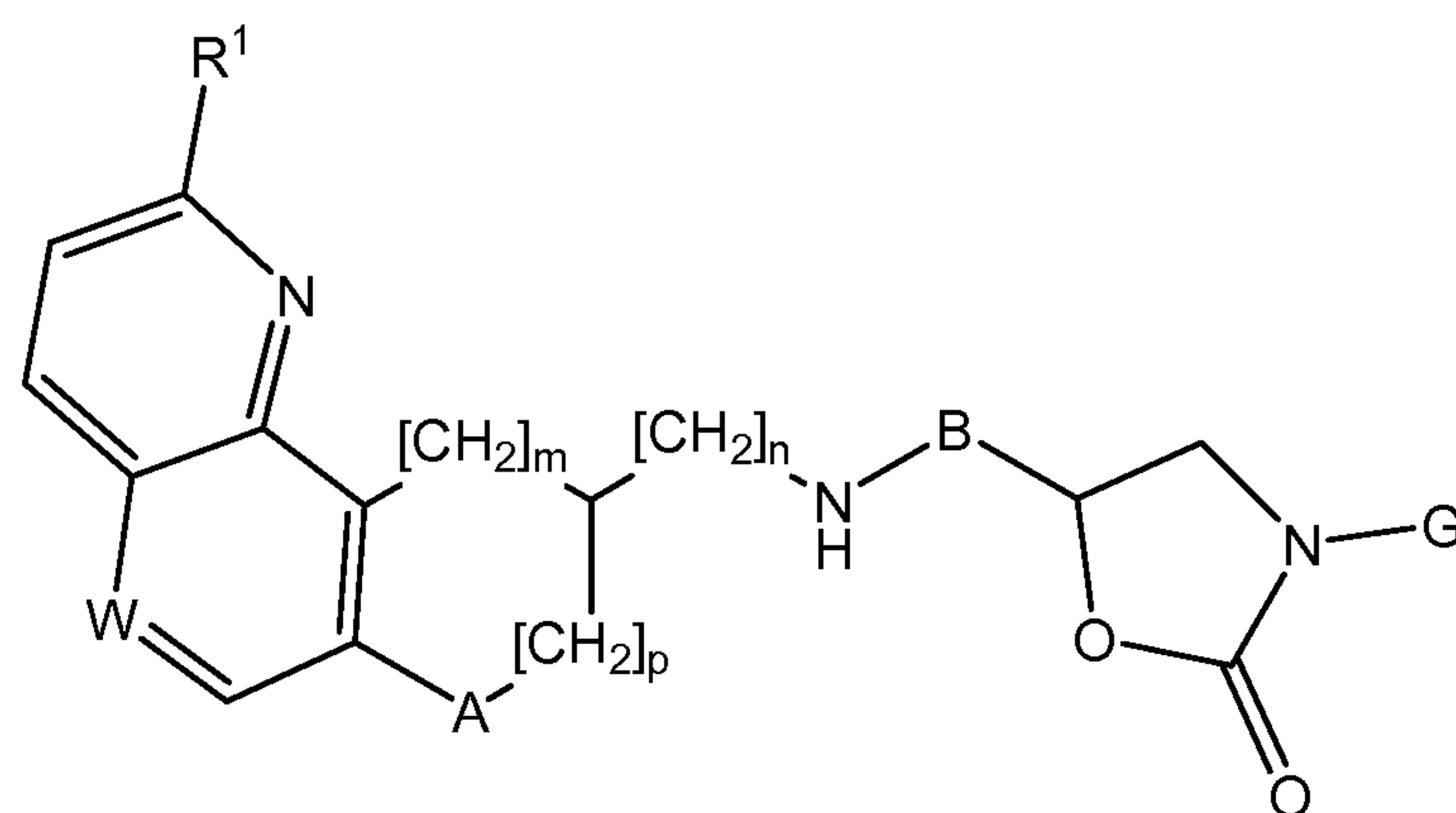
n is 1 or 2;

p is 0 or 1, provided m and p are not each 0; and

q is 1 or 2;

or a salt of such a compound.

2. A compound of formula I according to claim 1, which is also a compound of formula I_{CE}

I_{CE}

wherein

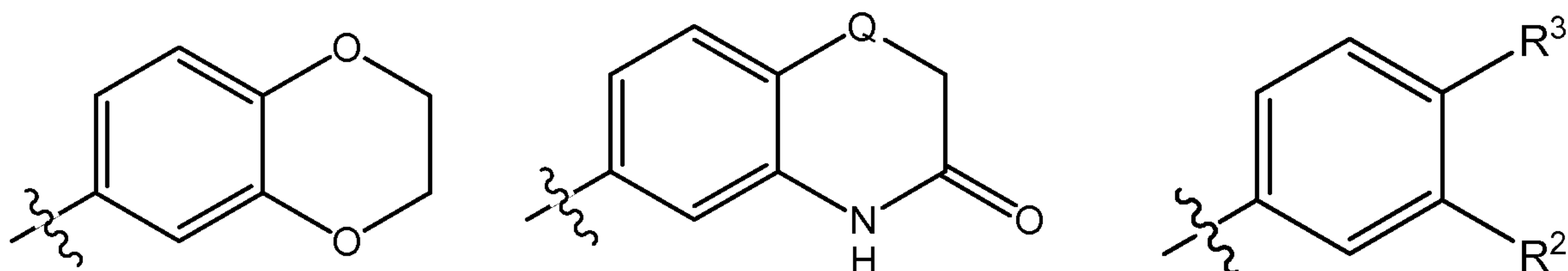
R¹ is alkoxy;

W is CH or N;

5 A is O or NH;

B is CO or (CH₂)_q;

G is a group of the formula



wherein Q represents O or S, R² represents halogen and R³ represents alkyl;

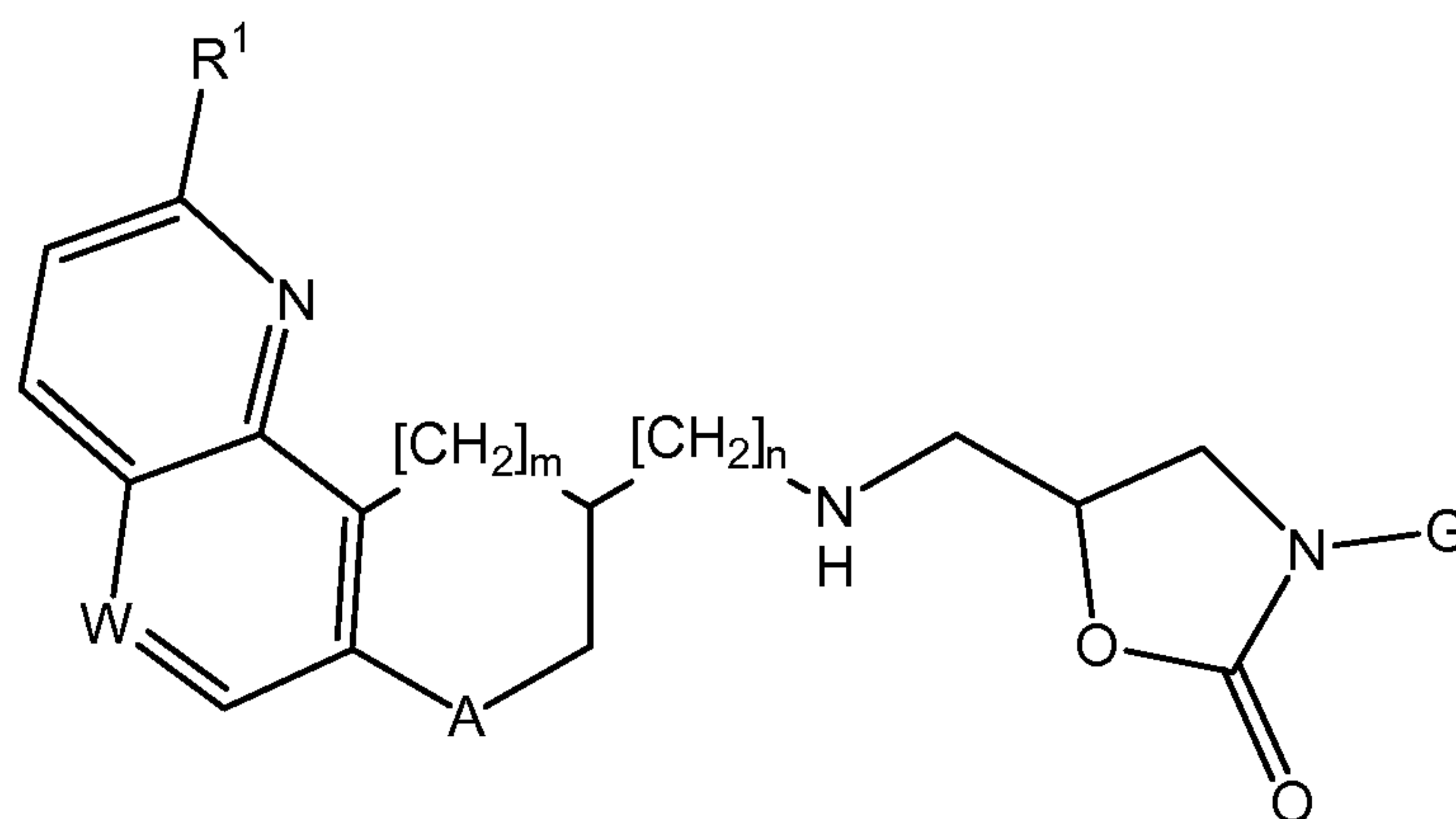
m is 0 and n is 1 or 2 or m is 1 and n is 1;

10 p is 0 or 1, provided m and p are not each 0; and

q is 1 or 2;

or a salt of such a compound.

3. A compound of formula I according to claim I, which is also a compound of formula I_p

I_p

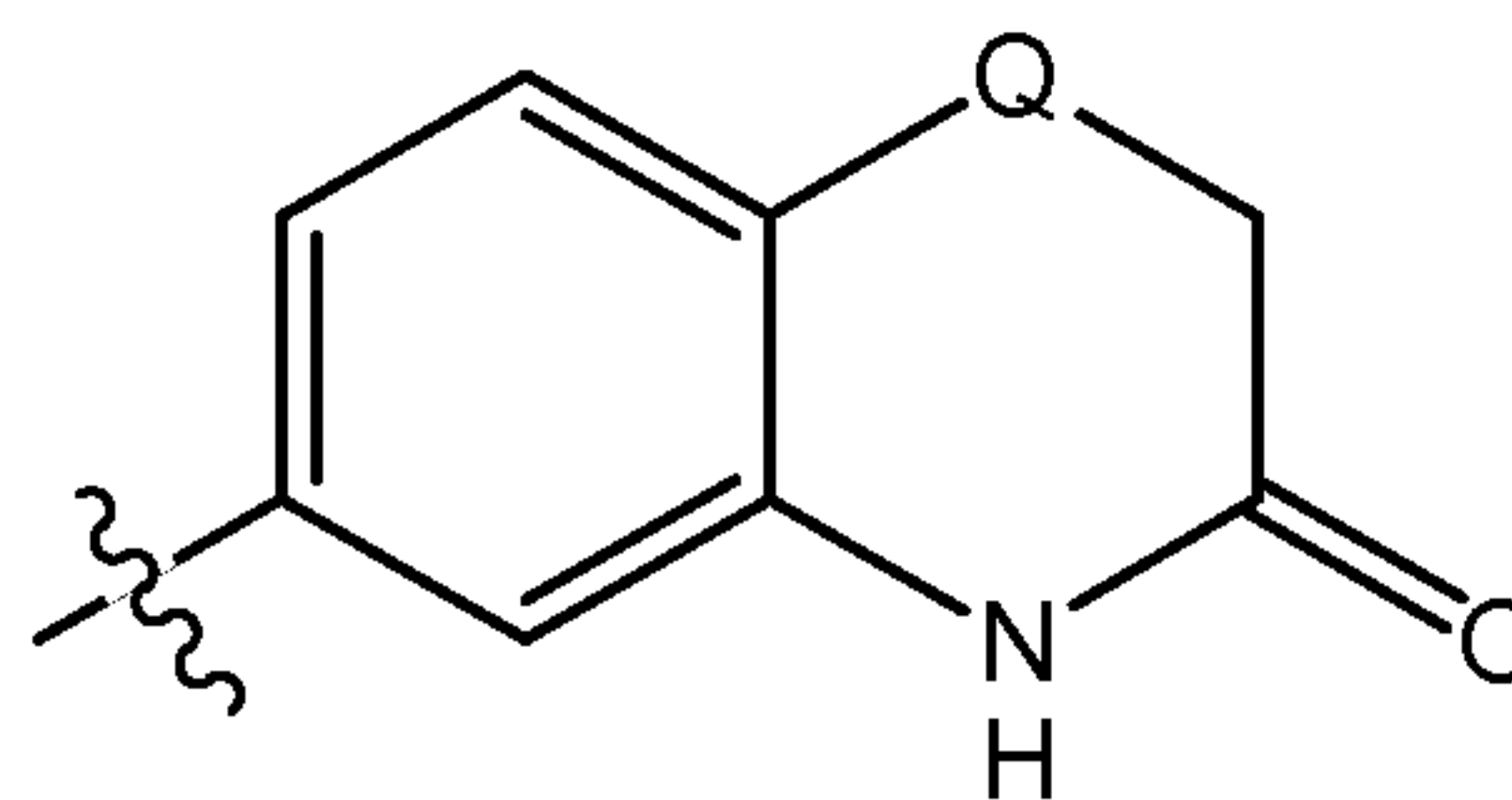
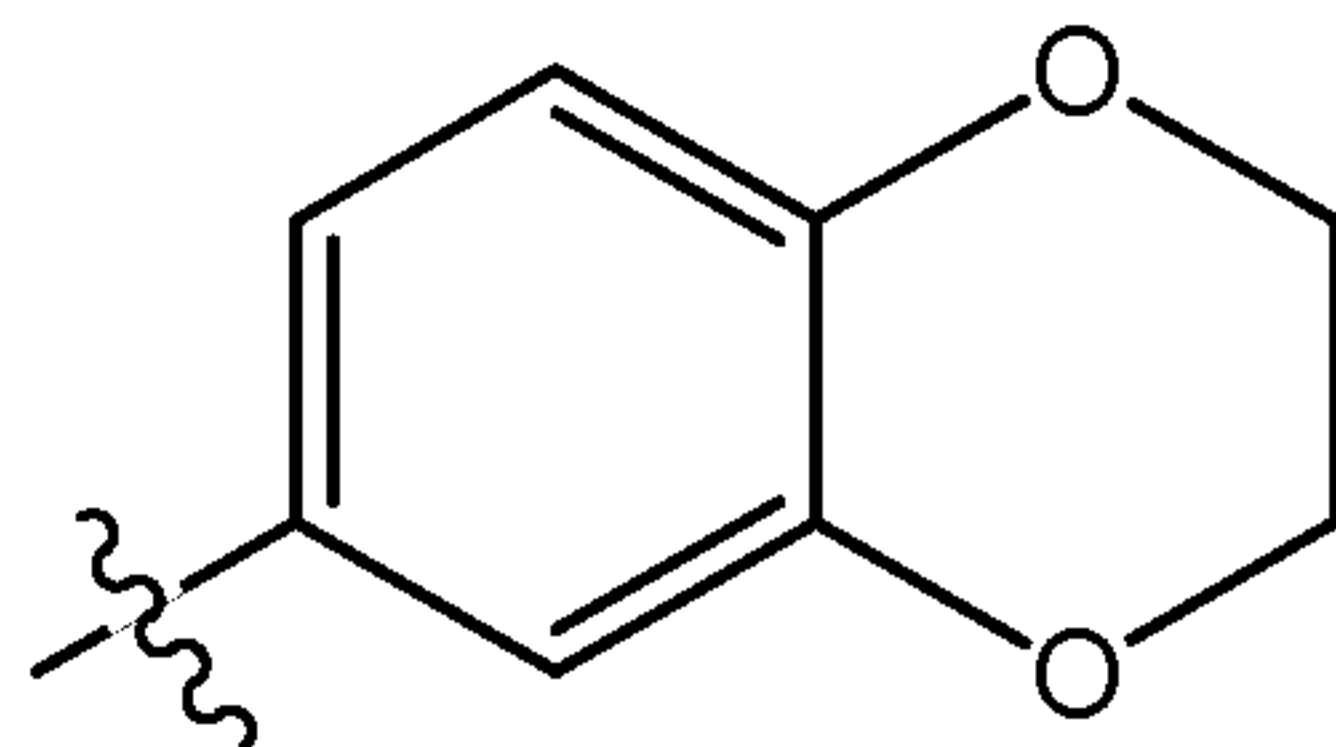
wherein

R¹ is alkoxy or halogen;

W is CH or N;

5 A is O or NH;

G is a group having one of the two formulae below



wherein Q represents O or S;

m is 0 or 1; and

n is 1 or 2;

10 or a salt of such a compound.

4. A compound of formula I according to one of claims 1 to 3, wherein R¹ is methoxy;
or a salt of such a compound.

5. A compound of formula I according to one of claims 1 to 4, wherein W is CH;
or a salt of such a compound.

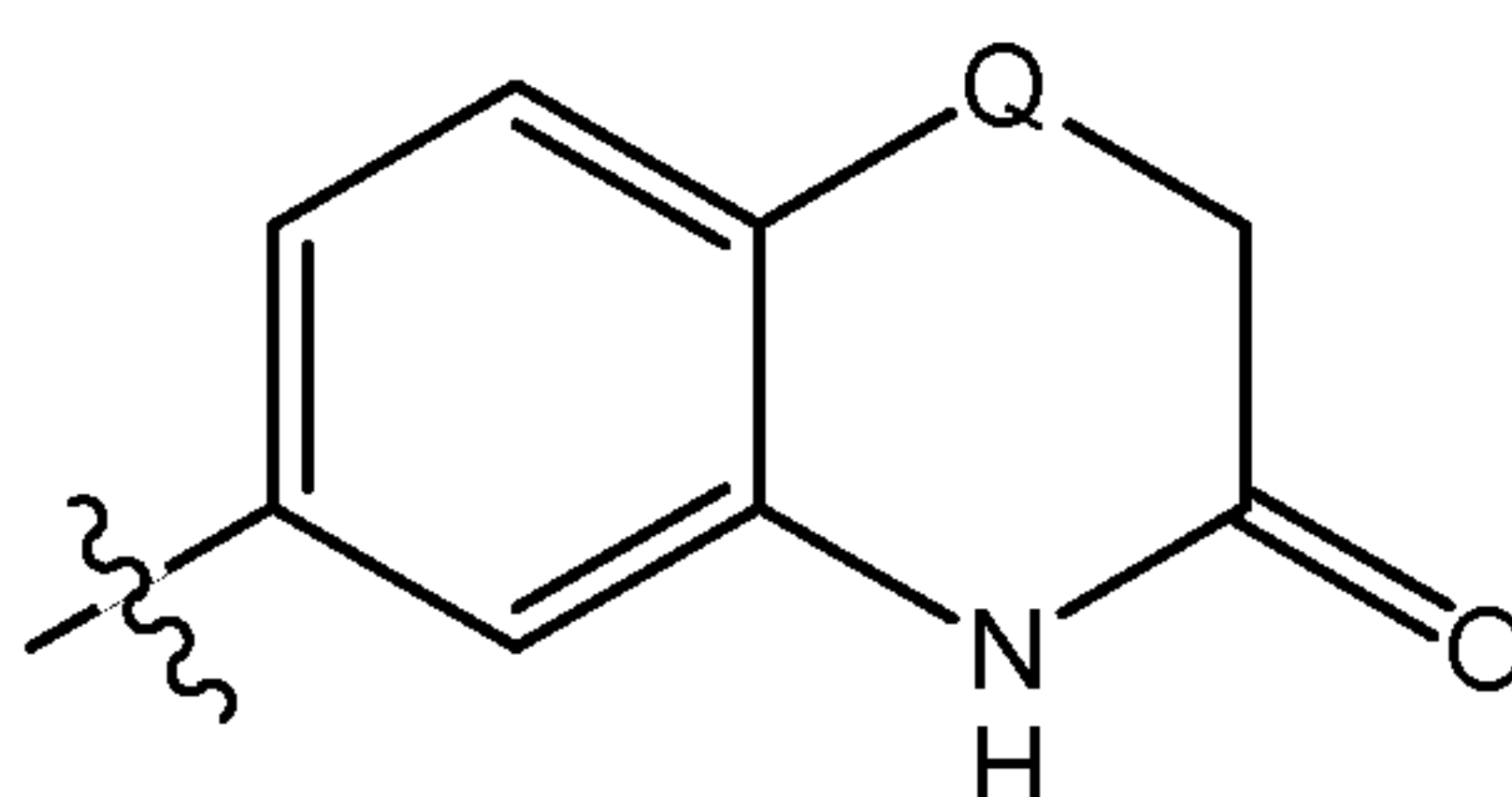
15 6. A compound of formula I according to one of claims 1 to 4, wherein W is N;
or a salt of such a compound.

7. A compound of formula I according to one of claims 1 to 6, wherein A is O;
or a salt of such a compound.

8. A compound of formula I according to claim 7, wherein p, if present, is 1;
or a salt of such a compound.

5 9. A compound of formula I according to one of claims 1 to 6, wherein A is NH;
or a salt of such a compound.

10. A compound of formula I according to one of claims 1 to 9, wherein G is a group of the
formula



wherein Q represents O or S.

10 or a salt of such a compound.

11. A compound of formula I according to claim 1 or 2, which is selected from the
following:

- 6-((*R*)-5-{[(6-methoxy-3,4-dihydro-2*H*-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-
methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

15 - 6-((*R*)-5-{[(6-methoxy-3,4-dihydro-2*H*-1-oxa-5-aza-phenanthren-3-ylmethyl)-amino]-
methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;

- 6-((*R*)-5-{[(6-methoxy-3,4-dihydro-2*H*-1-oxa-5,9-diaza-phenanthren-3-ylmethyl)-
amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;

20 - 6-((*R*)-5-{[(6-methoxy-3,4-dihydro-2*H*-1-oxa-5,9-diaza-phenanthren-3-ylmethyl)-
amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

- 6-((*R*)-5-{[(6-methoxy-1,2,3,4-tetrahydro-1,5,9-triaza-phenanthren-3-ylmethyl)-amino]-
methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

- 6-((*R*)-5-{[2-(2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamino]-methyl}-
2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;

- 6-((*R*)-5-{[2-(2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
 - 6-((*R*)-5-{[(2-methoxy-8,9-dihydro-furo[2,3-*h*]quinolin-9-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
 - 5 - 6-((*R*)-5-{[2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
 - 6-((*R*)-5-{[2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
 - (*R*)-3-(3-fluoro-4-methyl-phenyl)-5-{[2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-
 - 10 cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-oxazolidin-2-one;
 - 6-((*S*)-5-{[2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
 - 6-((*R*)-5-{2-[2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
 - 15 - 6-((*R*)-5-{2-[(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
 - 6-((*S*)-5-{2-[(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
 - (*S*)-3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-2-oxo-oxazolidine-5-carboxylic acid
 - 20 [2-(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethyl]-amide;
 - 6-((*R*)-5-{[(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
 - 6-((*R*)-5-{2-[(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]oxazin-3-one;
 - 25 - 6-((*R*)-5-{2-[(8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-2-ylmethyl)-amino]-ethyl}-2-oxo-oxazolidin-3-yl)-4*H*-benzo[1,4]thiazin-3-one;
 - 3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-5-{[2-((*R*)-8-methoxy-1,2-dihydro-3-oxa-5,9-diaza-cyclopenta[*a*]naphthalen-1-yl)-ethylamino]-methyl}-oxazolidin-2-one;
- or a salt of such a compound.
- 30 **12.** As a medicament, a compound of formula I as defined in one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition containing, as active principle, a compound of formula I as defined in one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

14. Use of a compound of formula I as defined in one of claims 1 to 11, or of a
5 pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment of a bacterial infection.

15. A compound of formula I as defined in one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of a bacterial infection.

