



(86) Date de dépôt PCT/PCT Filing Date: 1999/03/19
(87) Date publication PCT/PCT Publication Date: 1999/09/30
(45) Date de délivrance/Issue Date: 2008/05/13
(85) Entrée phase nationale/National Entry: 2000/09/20
(86) N° demande PCT/PCT Application No.: EP 1999/001853
(87) N° publication PCT/PCT Publication No.: 1999/048896
(30) Priorité/Priority: 1998/03/23 (ATA 515/98)

(51) Cl.Int./Int.Cl. *C07D 501/46* (2006.01),
A61K 31/545 (2006.01), *A61P 31/04* (2006.01),
C07D 501/00 (2006.01)

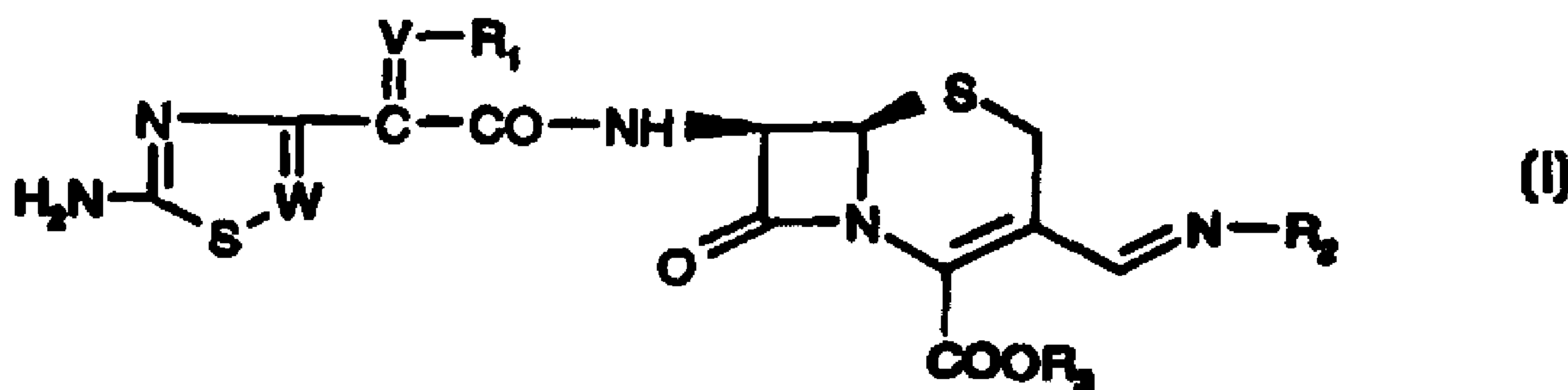
(72) Inventeurs/Inventors:
ASCHER, GERD, AT;
HEILMAYER, WERNER, AT;
LUDESCHER, JOHANNES, AT;
WIESER, JOSEF, AT;
HILDEBRANDT, JOHANNES, AT;
SCHRANZ, MICHAEL, AT

(73) Propriétaire/Owner:
NABRIVA THERAPEUTICS FORSCHUNGS GMBH, AT

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : CEPHALOSPORINES AVEC SUBSTITUANTS AMINOGUANIDINES CYCLIQUES, UTILISEES COMME ANTIBIOTIQUES

(54) Title: CEPHALOSPORINES HAVING CYCLIC AMINOGUANIDINE SUBSTITUENTS AS ANTIBIOTICS



(57) Abrégé/Abstract:

A compound of formula (I), wherein R₂ together with the nitrogen atom to which it is attached forms a cyclic aminoguanidine group or derivative thereof and the other substituents have various meanings, useful as a pharmaceutical.



PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

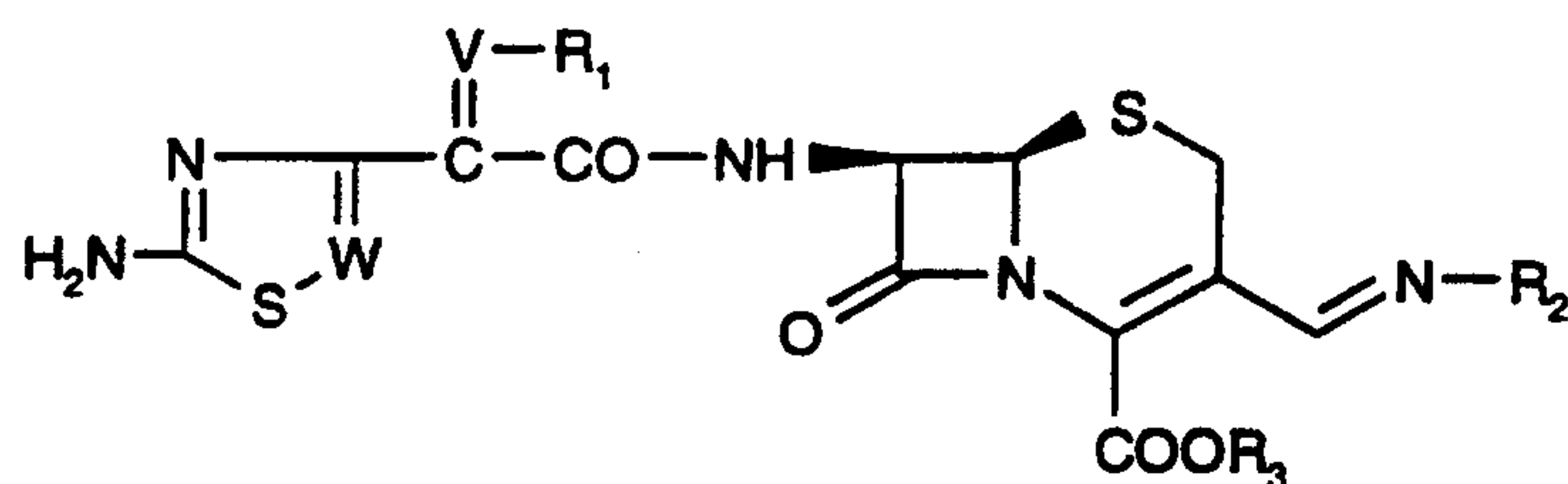
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 501/46, A61K 31/545	A1	(11) International Publication Number: WO 99/48896 (43) International Publication Date: 30 September 1999 (30.09.99)		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> (21) International Application Number: PCT/EP99/01853 (22) International Filing Date: 19 March 1999 (19.03.99) (30) Priority Data: A 515/98 23 March 1998 (23.03.98) AT (71) Applicant (for all designated States except US): BIOCHEMIE GESELLSCHAFT MBH [AT/AT]; A-6250 Kundl (AT). (72) Inventors; and (75) Inventors/Applicants (for US only): ASCHER, Gerd [AT/AT]; Daxerfeld 3, A-6250 Kundl (AT). HEILMAYER, Werner [AT/AT]; Payergasse 4, A-2340 Mödling (AT). LUDESCHER, Johannes [AT/AT]; Kleinsoell 101, A-6252 Breitenbach (AT). (74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH). </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. </td> </tr> </table>			(21) International Application Number: PCT/EP99/01853 (22) International Filing Date: 19 March 1999 (19.03.99) (30) Priority Data: A 515/98 23 March 1998 (23.03.98) AT (71) Applicant (for all designated States except US): BIOCHEMIE GESELLSCHAFT MBH [AT/AT]; A-6250 Kundl (AT). (72) Inventors; and (75) Inventors/Applicants (for US only): ASCHER, Gerd [AT/AT]; Daxerfeld 3, A-6250 Kundl (AT). HEILMAYER, Werner [AT/AT]; Payergasse 4, A-2340 Mödling (AT). LUDESCHER, Johannes [AT/AT]; Kleinsoell 101, A-6252 Breitenbach (AT). (74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
(21) International Application Number: PCT/EP99/01853 (22) International Filing Date: 19 March 1999 (19.03.99) (30) Priority Data: A 515/98 23 March 1998 (23.03.98) AT (71) Applicant (for all designated States except US): BIOCHEMIE GESELLSCHAFT MBH [AT/AT]; A-6250 Kundl (AT). (72) Inventors; and (75) Inventors/Applicants (for US only): ASCHER, Gerd [AT/AT]; Daxerfeld 3, A-6250 Kundl (AT). HEILMAYER, Werner [AT/AT]; Payergasse 4, A-2340 Mödling (AT). LUDESCHER, Johannes [AT/AT]; Kleinsoell 101, A-6252 Breitenbach (AT). (74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.			
(54) Title: CEPHALOSPORINES HAVING CYCLIC AMINO GUANIDINE SUBSTITUENTS AS ANTIBIOTICS (I) (57) Abstract A compound of formula (I), wherein R₂ together with the nitrogen atom to which it is attached forms a cyclic aminoguanidine group or derivative thereof and the other substituents have various meanings, useful as a pharmaceutical.				

CEPHALOSPORINES HAVING CYCLIC AMINOGUANIDINE SUBSTITUENTS AS ANTIBIOTICS

The present invention relates to antibacterial compounds which are 7-acylamino-3-(cyclic aminoguanidine)methylene cephalosporins, including 3-cyclic aminoguanidine-like structured compounds having a triamino-methylidyne group instead of an aminoguanidine group.

In one aspect the present invention provides a compound of formula



wherein

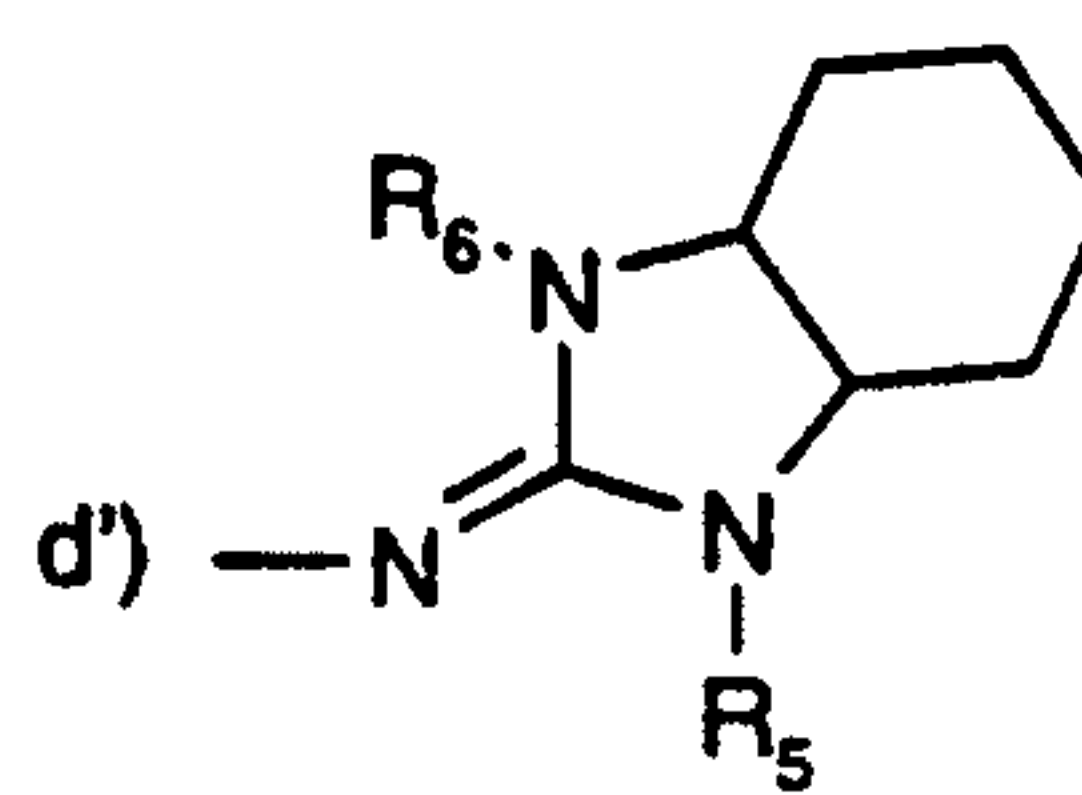
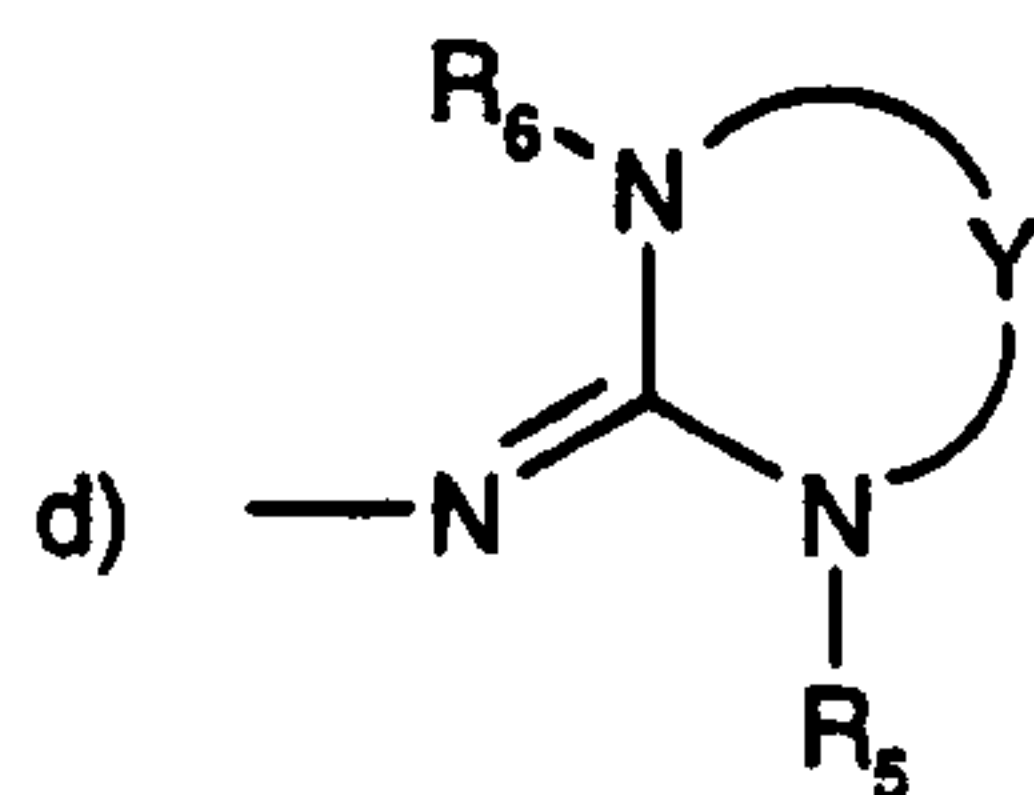
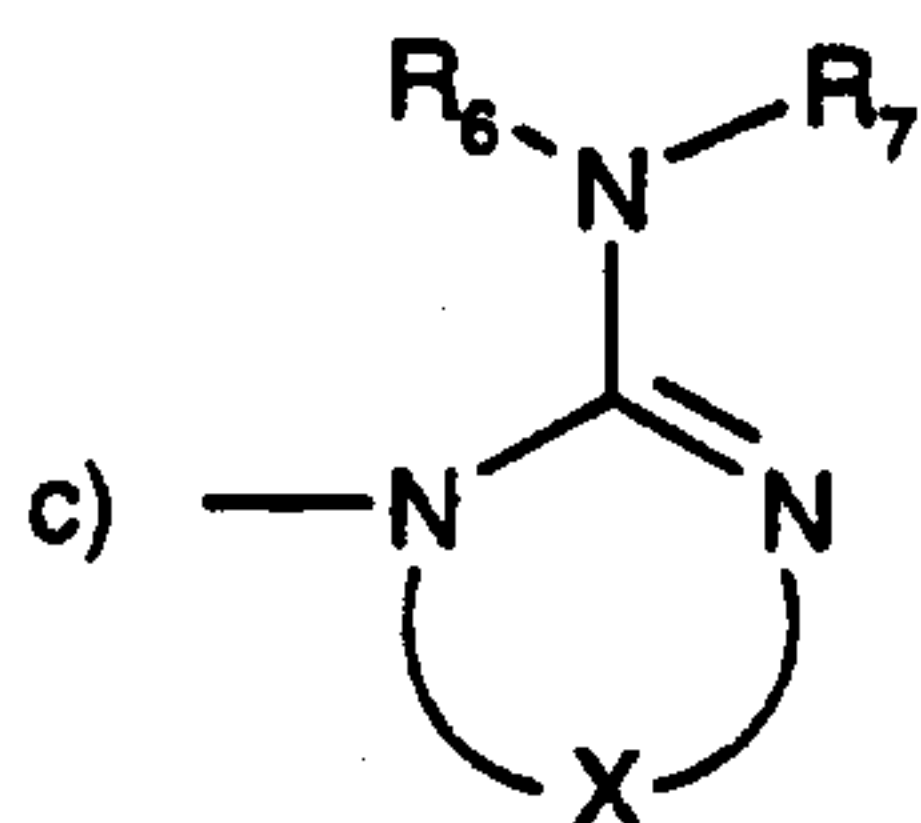
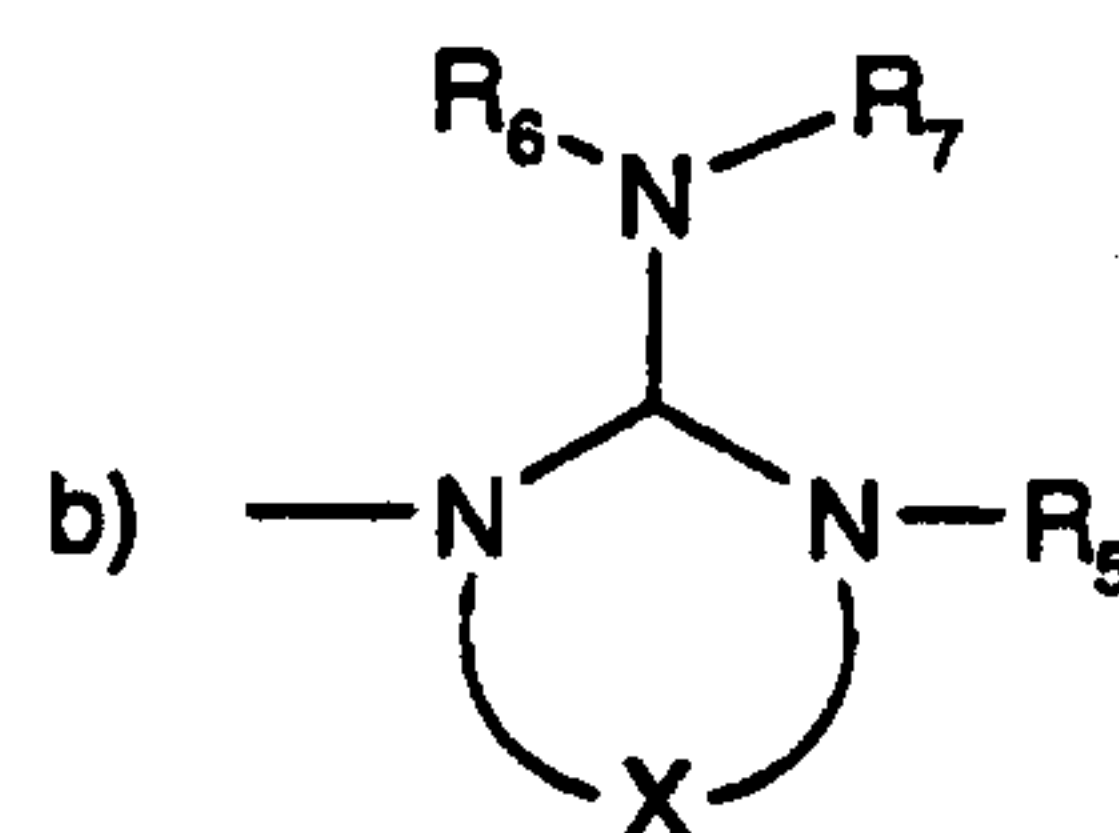
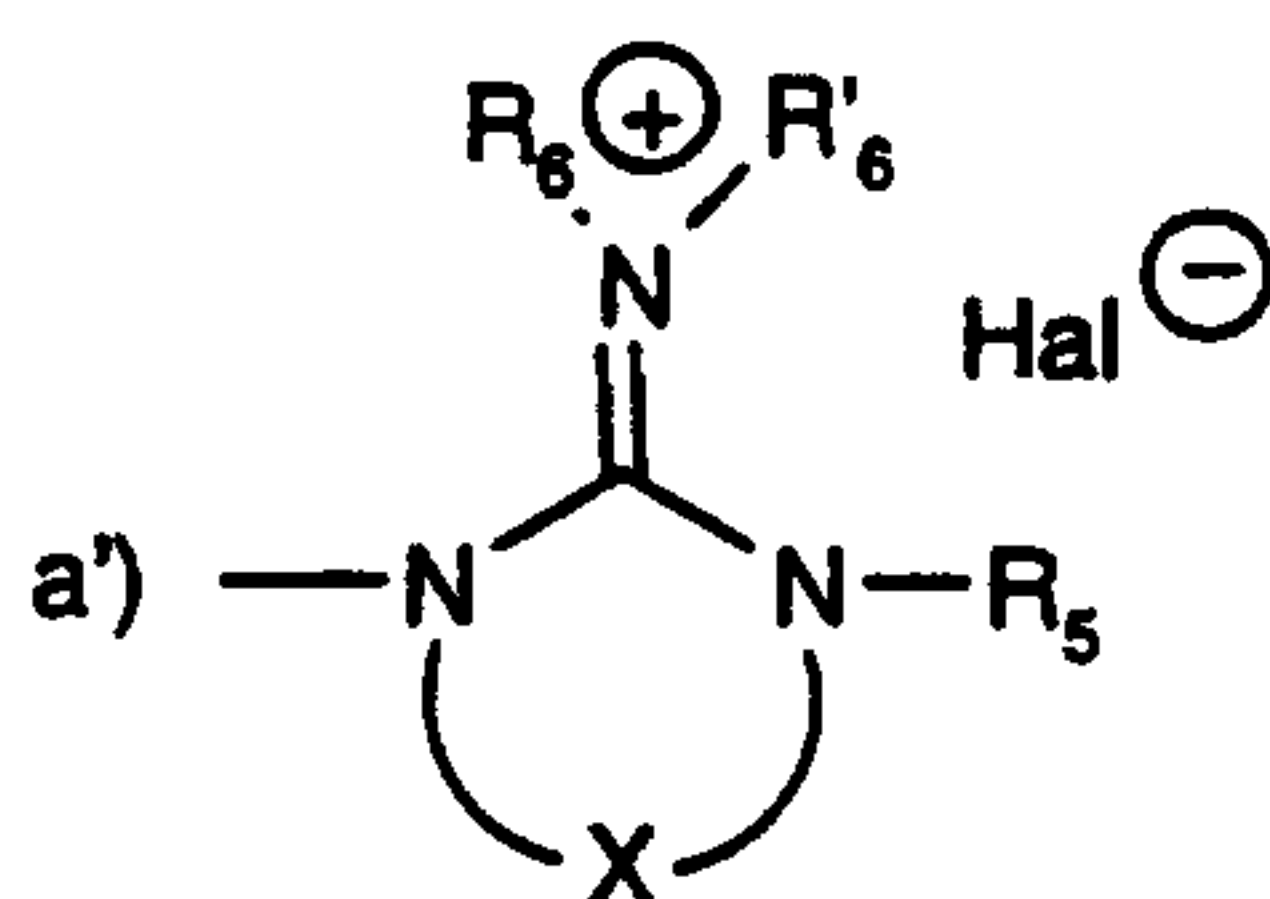
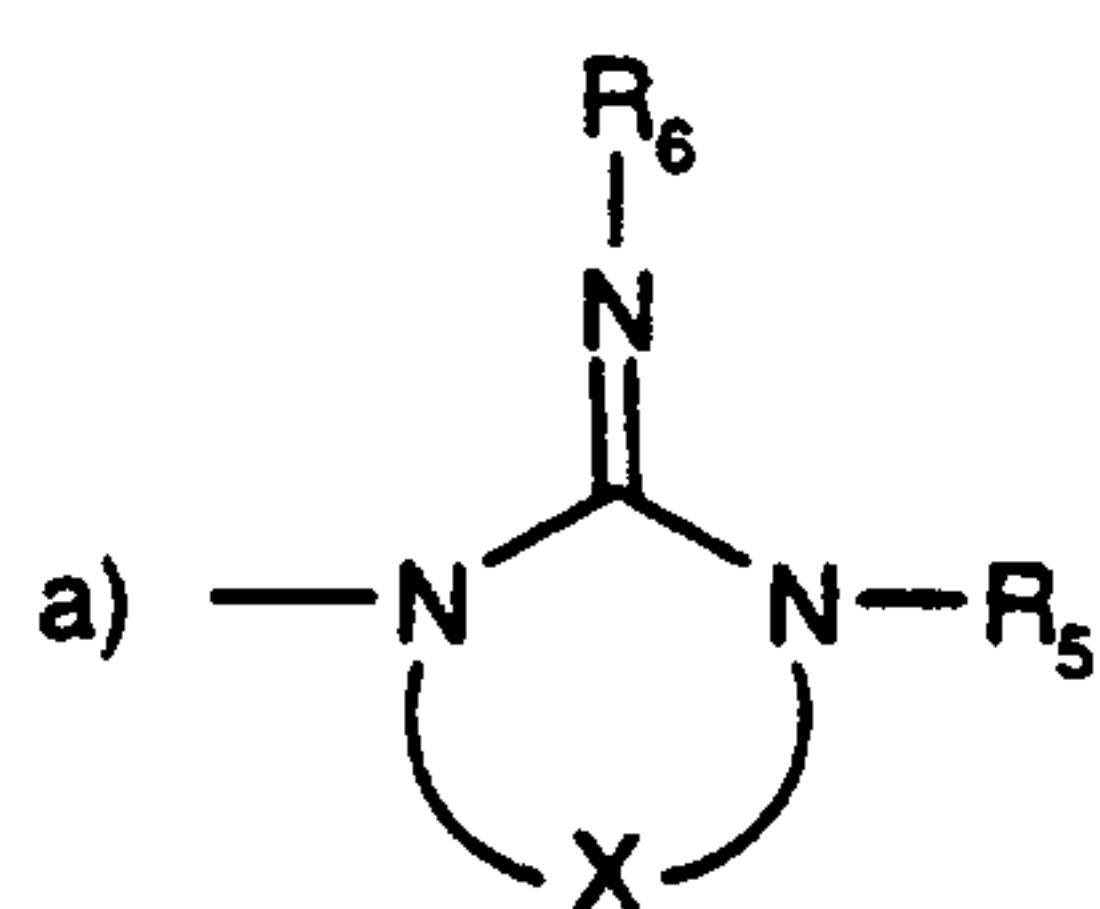
W denotes CH or N,

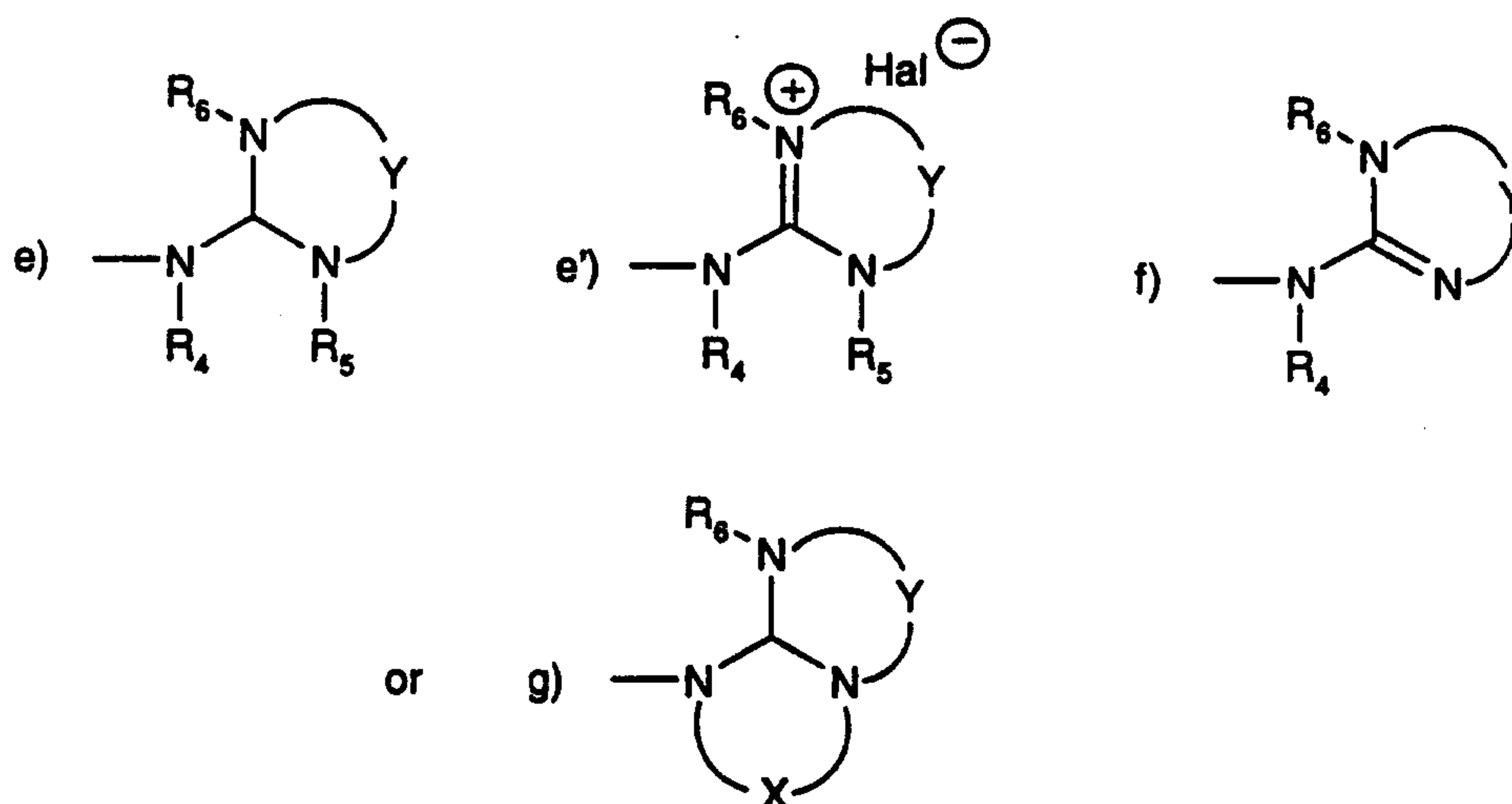
V denotes CH or NO,

R₁ denotes hydrogen, acyl, carboxyl or alkyl,

R₃ denotes hydrogen or an ester moiety,

R₂ denotes a group of formula





5 wherein

X and Y independently of each other each denote (C₂₋₅)alkylene, or (C₂₋₅)alkenylene wherein one -C=C- double bond is present, or, in case of at least C₄-alkenylene, wherein two -C=C- double bonds are present,

R₄ denotes hydrogen or alkyl,

10 R₅ denotes hydrogen, alkyl, or aminoiminomethyl,

R₆ denotes hydrogen, alkyl, cycloalkyl, amino, hydroxy, alkoxy, heterocyclyl or a group of formula -N=CHR₈, wherein

R₈ denotes alkyl, aryl or heterocyclyl, or

R₅ and R₆ together with the nitrogen atoms to which they are attached denote

15 heterocyclyl,

R'₆ denotes alkyl,

R₇ denotes hydrogen, or

R₆ and R₇ together with the nitrogen atom to which they are attached form heterocyclyl.

20

In formula I R₃ is hydrogen or an ester moiety.

An ester moiety includes alkyl; e.g. unsubstituted alkyl or substituted alkyl, e.g. by - aryl, such as benzyl, alkoxybenzyl, such as 4-methoxybenzyl, alkoxy, such as methoxymethyl; alkyloxycarbonyloxy; alkyl; alkoxy, such as glycyloxy,

25 phenylglycyloxy, e.g. glycyloxymethyl, phenylglycyloxymethyl; heterocyclyl e.g. 5-methyl-2-oxo-1,3-dioxolen-4-yl;

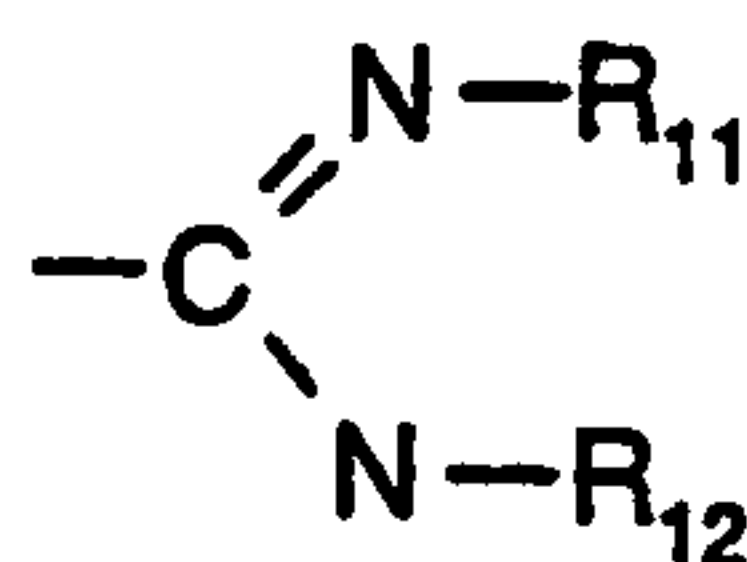
indanyl, phthalidyl, alkoxycarbonyloxy and ester moieties which form with the COO-group a physiologically hydrolysable and acceptable ester, *e.g.* such known to be hydrolysable ester groups in the field of cephalosporins. A compound of formula I may thus be in the form of an physiologically-hydrolysable and -acceptable ester. By

5 physiologically-hydrolysable and -acceptable esters as used herein is meant an ester in which the COO- group is esterified and which is hydrolysable under physiological conditions to yield an acid which is itself physiologically tolerable at dosages to be administered. The term is thus to be understood as defining regular pro-drug forms. An ester moiety may be preferably a group which is easily hydrolysable under

10 physiological conditions. Such esters may be administered preferably orally. Parenteral administration may be indicated if the ester *per se* is an active compound or, if hydrolysis occurs in the blood.

In a compound of formula I:

- 15 V denotes preferably NO.
- R₁ denotes preferably hydrogen or alkyl, *e.g.* lower alkyl, *e.g.* including unsubstituted alkyl and substituted alkyl; *e.g.* by halogen, carboxyl, preferably by halogen.
- R₂ denotes preferably a group of formula a), a'), c), d), d'), e') or f);
- R₄ denotes preferably hydrogen or alkyl, *e.g.* lower alkyl.
- 20 X and Y independently of each other denote preferably alkylene or alkenylene, *e.g.* (C₁₋₄)alkylene or (C₁₋₄)alkenylene, such as (C₂₋₃)alkylene or (C₂₋₃)alkenylene, *e.g.* including unsubstituted and substituted alkylene or alkenylene, *e.g.* by
- halogen, alkyl, *e.g.* lower alkyl; cycloalkyl, carboxyl or alkylcarbonyl; preferably by alkyl, *e.g.* including hydroxyalkyl, aminoalkyl; carboxyl and (lower alkyl)carbonyl.
- 25 R₅ denotes preferably hydrogen, alkyl, *e.g.* including unsubstituted alkyl and substituted alkyl, *e.g.* by
- hydroxy, carboxyl, amino, *e.g.* including lower alkylamino or di-lower alkylamino; heterocyclyl, *e.g.* including 5 or 6 ring members and including one or two heteroatoms, *e.g.* one, *e.g.* selected from O, S and N; an ester of a carboxylic,
- 30 sulfonic- or phosphoric acid, *e.g.* an alkyl or aryl ester, *e.g.* wherein the carboxylic acid part contains 1 to 12 carbon atoms and wherein the ester part contains 1 to 8 carbon atoms; or
- amino-iminomethyl, *e.g.* of formula

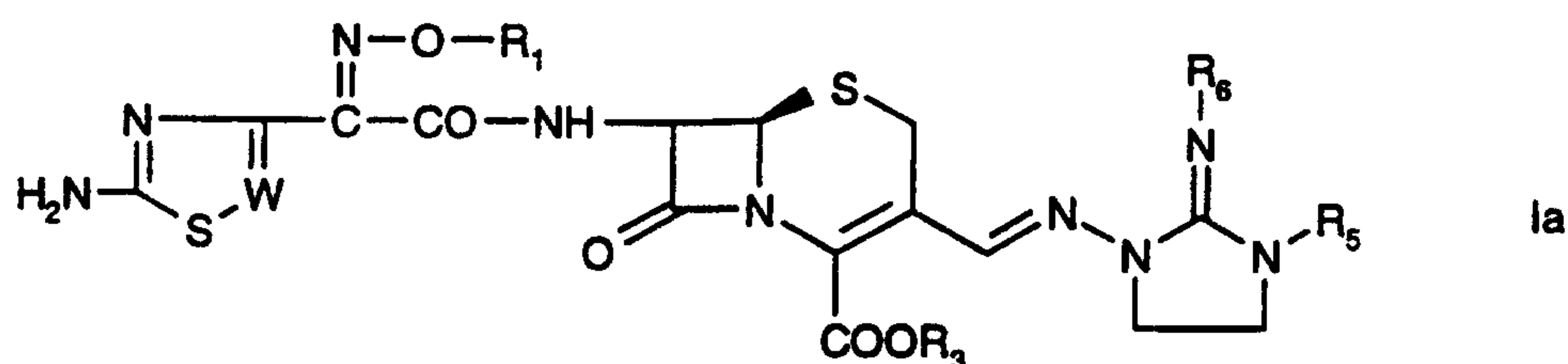


wherein R_{11} and R_{12} independently of each other denote hydrogen or alkyl, e.g. lower alkyl,

- R_6 denotes preferably hydrogen; amino, alkylamino, dialkylamino, e.g. wherein the alkyl part is unsubstituted or substituted, e.g. by hydroxy, amino; arylamino; e.g. R_6 denotes a group of formula $-\text{NR}_9\text{R}_{10}$, wherein R_9 and R_{10} independently of each other denote hydrogen, alkyl, e.g. including hydroxyalkyl, aminoalkyl, aryl;
- alkyl, e.g. including unsubstituted alkyl and substituted alkyl, e.g. by
- heterocyclyl, e.g. having 5 to 6 ring members and one or two heteroatoms, e.g. selected from N, O, S; e.g. including unsubstituted heterocyclyl and substituted heterocyclyl; e.g. by hydroxy;
 - hydroxy; alkoxy, e.g. including unsubstituted alkoxy and substituted alkoxy, e.g. by hydroxy, alkoxy, amino;
 - guanidino, e.g. wherein the amine groups are unsubstituted or substituted, e.g. the terminal amine group is part of heterocyclyl;
 - amino, alkylamino, and dialkylamino, e.g. (lower alkyl)amino and (lower dialkyl)amino;
 - alkyl, e.g. lower alkyl;
 - guanidino; wherein any amine group is unsubstituted or substituted, e.g. by alkyl; hydroxy, cycloalkyl, e.g. including unsubstituted and substituted cycloalkyl, e.g. by amino;
- heterocyclyl, e.g. including heterocyclyl having 5 or 6 ring members and one or two heteroatoms, e.g. selected from N, O, S; including e.g. unsubstituted heterocyclyl and substituted heterocyclyl e.g. by alkyl, e.g. R_6 denotes a group of formula $-\text{NR}_9\text{R}_{10}$, wherein R_9 and R_{10} together with the nitrogen atom to which they are attached form heterocyclyl; or
- a group of formula $-\text{N}=\text{CHR}_8$ wherein R_8 preferably denotes aryl, heterocyclyl, including substituted and unsubstituted heterocyclyl; e.g. by alkyl; e.g. having 5 or 6 ring members and one or two heteroatoms, e.g. selected from N, O, S;
- R_5 and R_6 , if together with the nitrogen atoms to which they are attached form heterocyclyl, denote preferably alkylene, e.g. (C_{2-4}) alkylene, such as (C_{2-3}) alkylene; R'_6 denotes preferably alkyl, e.g. lower alkyl;

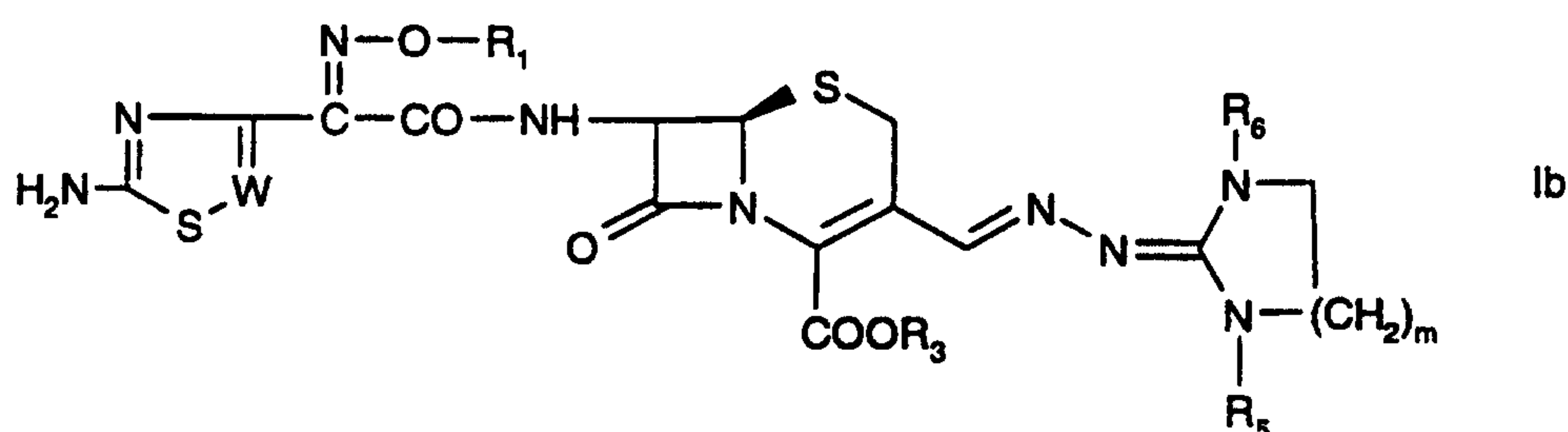
If R_6 and R_7 together with the nitrogen atom to which they are attached form heterocyclyl, heterocyclyl having preferably 5 to 7 ring members and one or two hetero atoms, e.g. selected from N, O, S.

5 In another aspect the present invention provides a compound of formula



wherein W, R_1 , R_3 , R_5 and R_6 are as defined above.

10 In another aspect the present invention provides a compound of formula



wherein W, R_1 , R_3 , R_5 and R_6 are as defined above and m denotes 1 or 2.

15

In another aspect the present invention provides the compound 7-[(5-amino-1,2,4-thiadiazole-3-yl)-(Z)-(fluoromethoxyimino)acetyl]amino-3-[[3-ethyl-2-methyliminoimidazolidine-1-yl]imino]methyl-3-cephem-4-carboxylic acid, e.g. in the form of a hydrochloride.

20

In this specification unless otherwise indicated terms such as "compound of formula I, Ia and Ib" embrace the compound in any form, for example in the form of a salt and in free base form. The present invention thus includes a compound in free base form or, e.g. where such forms exist, in the form of a salt, for example in the form of an acid addition salt, inner salt, quaternary salt and/or in the form of a solvate, for example in the form of a hydrate. A salt may be a pharmaceutically acceptable salt of a compound of formula I, Ia and Ib, such as a metal salt or an amine salt. Metal salts include for example sodium, potassium, calcium, barium, zinc, aluminum salts,

25

preferably sodium or potassium salts. Amine salts include for example trialkylamine, procaine, dibenzylamine and benzylamine salts. A free form of a compound of formula I, Ia and Ib may be converted into a salt form and *vice versa*.

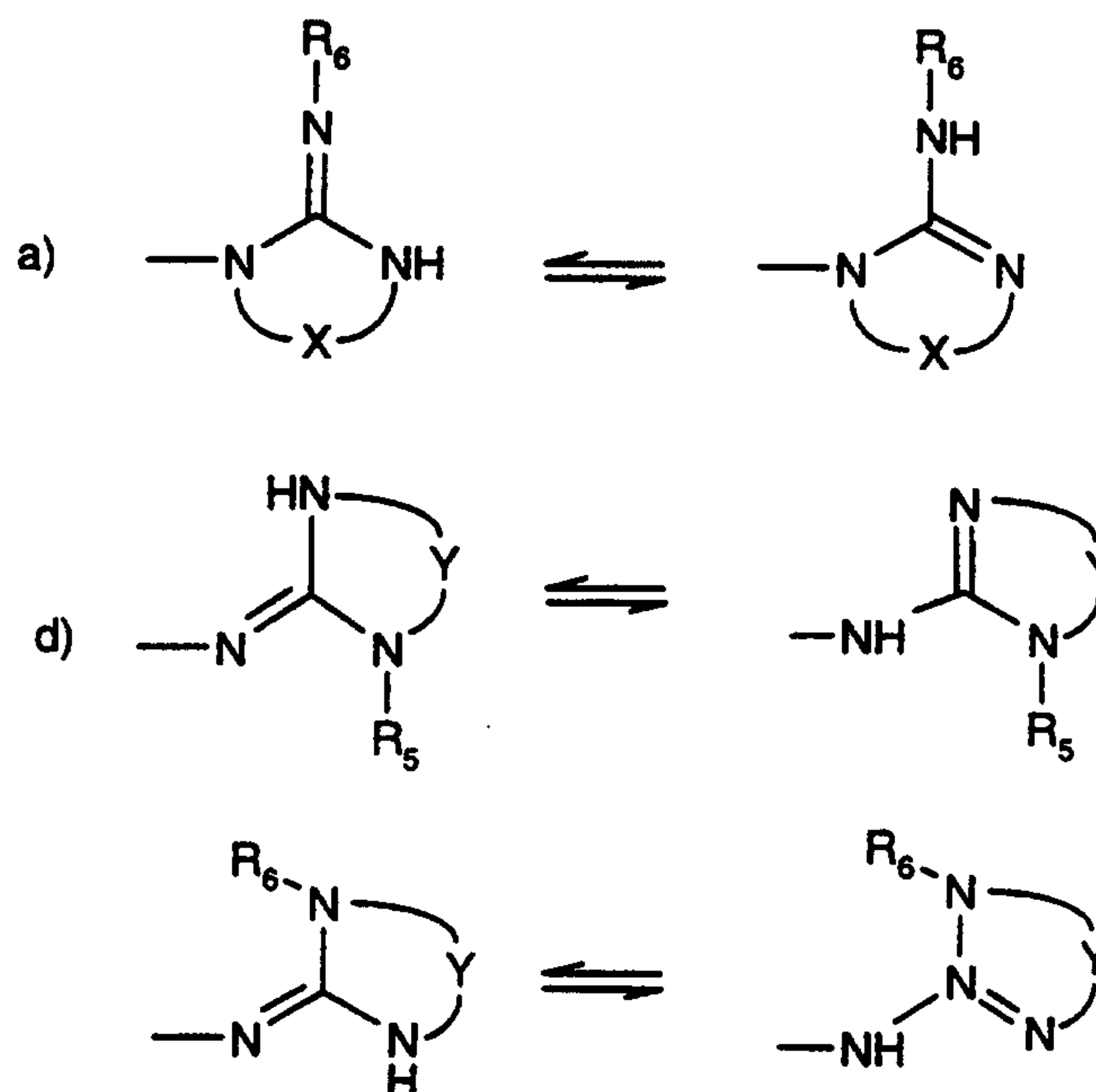
- 5 In a further aspect the present invention provides a compound of formula I, Ia and Ib, in free form and in the form of a salt, for example an acid addition salt or a metal salt; and a compound of formula I, Ia and Ib e.g. in free form or in the form of a salt, in the form of a solvate.
- 10 If not otherwise stated herein any carbon containing group may contain up to 20 carbon atoms, e.g. alkyl includes, e.g. straight chain and branched, (C₁₋₂₀), e.g. (C₁₋₈)alkyl, such as (C₁₋₆)alkyl and lower alkyl. Lower alkyl includes e.g. (C₁₋₄)alkyl, such as (C₁₋₂)alkyl. Cycloalkyl includes, for example (C₃₋₇)cycloalkyl, particularly C₃, C₅ or C₆ cycloalkyl. Acyl includes alkylcarbonyl and arylcarbonyl, e.g. (C₁₋₁₂)acyl, e.g. (C₁₋₆)acyl, such as (C₁₋₄)acyl. Aryl includes phenyl, naphthyl, e.g. phenyl. Heterocyclyl includes heterocyclyl having 4 to 7, e.g. 5 to 6 ring members and 1 to 3 nitrogen, sulphur and/or oxygen hetero atoms (N,O,S) including, for example, condensed heterocyclyl, such as for example benzthiazolyl. Amino includes a free amine group, e.g. in the form of a salt, alkylamino, dialkylamino and arylamino, and e.g. protected amino.
- 20 Guanidino includes a guanidino group wherein the 3 nitrogen atoms are unsubstituted or independently of each other are substituted, e.g. by alkyl.
- If not otherwise stated any group mentioned herein may be unsubstituted or substituted, e.g. one fold or several fold, e.g. by groups which are conventional in β -lactam chemistry, such as by
- 25 - alkyl, e.g. - CF₃, aryl, alkoxy, halogen, hydroxy, carboxyl, a sulphonic acid derivative, such as SO₃H, a phosphoric acid derivative, acyl, amino; guanidino, heterocyclyl, e.g. pyridyl, oxo, thiono, mercapto, alkyl- or arylthio, imino, alkylimino, CHO.
- 30 Halogen includes fluoro, chloro, bromo and iodo.

The present invention includes a compound of formula I in any isomeric form in which it may exist. E.g. the configuration in group -C=V-R₁, wherein V-R₁ denotes N-O, may be syn [(Z)] and anti [(E)] and is preferably syn [(Z)]. E.g. geometric isomers may be obtained, e.g. during a production process of a compound of formula I, e.g.

due to the presence of a $-CX'=CX''$ - double bond wherein X' and X'' are groups which have a different meaning. E.g. a chiral carbon atom may be introduced, e.g. during a production process of a compound of formula I and corresponding stereoisomeric forms of a compound of formula I may be obtained, e.g. a mixture of the individual stereoisomers, e.g. a racemate, or pure isostereoisomeric forms. Mixtures of isomers may be separated.

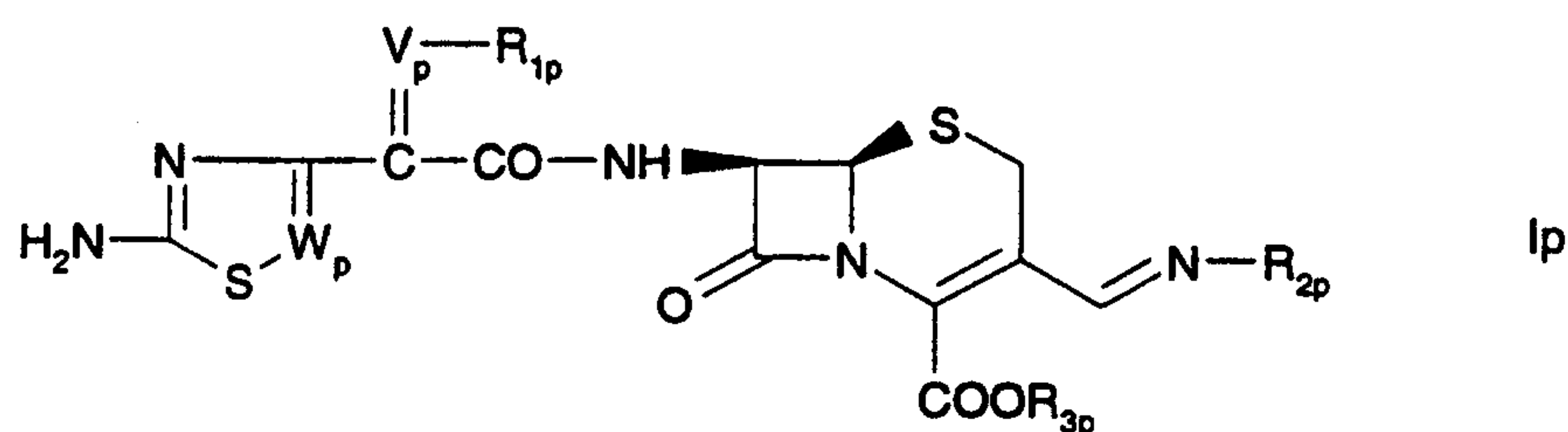
The present invention includes a compound of formula I in any tautomeric form. E.g. a compound of formula I, wherein

- 10 R_2 is a group of formula a), wherein R_5 is hydrogen, or R_2 is a group of formula d), wherein R_5 or R_6 is hydrogen may exist in a tautomeric form, e.g. as described below::



15

In another aspect the present invention provides a compound of formula



wherein

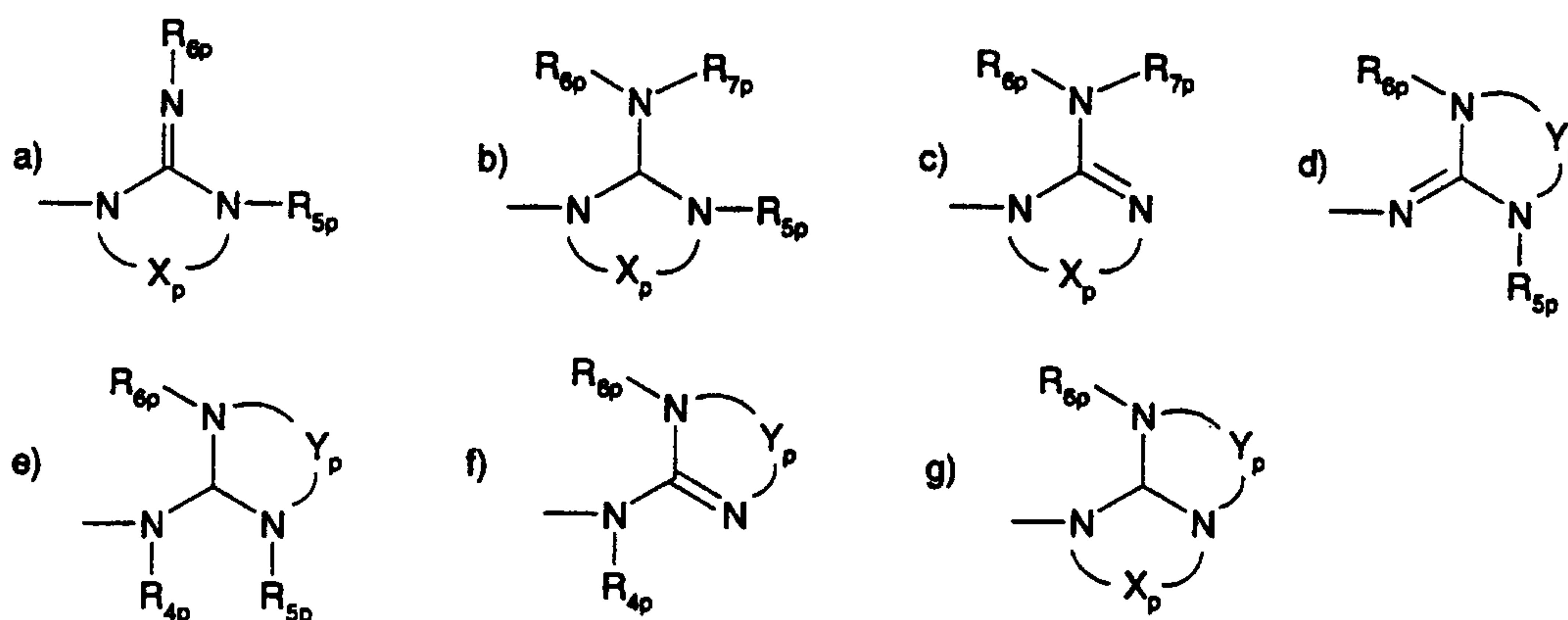
W_p denotes CH or N,

V_p denotes =CH- oder =N-O-,

5 R_{1p} denotes hydrogen, acyl, carboxyl, unsubstituted alkyl, or alkyl substituted by halogen or carboxyl,

R_{3p} denotes hydrogen, an ester forming group or a cation,

R_{2p} denotes a group of formula



10

wherein X_p and Y_p are the same or different and each denote a $-(CH_2)_n$ -group, wherein n denote a number from 2 to 5, and optionally one or two CH_2 -groups are replaced by a $-CH=CH-$ group and optionally one or more hydrogen atoms are replaced by halogen, alkyl, cycloalkyl, hydroxyalkyl, aminoalkyl, carboxyl or ethoxycarbonyl,

15 R_{4p} denotes hydrogen, alkyl or hydroxyalkyl,

R_{5p} denotes hydrogen, alkyl, (poly)hydroxyalkyl or aminoalkyl, wherein optionally the alkyl groups are additionally substituted by a functional group, e.g. a carboxyl acid residue, a sulphonic acid residue or a phosphoric acid residue,

20 R_{6p} denotes hydrogen, alkyl, hydroxyalkyl, aminoalkyl, amino, hydroxy, alkoxyalkyl, cycloalkyl, a group $N=CHR_{8p}$, wherein

R_{8p} denotes aryl or heteroaryl,

or a group $-NR_{9p}R_{10p}$, wherein

R_{9p} and R_{10p} are the same or different and each denote hydrogen, alkyl, hydroxyalkyl or aryl or denote together with the nitrogen atom a saturated, unsubstituted

25 heterocycle with 5 or 6 ring members with one or two nitrogen and/or oxygen atoms, and

R_{7p} denotes hydrogen, or

R_{7p} and R_{6p} denote together with the nitrogen atom a heterocycle with 5 to 7 ring members containing one or two nitrogen and/or oxygen atoms, with the proviso that,

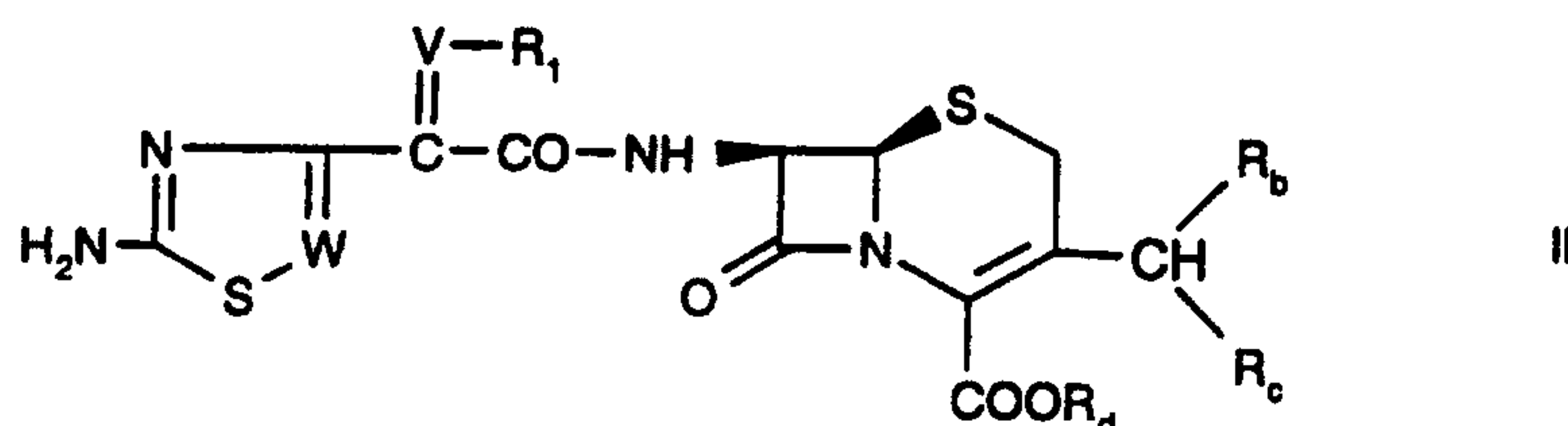
if W_p denotes CH , V_p denotes $=N-O-$, R_{1p} denotes hydrogen or methyl, R_{2p} denotes a group of formula d) and R_{3p} denotes hydrogen, R_{5p} and R_{6p} denote at the same time another group than hydrogen or methyl, in free form, or, where such forms exist, in the form of acid addition salts, inner salts, quaternary salts or hydrates thereof.

5

A compound of formula I may be produced e.g. as described below and in the examples, and e.g. analogously to a method as conventional in β -lactam chemistry.

In another aspect the present invention provides a process for the production of a compound of formula I, comprising reacting a compound of formula

10



wherein W , V and R_1 are as defined above and

- $\alpha)$ R_b denotes hydroxy and R_c and R_d together denote a bond, or
- $\beta)$ R_d denotes hydrogen, a cation, an ester forming group or a silyl group, and R_b and R_c together denote the oxo group,
- in free form or in the form of an acid addition salt thereof with an amine of formula



20

wherein R_2 is as defined above, e.g. desired (reactive) groups may be protected with protecting groups, e.g. as conventional in β -lactam chemistry, which may be, or, which are split off under the reaction conditions, or after termination of the reaction described above. A compound of formula I wherein R_3 denotes hydrogen may be converted into a compound of formula I, wherein R_3 denotes an ester moiety, e.g. a carboxylic acid ester group, and vice versa, e.g. by a method analogously to a method as conventional. A compound of formula I may be isolated from the reaction mixture in conventional manner, e.g. analogously to a method as conventional.

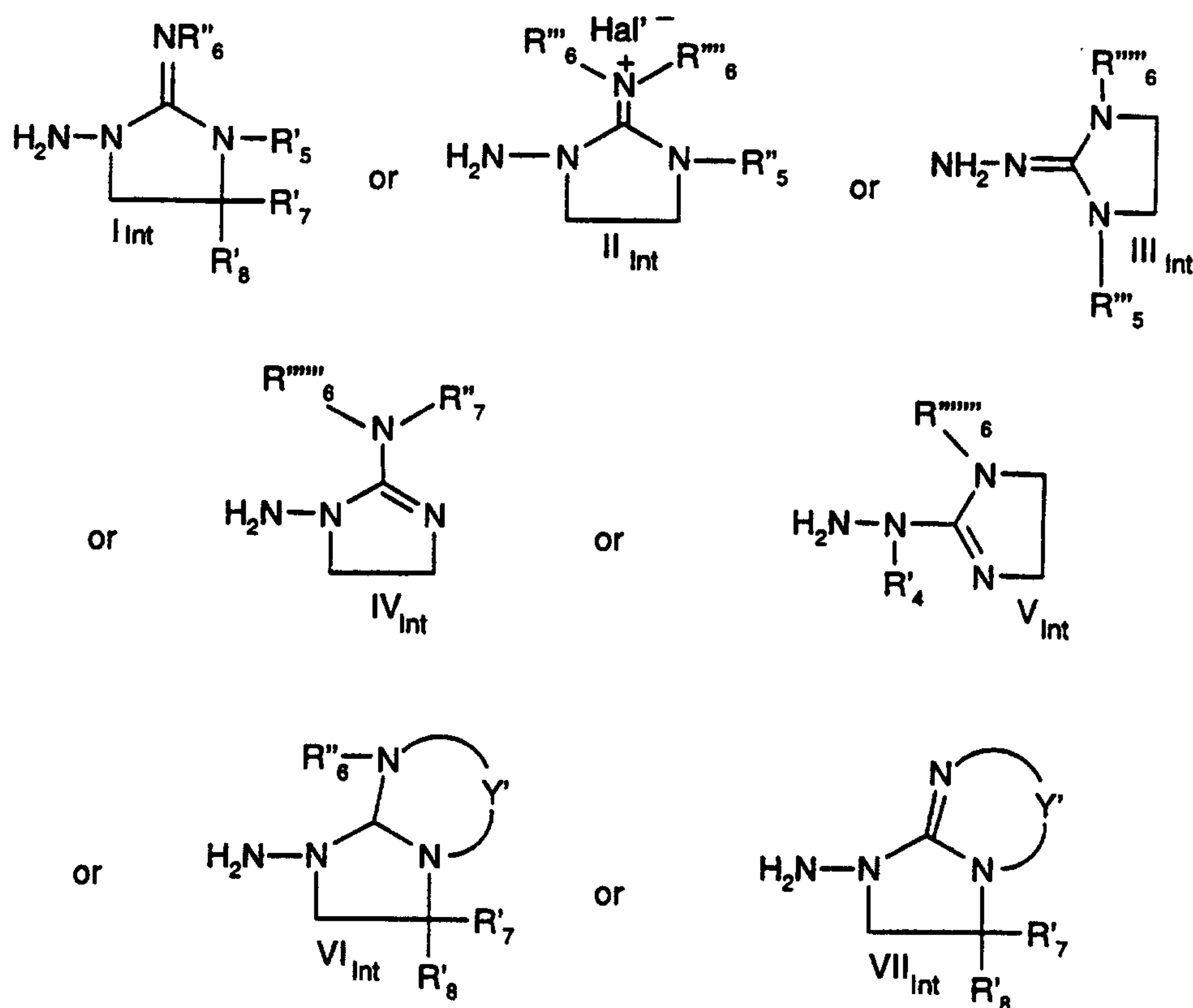
E.g. a compound of formula I may be produced as follows:

A compound of formula II may be reacted in a solvent which is inert under the reaction conditions, e.g. a polar solvent, e.g. water and a mixture of water with a

30

lower alcohol or dioxan, or a dipolar aprotic solvent, e.g. dimethylformamide, dimethylsulfoxide, dimethylacetamide, preferably dimethylacetamide, or a mixture of individual solvents, e.g. as described above, e.g. dimethylacetamide with alcohol or water, e.g. at a temperature from -20 to 50°C with a compound of formula III. An appropriate, e.g. optimal pH may be adjusted, e.g. by addition of a base or an acid, e.g. an inorganic or an organic acid. A compound of formula I obtained may be isolated from the reaction mixture, e.g. analogously to a method as conventional, e.g. by addition of an anti-solvent to the reaction mixture or, e.g. by chromatography. If desired, any group, e.g. a reactive group, may be protected before reaction, e.g. by silyl protecting group technology in a suitable solvent, e.g. in a solvent which is inert under the reaction conditions, e.g. halogenated carbohydrates, e.g. dichloromethane, nitriles, such as acetonitrile, ethers, e.g. tetrahydrofuran, or dipolar aprotic solvents, e.g. dimethylformamide, including a mixture of individual solvents, e.g. as defined above. Protecting groups may be split off, e.g. by a deprotection method, e.g. a method as conventional.

Starting compounds are known or may be obtained by a method as conventional, e.g. analogously or e.g. as described in the examples. Starting compounds, e.g. in free form or in the form of a salt, e.g. in the form of a hydrochloride, of formula



wherein Y' denotes alkylene, e.g. (C₂₋₃)alkylene,

R'₅ denotes hydrogen, alkyl or alkylimino;

e.g. unsubstituted alkyl, alkyl substituted by

- 5 - hydroxy,
- carboxyl,
- amino, e.g. including an amine group, alkylamino and dialkylamino;
- heterocyclyl, e.g. having 5 or 6 ring members and one or two heteroatoms, selected from N,O,S, e.g. N, e.g. piperidino, pyrrolidino;

10 - guanidino;

pyridylmethylimino;

R''₆ denotes hydrogen, alkyl, hydroxy, alkoxy, cycloalkyl, amino or heterocyclyl;

e.g. alkylamino, hydroxyalkylamino, phenylamino; unsubstituted alkyl, alkyl substituted by

- 15 - heterocyclyl, e.g. having 5 to 6 ring members and containing one or two heteroatoms, e.g. selected from N,O, S, e.g. N, e.g. piperazino, piperidino, pyridino, morpholino, pyridoxal; including unsubstituted heterocyclyl and substituted heterocyclyl, e.g. by alkyl;
- amino, e.g. including an amine group, alkylamino, dialkylamino,
- 20 hydroxyalkylamino, (di)aminoalkylamino;
- hydroxy, hydroxyalkoxy, alkoxy, e.g. hydroxyalkoxy, alkoxyalkoxy, aminoalkoxyalkoxy;
- guanidino, e.g. wherein the amine groups are unsubstituted or substituted, e.g. by alkyl; e.g. and guanidino wherein the terminal amino group is part of a heterocyclic
- 25 ring system, e.g. having 5 to 6 ring members and one or two heteroatoms selected from N,O,S; at least from N;
- alkyl, e.g. lower alkyl;

heterocyclyl, e.g. having 5 to 6 ring members and containing one or two heteroatoms, e.g. selected from N,O, S; (C₃₋₇)cycloalkyl, e.g. unsubstituted cycloalkyl or substituted cycloalkyl by amino;

30 R'₇ and R'₈ independently of each other denote hydrogen, carboxyl, alkoxycarbonyl, or alkyl; e.g. lower alkyl, e.g. unsubstituted alkyl and substituted alkyl, e.g. by hydroxy;

R'''₆ and R''''₆ independently of each other denote alkyl, e.g. lower alkyl; or,

R''₆ and R'''₆ together with the nitrogen atom to which they are attached denote heterocyclyl, e.g. having 5 to 6 ring members and containing one or two hetero atoms, e.g. selected from N, O, S; at least one N;

R''₅ denotes alkyl, e.g. lower alkyl; or

5 R''₅ and R'''₆ together denote alkylene, e.g. (C₂₋₃)alkylene;

R'''₅ and R''''₆ independently of each other denote alkyl, e.g. lower alkyl;

R''''₆ and R''₇ together with the nitrogen atom to which they are attached form heterocyclyl, e.g. having 5 or 6 ring members and one or two heteroatoms, e.g. selected from N, O, S, e.g. N;

10 R'₄ and R''''''₆ independently of each other denote alkyl, e.g. lower alkyl; and

Hal denotes halogen, e.g. chloro, bromo;

with the proviso that a compound of formula I_{Int} wherein R'₅, R'₇ and R'₈ are hydrogen and R''₆ is hydrogen, 2-(N-morpholino)ethyl, 3-(N,N-dimethylamino)-propyl; (2-hydroxyethyl)amino or 2-hydroxyethyl is excluded,

15 are novel.

In another aspect the present invention provides a compound of formula I_{Int}, II_{Int}, III_{Int}, IV_{Int}, V_{Int} or VI_{Int}, wherein the residues are as defined above, with the proviso as stated above.

20

The compounds of formula I, hereinafter designated as "active compound(s) of the invention" exhibits pharmacological activity, e.g. beside low toxicity and are therefore useful as pharmaceuticals. In particular, the active compounds of the invention show antimicrobial, e.g. antibacterial, activity against e.g. gram negative and gram positive

25 bacteria, e.g. gram positive bacteria such as *Pseudomonas*, e.g. *Pseudomonas aeruginosa*; *Escherichia*, e.g. *Escherichia coli*; *Enterobacter*, e.g. *Enterobacter cloacae*; *Klebsiella*, e.g. *Klebsiella edwardsii*, *Klebsiella pneumoniae*; *Enterococcus*, e.g. *Enterococcus faecalis*; *Moraxella*, e.g. *Moraxella catarrhalis*; *Streptococcus*, e.g. *Streptococcus pneumoniae*, *Streptococcus pyogenes*; and *Staphylococcus*, e.g.

30 *Staphylococcus aureus*; *in vitro* in the Agar Dilution Test according to National Committee for Clinical Laboratory Standards (NCCLS) 1993, Document M7-A3 Vol.13, No. 25: "Methods for dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition, Approved Standard". The active compounds show an MIC (µg/ml) in the Agar Dilution Test from about <0.0125 to

35 ca. >25.6. The active compounds of the invention show an surprising overall activity spectrum.

It has, for example, been determined that the MIC ($\mu\text{g/ml}$) of the compound of Example 48 against, for example *E.coli* strains ATCC 35218 and ATCC 10536 is of <0.0125 ; and against *Enterobacter cloacae* strains is of <0.0125 .

5

The active compounds of the invention are, therefore, useful for the treatment of microbial, e.g. bacterial diseases.

10

In another aspect the present invention provides a compound of claim 1 for use as a pharmaceutical, preferably as an antimicrobial agent, such as an antibiotic.

In a further aspect the present invention provides a compound of claim 1 for use in the preparation of a medicament for the treatment of microbial diseases, for example of diseases caused by bacterias selected from *Pseudomonas*, *Escherichia*, *Enterobacter*, *Klebsiella*, *Enterococcus*, *Moraxella*, *Streptococcus* and *Staphylococcus*.

15

In a further aspect the present invention provides a method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of a compound of formula I.

20

For this indication, the appropriate dosage will, of course, vary depending upon, for example, the compound of formula I employed, the host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage is in the range from about 0.05 to 5 g, for example 0.1 to about 2.5 g, of an active compound of the invention conveniently administered, for example, in divided doses up to four times a day.

25

An active compound of the invention may be administered by any conventional route, for example orally, e.g. in form of tablets or capsules, or parenterally in the form of injectable solutions or suspensions, e.g. in analogous manner to ceftazidime.

30

The compound 7-[[[(5-amino-1,2,4-thiadiazole-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino]-3-[[[(3-ethyl-2-methylimino-imidazolidine-1-yl)imino]methyl]-3-cephem-4-carboxylic acid, (compound of Example 48) is the preferred compound of the invention for use as an antimicrobial agent.

35

It has, for example been determined that the MIC ($\mu\text{g/ml}$) of the compound of Example 48 (tested in form of the hydrochloride) against, for example *Klebsiella edwardsii*, strain ATCC 10896 is ca. 0.8 whereas, for example ceftazidime shows an

MIC ($\mu\text{g/ml}$) of ca. 1.6. It is therefore, indicated that for the treatment of microbial diseases, *e.g.* bacterial diseases the preferred compounds of the invention may be administered to larger mammals, for example humans, by similar modes of administration at similar dosages than conventionally employed with ceftazidime.

5

The compounds of formula I may be administered in pharmaceutically acceptable salt form, *e.g.* acid addition salt form or base addition salt form or in the corresponding free forms, optionally in solvate form. Such salts exhibit the same order of activity as the free forms.

10

The present invention also provides pharmaceutical compositions comprising a compound of formula I in pharmaceutically acceptable salt form or free form in association with at least one pharmaceutical carrier or diluent.

Such compositions may be manufactured in conventional manner.

15

The present invention provides in further aspects

- a compound of formula 1 for use as a pharmaceutical in the treatment of microbial diseases caused by bacterias selected from *Pseudomonas*, *Escherichia*, *Enterobacter*, *Klebsiella*, *Moraxella*, *Enterococcus*, *Streptococcus*, *Staphylococcus*;
- 20 - the use of a compound of formula I, or use of a pharmaceutical composition comprising a compound of formula I as a pharmaceutical and
- a method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of a compound of formula I.

25 In the following examples which illustrate the present invention all temperatures are given in degree Celsius.

The following abbreviations are used:

t-BOC = N-tert.butyloxycarbonyl

BOC anhydride = di-tert.butyldicarbonate

Example 1

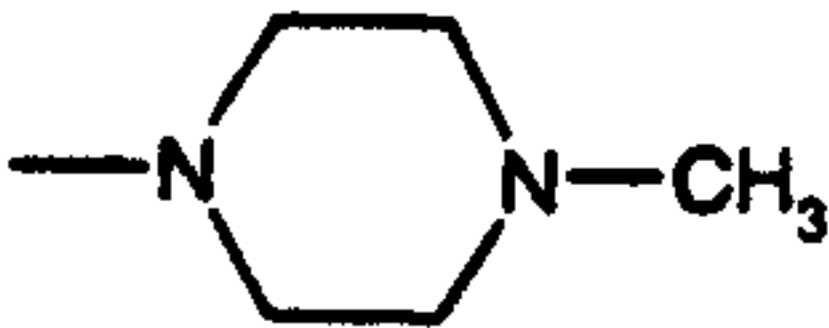
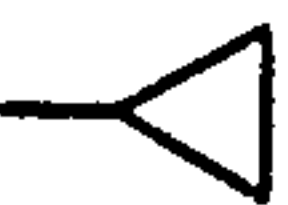
To a mixture of 0.2 g of 1,2-diamino-4,5-dihydro-1H-imidazole in the form of a dihydrochloride, 0.73 ml of 2 N HCl, 0.57 ml of dimethylacetamide and 0.57 ml of water 0.57 g of N-(1,4,5a,6-tetrahydro-3-hydroxy-1,7-dioxo-3H,7H-azeto[2,1-b]furo[3,4-d][1,3]-thiazine-6-yl)-2-(5-amino-1,2,4-thiadiazole-3-yl)-(Z)-2-(fluoromethoxyimino)acetic acid amide are added and the mixture obtained is stirred for ca. 3 hours at room temperature. The mixture obtained is poured onto 150 ml of acetonitrile under stirring. A precipitate is obtained, filtrated off, washed and dried.

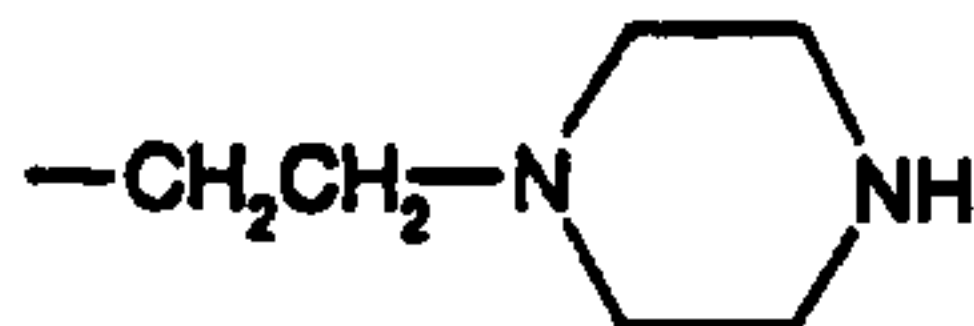
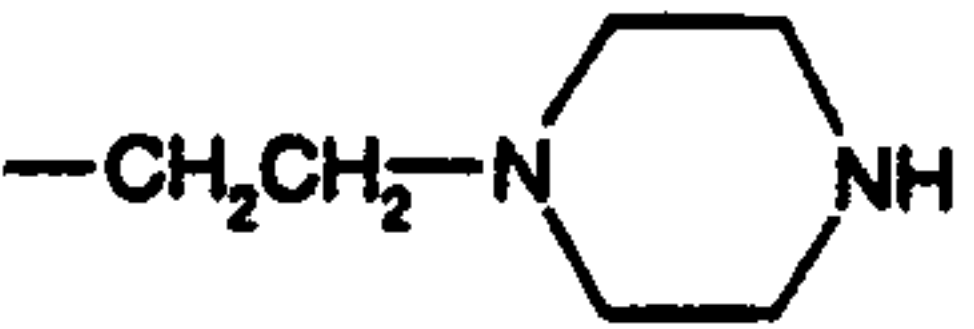
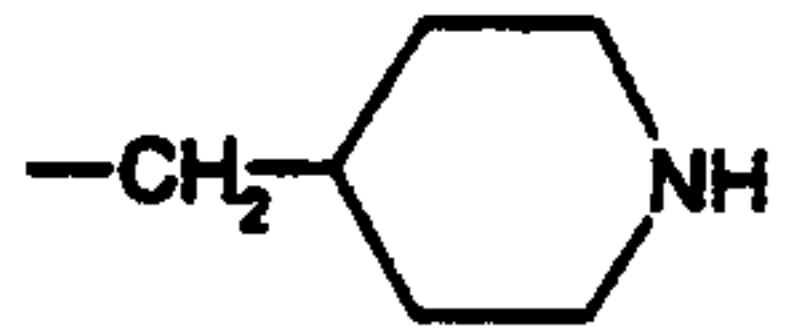
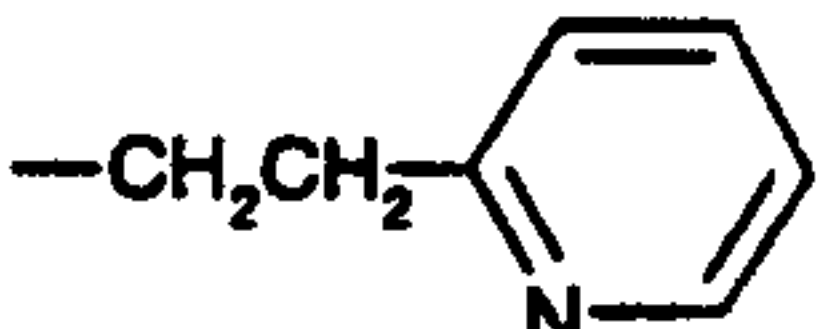
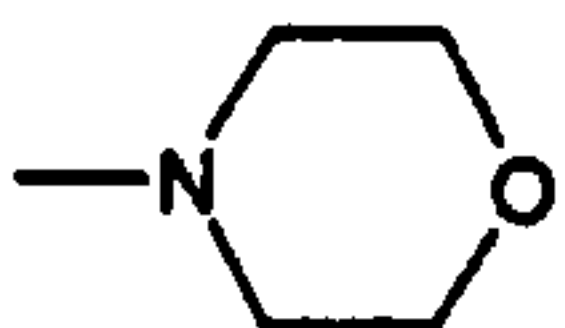
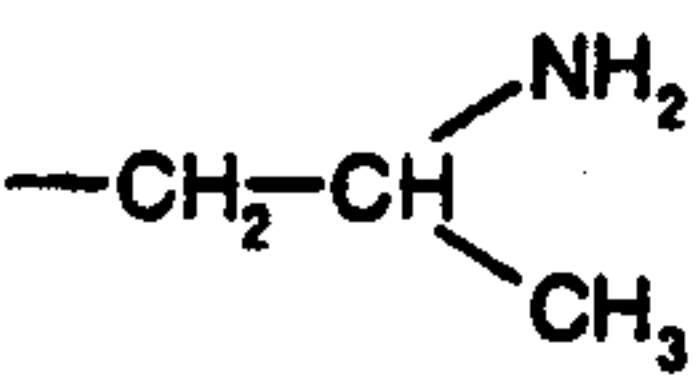
7-[[[(5-Amino-1,2,4-thiadiazole-3-yl)-(Z)-(fluoromethoxyimino)acetyl]amino]-3-[[[(2-amino-4,5-dihydro-1H-imidazole-1-yl)imino]methyl]-3-cephem-4-carboxylic acid in the form of a tri-hydrochloride is obtained in the form of a yellow powder.

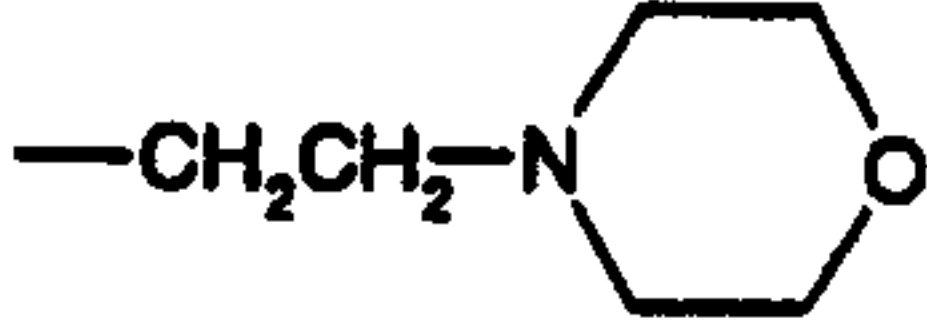
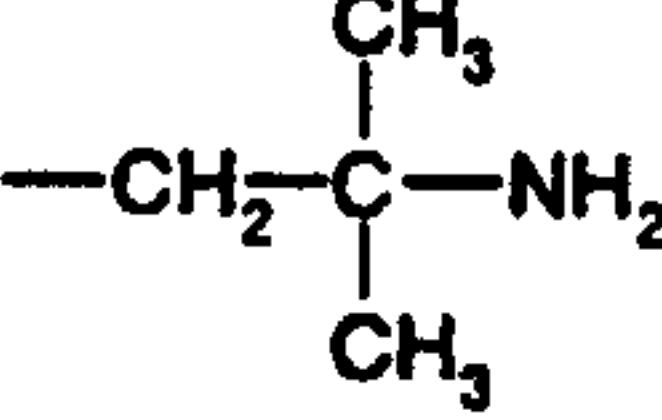
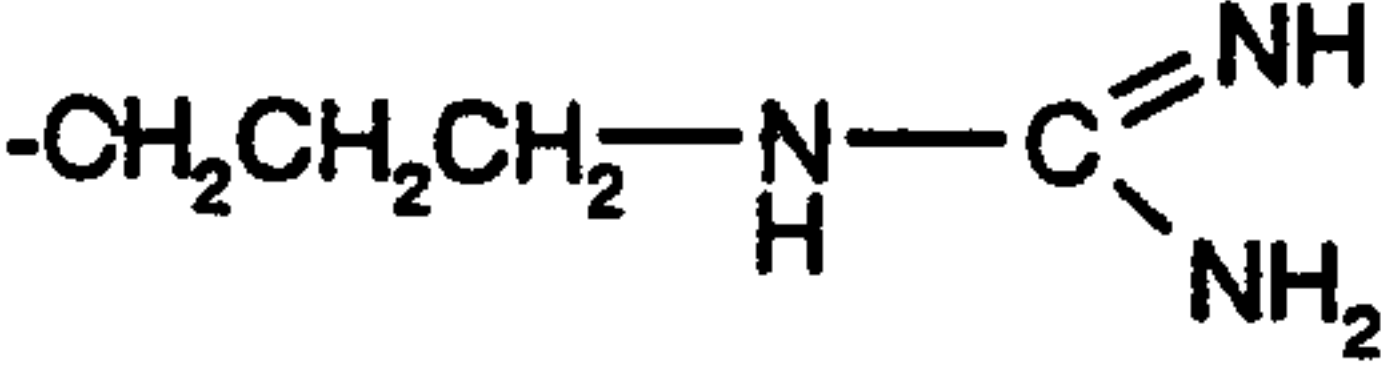
For further purification a crude compound obtained is dissolved in water, poured over a chromatography column (LiChroprep RP-18^R, Merck) and eluated with water or water/methanol. Fractions containing the desired compound (determined by HPLC) are combined and lyophilized.

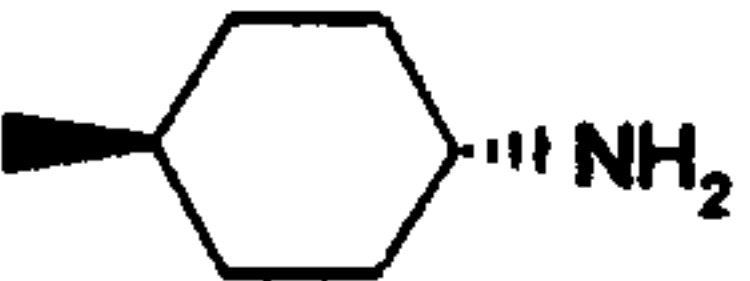
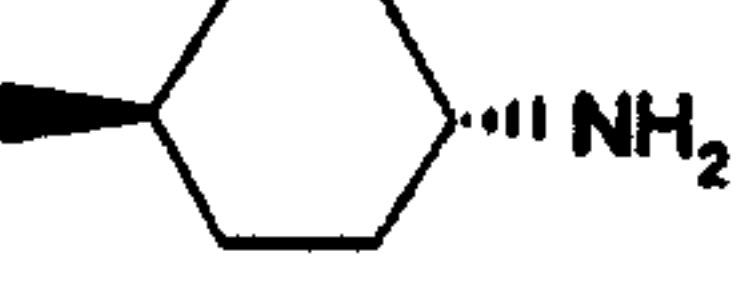
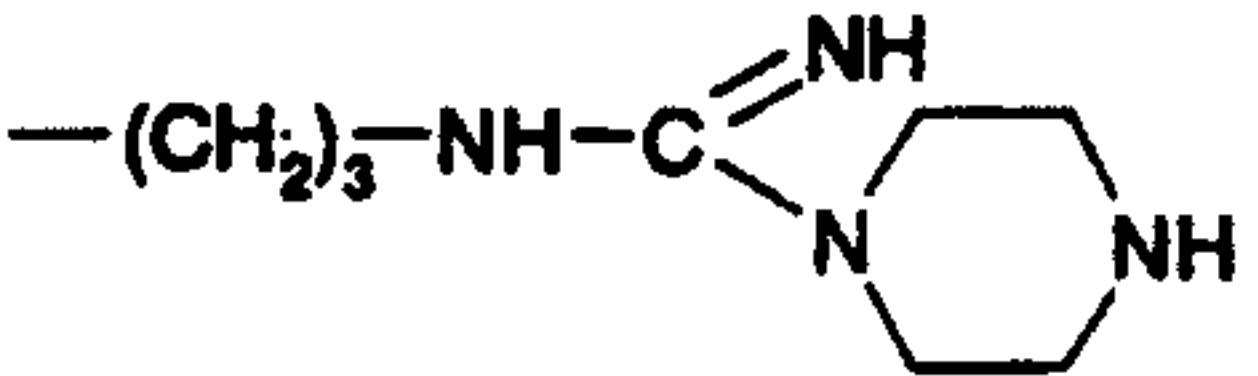
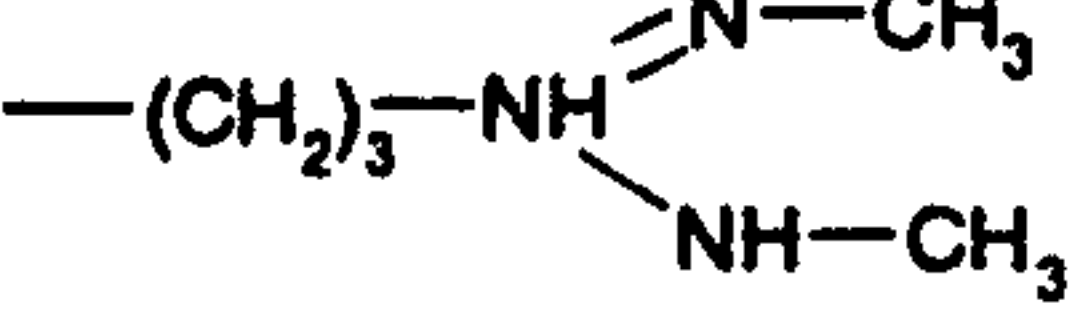
Analogously as described in Example 1 the compounds described in TABLE 1 below under Examples (Ex.) 2 to 83, which are compounds of formula I wherein V-R₁ = N-OCH₂F; W is as defined in TABLE 1; R₃ = hydrogen; and R₂ = a compound of formula a), wherein R₅ and R₆ are as defined in TABLE 1 and X = -CH₂CH₂-; in the form of a salt as defined in TABLE 1; are obtained:

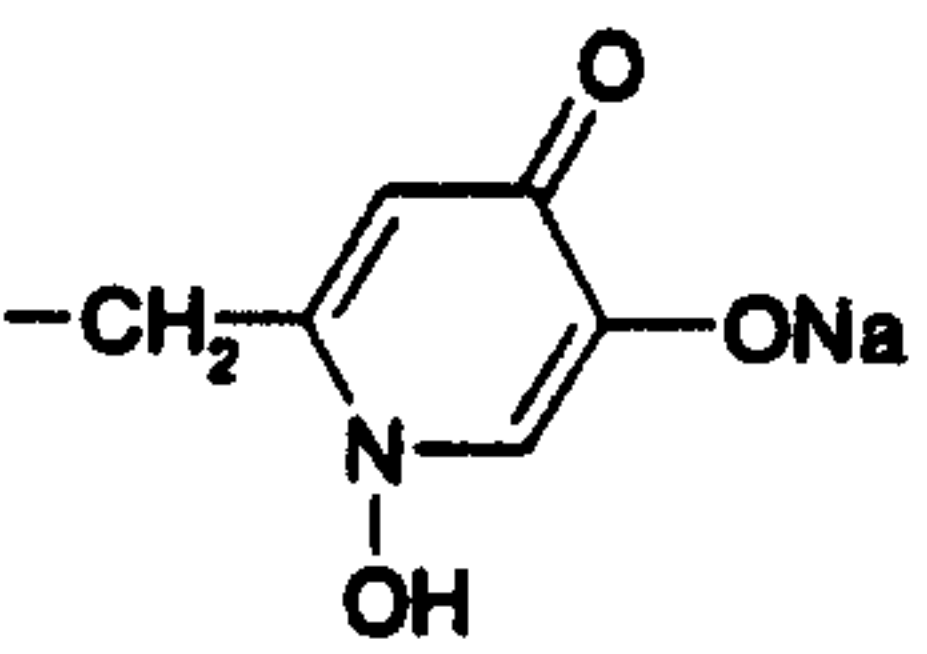
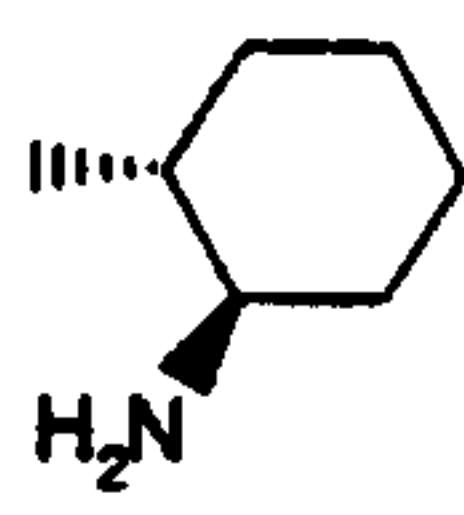
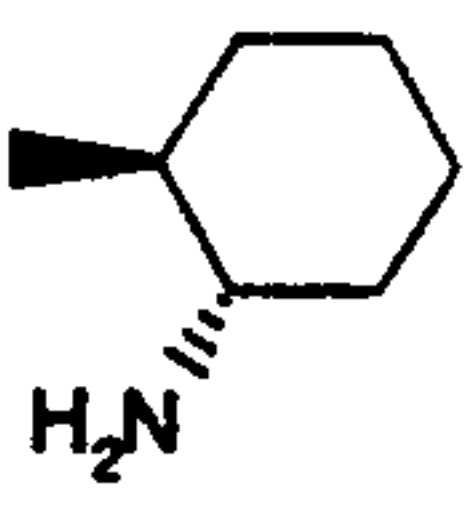
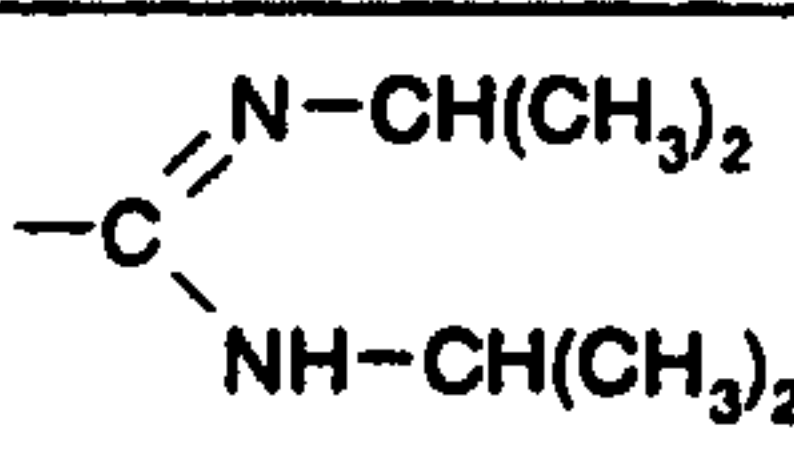
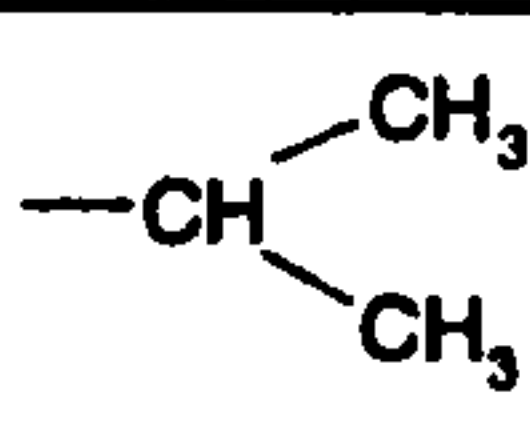
TABLE 1

Ex.	W	R ₅	R ₆	Salt
2	N	H	-NH-CH ₃	2HCl
3	N	H	-NH-C ₆ H ₅	2HCl
4	N	H	CH ₃	2HCl
5	N	H		3HCl
6	N	H		2HCl

Ex.	W	R ₅	R ₆	Salt
7	N	H		3HCl
8	N	-CH ₂ CH ₂ OH	H	2HCl
9	N	H	-CH ₂ CH ₂ -NH-C ₂ H ₅	3HCl
10	N	H	-CH ₂ CH ₂ -N(CH ₃) ₂	3HCl
11	N	H	-CH ₂ CH ₂ -NH ₂	HCl
12	N	H	-NH-CH ₂ CH ₂ OH	HCl
13	N	H	-(CH ₂) ₃ -NH ₂	HCl
14	N	H	-CH ₂ CH ₂ -NH-CH ₂ CH ₂ OH	3HCl
15	N	-CH ₂ CH ₂ OH		HCl
16	N	H		HCl
17	N	H		3HCl
18	N	H	-CH ₂ CH ₂ -O-CH ₂ CH ₂ OH	HCl
19	N	H	OH	2HCl
20	N	H		2HCl
21	N	H	-(CH ₂) ₄ -NH ₂	HCl
22	N	H	-CH ₂ CH ₂ OH	HCl
23	N	H	-(CH ₂) ₆ -NH ₂	3HCl
24	N	H		HCl

Ex.	W	R ₅	R ₆	Salt
25	N	H		HCl
26	N	H		3HCl
27	N	H	-C ₂ H ₅	2HCl
28	N	H	-C ₃ H ₇	2HCl
29	N	H	-CH ₂ CH ₂ -O-CH ₂ CH ₂ -O-CH ₂ CH ₂ -NH ₂	2HCl
30	N	H	-(CH ₂) ₃ -NH-CH ₃	3HCl
31	N	H	-(CH ₂) ₃ -NH-CH ₂ CH ₂ OH	HCl
32	N	H	-(CH ₂) ₃ -N(CH ₃) ₂	3HCl
33	N	-CH ₂ CH ₂ OH	-(CH ₂) ₃ -NH ₂	HCl
34	N	-CH ₂ CH ₂ OH	-(CH ₂) ₃ -NH-CH ₃	HCl
35	N	-CH ₂ CH ₂ OH	-(CH ₂) ₃ -NH-CH ₂ CH ₂ OH	HCl
36	N	-CH ₂ CH ₂ OH	-(CH ₂) ₃ -N(CH ₃) ₂	HCl
37	N	-CH ₂ CH ₂ OH	-N(CH ₃) ₂	HCl
38	N	H	-CH ₂ CH ₂ CH ₂ OH	2HCl
39	N	-CH ₂ CH ₂ OH	CH ₃	2HCl
40	N	H	-CH ₂ -CH(OH)-CH ₂ NH ₂	2HCl
41	N	H	-CH ₂ CH ₂ -N(CH ₂ CH ₂ NH ₂) ₂	2HCl
42	N	H		3HCl
43	N	-CH ₂ CH ₂ OH	-C ₂ H ₅	2HCl
44	N	H	-(CH ₂) ₃ -NH-(CH ₂) ₃ -NH ₂	2HCl

Ex.	W	R ₅	R ₆	Salt
45	N	H		3HCl
46	N	-C ₂ H ₅	H	2HCl
47	N	H	-CH ₂ -CH(OH)-CH ₂ OH	2HCl
48	N	-C ₂ H ₅	CH ₃	HCl
49	N	-C ₂ H ₅	-(CH ₂) ₃ -N(CH ₃) ₂	HCl
50	N	-C ₂ H ₅	-(CH ₂) ₃ -NH ₂	HCl
51	N	-C ₂ H ₅		3HCl
52	N	-CH ₂ CH ₂ OH		HCl
53	N	H		4HCl
54	N	H		2HCl
55	N	CH ₃	H	2HCl
56	N	CH ₃	CH ₃	2HCl
57	N	CH ₃	-C ₂ H ₅	2HCl
58	N	CH ₃		3HCl
59	N	CH ₃	-CH ₂ CH ₂ OH	HCl
60	N	-CH ₂ CH ₂ OH	-CH ₂ CH ₂ OH	HCl
61	N	-CH ₂ CH ₂ -N(C ₂ H ₅) ₂	H	2HCl
62	N	-(CH ₂) ₃ -N(CH ₃) ₂	H	2HCl

Ex.	W	R ₅	R ₆	Salt
63	N	H	$-\text{CH}_2\text{CH}_2-\text{N}(\text{C}_2\text{H}_5)_2$	2HCl
64	N	$-\text{CH}_2\text{CH}_2-\text{N}(\text{C}_2\text{H}_5)_2$	CH_3	2HCl
65	N	$-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2$	H	2HCl
66	N	H		---
67	N	H		HCl
68	N	H		HCl
69	N	$-\text{CH}_2\text{CH}_2\text{CH}_3$	H	2HCl
70	N	$-\text{CH}_2\text{CH}_2\text{CH}_3$	CH_3	2HCl
71	N		H	3HCl
72	N		H	2HCl
73	N	$-\text{CH}_2\text{CH}_2-\text{N}$ 	H	2HCl
74	N	$-(\text{CH}_2)_3-\text{CH}_3$	CH_3	2HCl
75	N	$-(\text{CH}_2)_3-\text{CH}_3$	H	2HCl
76	N	$-\text{CH}_2\text{CH}_2-\text{N}$ 	CH_3	2HCl
77	N	$-\text{CH}_2\text{CH}_2-\text{N}$ 	H	2HCl

Ex.	W	R ₅	R ₆	Salt
78	N	-CH ₂ COOH	H	2HCl
79	N	-(CH ₂) ₄ -CH ₃	H	2HCl
80	N	-(CH ₂) ₅ -CH ₃	H	2HCl
81	N	-(CH ₂) ₆ -CH ₃	H	2HCl
82	N	-CH ₂ CH ₂ -		2HCl
83	N	-CH ₂ CH ₂ CH ₂ -		2HCl

Example 84

Analogously as described in Example 1, a compound of formula I, wherein
V-R₁ = N-OCH₂F; R₃ = -CH₂-O-CO-C(CH₃)₃; W = N and R₂ = a compound of
5 formula a), wherein R₅ = -C₂H₅, R₆ = CH₃ and X = -CH₂CH₂-; in the form of a
hydrochloride is obtained.

Analogously as described in Example 1, the compounds described in TABLE 2 below
under Examples (Ex.) 85 to 90 which are compounds of formula I, wherein W = N;
10 V-R₁ = N-OCH₂F; R₃ = hydrogen; and R₂ = a compound of formula a'), wherein R₅,
R₆, R₆' and Hal are as defined in TABLE 2 and X = -CH₂CH₂-; in the form of a salt as
defined in TABLE 2; are obtained:

TABLE 2

Ex.	R ₅	R ₆	R' ₆	Hal	Salt
85	-C ₂ H ₅	CH ₃	CH ₃	Cl	HCl
86	CH ₃	CH ₃	CH ₃	Cl	HCl
87	-C ₂ H ₅	CH ₃	-C ₂ H ₅	Cl	HCl
88	-CH ₂ CH ₂ CH ₃	CH ₃	CH ₃	Cl	HCl
89	-CH ₂ CH ₂ -		CH ₃	Cl	HCl
90	-CH ₂ CH ₂ CH ₂ -		CH ₃	Cl	HCl

Analogously as described in Example 1 the compounds described in TABLE 3 below under Examples (Ex.) 91 to 97, which are compounds of formula I wherein $W = N$; $V-R_1 = N-OCH_2F$; $R_3 = \text{hydrogen}$ and $R_2 = \text{a compound of formula a)}$, wherein R_5 , R_6 and X are as defined in TABLE 3; in the form of a salt as defined in TABLE 3; are obtained:

TABLE 3

Ex.	X	R_5	R_6	Salt
91	$\begin{array}{c} \text{---CH}_2\text{---CH---} \\ \\ \text{CH}_3 \end{array}$	H	H	2HCl
92	$\begin{array}{c} \text{---CH}_2\text{---CH---} \\ \\ \text{CH}_3 \end{array}$	H	CH_3	2HCl
93	$\begin{array}{c} \text{---CH}_2\text{---CH---} \\ \\ \text{CH}_3 \end{array}$	H	$-(\text{CH}_2)_3\text{---NH}_2$	HCl
94	$\begin{array}{c} \text{---CH}_2\text{---CH---} \\ \\ \text{CH}_3 \end{array}$	H	$-(\text{CH}_2)_3\text{---NH}_2$	HCl
95	$\begin{array}{c} \text{CH}_3 \\ \\ \text{---CH}_2\text{---C---} \\ \\ \text{CH}_3 \end{array}$	H	H	2HCl
96	$\begin{array}{c} \text{CH}_3 \\ \\ \text{---CH}_2\text{---C---} \\ \\ \text{CH}_3 \end{array}$	H	CH_3	2HCl
97	---CH=CH---	CH_3	CH_3	HCl

Analogously as described in Example 1 the compounds described in TABLE 4 below under Examples (Ex.) 98 to 100 which are compounds of formula I wherein $V-R_1 = N-OH$; $R_3 = \text{hydrogen}$; W is as defined in TABLE 4; and $R_2 = \text{a compound of formula a)}$, wherein R_5 and R_6 are as defined in TABLE 4 and $X = \text{---CH}_2\text{CH}_2\text{---}$; in the form of a salt as defined in TABLE 4; are obtained:

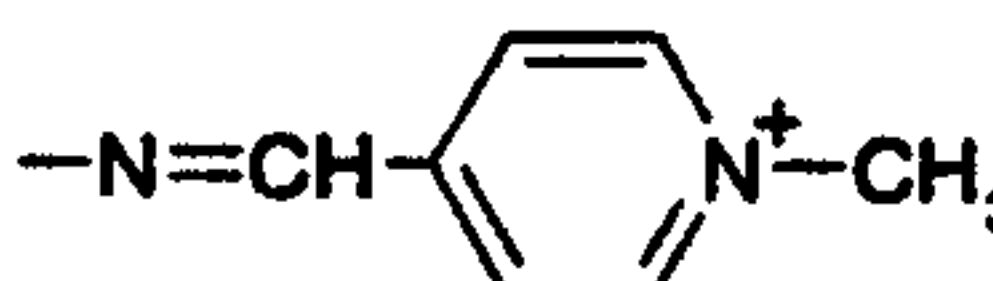
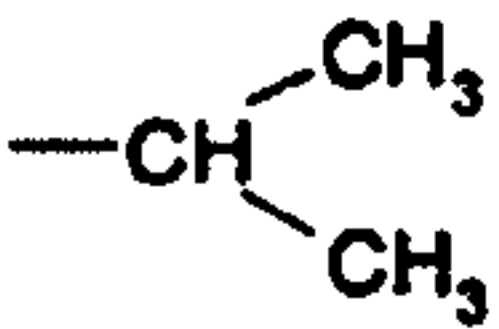
TABLE 4

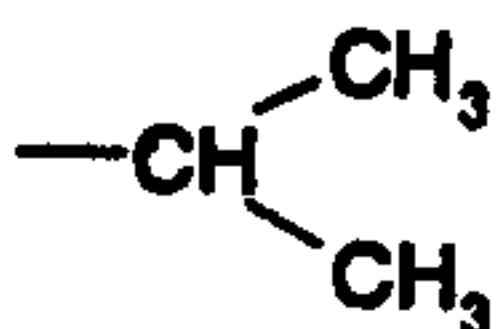
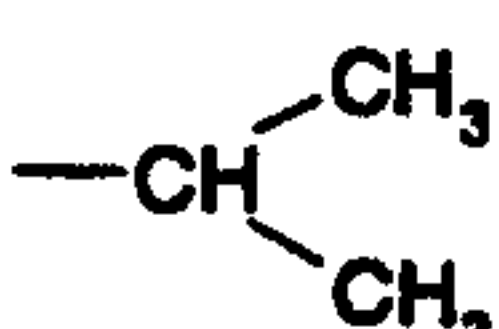
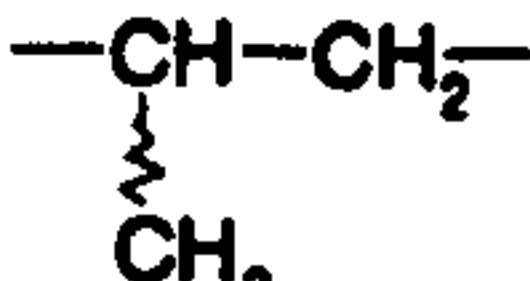
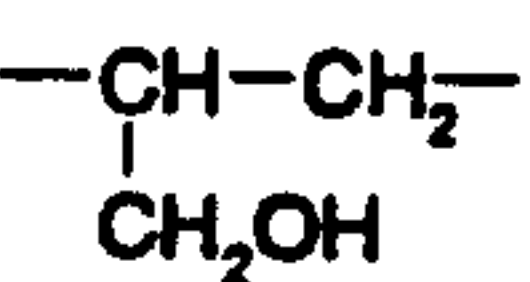
Ex.	W	R ₅	R ₆	Salt
98	CH	H	-(CH ₂) ₃ -NH ₂	HCl
99	CH	H	-CH ₂ CH ₂ -NH ₂	HCl
100	CH	-C ₂ H ₅	CH ₃	HCl

Analogously as described in Example 1 the compounds described in TABLE 5 below under Examples (Ex.) 101 to 115 which are compounds of formula I wherein

5 V-R₁ = N-OCH₂F; W = N; R₃ = hydrogen; and R₂ = a compound of formula d), wherein R₅, R₆ and Y are as defined in TABLE 5; in the form of a salt as defined in TABLE 5; are obtained:

TABLE 5

Ex.	Y	R ₅	R ₆	Salt
101	-CH ₂ CH ₂ -	H	-N=CH-C ₆ H ₅	2HCl
102	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ OH	HCl
103	-CH ₂ CH ₂ -	H	H	HCl
104	-CH ₂ CH ₂ CH ₂ -	H	H	2HCl
105	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -NH ₂	HCl
106	-CH ₂ CH ₂ -	H		2HCl
107	-CH ₂ CH ₂ -	CH ₃	CH ₃	2HCl
108	-CH ₂ CH ₂ -	H	-C ₂ H ₅	2HCl
109	-CH ₂ CH ₂ -	H	CH ₃	2HCl
110	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ CH ₃	2HCl
111	-CH ₂ CH ₂ -	H		2HCl

Ex.	Y	R ₅	R ₆	Salt
112	-CH ₂ CH ₂ -			2HCl
113		H	H	2HCl
114		H	H	HCl
115		H	H	HCl

Analogously as described in Example 1 the compounds described in TABLE 6 below under Examples (Ex.) 116 to 118 which are compounds of formula I wherein V-R₁ and W are as defined in TABLE 6; R₃ = hydrogen; and R₂ = a compound of formula f), wherein R₄ = CH₃, R₆ is as defined in TABLE 6 and Y = -CH₂CH₂-; in the form of a salt as defined in TABLE 6; are obtained:

TABLE 6

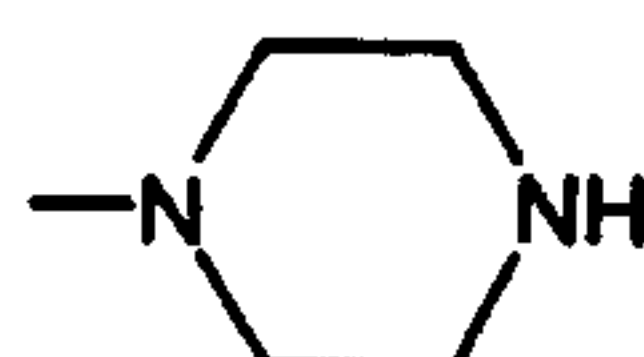
Ex.	W	V-R ₁	R ₆	Salt
116	CH	N-OCH ₃	CH ₃	2HCl
117	CH	N-OH	CH ₃	2HCl
118	N	N-OCH ₂ F	CH ₃	2HCl

10

Example 119

Analogously as described in Example 1, a compound of formula I, wherein W = N; V-R₁ = N-OCH₂F; R₃ = hydrogen; and R₂ = a compound of formula c), wherein R₆ and R₇ together with the nitrogen atom to which they are attached denote a group of formula

15



and X = -CH₂CH₂; in the form of a hydrochloride is obtained.

Example 120

Analogously as described in Example 1, a compound of formula I, wherein $W = N$; $V-R_1 = N-OCH_2F$; $R_3 = \text{hydrogen}$; and $R_2 = \text{a compound of formula d'}$), wherein R_5 and $R_6 = \text{hydrogen}$; in the form of a dihydrochloride is obtained.

Substituted 1,2-diamino-4,5-dihydro-1H-imidazoles are obtained as follows:

Example A

- 10 a. 5 g of 1- benzyldeneamino-imidazolidine-2-thion are suspended in 40 ml of methanol and treated with 1.7 ml of methyl iodide. The mixture obtained is refluxed for ca. one hour and the solvent is evaporated off. 1- Benzyldeneamino-2-methylthio-4,5-dihydro-1H-imidazole in the form of a hydroiodide is obtained in solid form, to which 120 ml of water and 70 ml of an anion exchange resin in chloride form
- 15 (Amberlite IRA-400 (Cl)^R) are added. The mixture is stirred for ca. 2 hours at room temperature, filtrated and lyophilized. 1- Benzyldeneamino-2-methylthio-4,5-dihydro-1H-imidazole in the form of a hydrochloride is obtained in the form of a lyophilisate.
- b. 1 g of 1- benzyldeneamino-2-methylthio-2-imidazoline in the form of a hydrochloride in 10 ml of methanol are treated with 0.33 ml of NH_3 (28% in H_2O).
- 20 The mixture obtained is refluxed for ca. 5 hours and a precipitate obtained is filtrated off. From the filtrate obtained the solvent is evaporated off. The residue obtained is treated with acetonitrile. The precipitate obtained is filtrated off and dried. Solid 2-amino-1-benzyldeneamino-4,5-dihydro-1H-imidazole in the form of a hydrochloride is obtained.
- 25 c. From a mixture of 0.89 g of derivative of 2-amino-1-benzyldeneamino-4,5-dihydro-1H-imidazole in the form of a hydrochloride in 5.9 ml of 2 N HCl, benzaldehyde is distilled off by steam distillation. The solvent from the remaining mixture is evaporated off. Solid 1,2-diamino-4,5-dihydro-1H-imidazole in the form of a dihydrochloride is obtained.

30

Example B

- A mixture of 0.79 g of 1- benzyldeneamino-2-methylthio-4,5-dihydro-1H-imidazole in the form of a hydrochloride in 10 ml of methanol with 0.18 ml of hydrazine hydrate is stirred for ca. 6 hours at room temperature. From the mixture obtained the
- 35 solvent is evaporated off and the residue is treated with acetonitrile. 1- benzyldeneamino-2-hydrazino-4,5-dihydro-1H-imidazole precipitates, is filtrated off and dried.

Example C

- a. 0.58 g of 1-(β -aminoethyl)imidazolidine-2-thion in 25 ml of dichloromethane are treated with 0.96 g of BOC-anhydride. The mixture obtained is stirred for ca. 4 hours at room temperature and the solvent is evaporated off. Solid 1-[β -(t-BOC-aminoethyl)]imidazolidine-2-thion is obtained.
- b. A mixture of 0.5 g of β -(t-BOC-aminoethyl)]imidazolidine-2-thion in 20 ml of methanol and 0.32 g of methyl iodide are refluxed for ca. one hour and the solvent is evaporated off. 1-[β -(t-BOC-aminoethyl)]-2-methylthio-4,5-dihydro-1H-imidazole in the form of a hydroiodide is obtained and is stirred in 20 ml of water and an anion exchange resin in chloride form (6 ml of IRA-400(Cl)^R) for ca. one hour at room temperature. From the mixture obtained the anion exchange resin is filtrated off and the filtrate obtained is lyophilized. 1-[β -(t-BOC-aminoethyl)]-2-methylthio-4,5-dihydro-1H-imidazole is obtained in the form of a lyophilisate.
- c. A mixture of 1.06 g of 1-[β -(t-BOC-aminoethyl)]-2-methylthio-4,5-dihydro-1H-imidazole in 25 ml of methanol and 0.2 g of hydrazine hydrate are refluxed for ca. 2 hours and the solvent is evaporated off. Solid 1-[β -(t-BOC-aminoethyl)]-2-hydrazino-4,5-dihydro-1H-imidazole is obtained.

Example D

- a. The pH of a solution of 1.59 g of 1-benzylideneamino-4,5-dihydro-2-methylamino-1H-imidazole in the form of a hydrochloride in 40 ml of water is adjusted to 12.0 with 2 M NaOH. The mixture obtained is extracted with dichloromethane. The organic phase is dried over Na₂SO₄ and evaporated off. 1-benzylideneamino-4,5-dihydro-2-methylamino-1H-imidazole is obtained in the form of a powder.
- b. A mixture of 1 g of 1-benzylideneamino-4,5-dihydro-2-methylamino-1H-imidazole in 30 ml of acetonitrile with 1.26 g of propyl iodide is refluxed for ca. 8 hours. The mixture obtained is stirred overnight at room temperature. 1-Benzylideneamino-2-methylimino-3-propyl-imidazolidine in the form of a hydroiodide precipitates, is filtrated off and dried.
- c. A mixture of 0.70 g of 1-benzylideneamino-2-methylimino-3-propyl-imidazolidine in the form of a hydroiodide in 20 ml of water H₂O with 10 ml of an anion exchange resin in chloride form (Amberlite IRA-400 (Cl)^R) is stirred for ca. 3 hours at room temperature, the anion exchange resin is filtrated off and the filtrate obtained is treated with 3.6 ml of 2 M HCl. Benzaldehyde is distilled off from the mixture obtained by

steam distillation. From the remaining mixture the solvent is evaporated off. 1-Amino-2-methylimino-3-propyl-imidazolidine in the form of a hydrochloride is obtained in the form of an oil.

5 Example E

- a. A mixture of 0.89 g of 1- benzylideneamino-2-methylimino-3-propyl-imidazolidine in the form of a hydroiodide in 20 ml H₂O with 10 ml of an anion exchange resin in chloride form (Amberlite IRA-400 (Cl)^R) is stirred for ca. 3 hours at room temperature, the anion exchange resin is filtrated off and the pH of the filtrate
10 obtained is adjusted to 12.6 with 2 M NaOH. 1- Benzylideneamino-2-methylimino-3-propyl-imidazolidine precipitates, is filtrated off, dried and obtained in the form of a powder.
- b. A mixture of 0.51 g of 1- benzylideneamino-2-methylimino-3-propyl-imidazolidine in 15 ml of acetonitrile with 0.36 g of methyl iodide is refluxed for ca. one hour and
15 the solvent is evaporated off. The residue is treated with acetonitrile and the solvent is evaporated off. (1- benzylideneamino-3-propyl-imidazolidine-2-yliden)-dimethyl-ammonium iodide is obtained in the form of a powder.
- c. Solid (1-amino-3-propyl-imidazolidine-2-yliden)-dimethyl-ammoniumchloride in the form of a hydrochloride is obtained analogously as described in Example D, c..

20

Example F

- A mixture of 0.72 g of 2-(3-amino-propylimino)-imidazolidine-1-yl-benzylideneamine in 15 ml of absolute ethanol with 0.53 g of S-methylisothiourrea chloride is refluxed for ca. 4 hours and the solvent is evaporated off. The residue obtained, dissolved in
25 4 ml of 2 M HCl and 4 ml of H₂O, is poured over a chromatography column (LiChroprep RP-18^R, Merck) and eluated with water. Fractions obtained containing 2-(3-guanidino-propylimino)-imidazolidine-1-yl-benzylideneamine in the form of a hydrochloride (determination by HPLC) are combined. Benzaldehyde is distilled off from a mixture of the combined fractions obtained with 2 M HCl by steam
30 distillation. From the remaining mixture the solvent is evaporated off. Solid 2-(3-guanidino-propylimino)-imidazolidine-1-yl-amine in the form of a dihydrochloride is obtained.

Example G

- 35 a. A mixture of 1.61 g of 2-(3-amino-propylimino)-imidazolidine-1-yl-benzylideneamine in 25 ml of dichloromethane with 0.48 g of methylisothiocyanate is stirred for

ca. 90 minutes at room temperature and the solvent is evaporated off. The residue obtained is treated with 40 ml of H₂O and the pH of the mixture obtained is adjusted to 1.00 with 2 M HCl. 1-[2-(1-Benzylideneamino-imidazolidine-2-ylidene-amino)-propyl]-3-methyl-thiourea in the form of a hydrochloride precipitates, is filtrated off,
 5 dried and obtained in the form of a powder.

b. A mixture of 1.79 g of 1-[2-(1-benzylideneamino-imidazolidine-2-ylidene-amino)-propyl]-3-methyl-thiourea in the form of a hydrochloride in 30 ml of methanol with 0.52 ml of methyl iodide are refluxed for ca. 3 hours, the solvent is evaporated off and the residue obtained is stirred with 80 ml of H₂O and 30 ml of an anion exchange resin in chloride form (Amberlite IRA-400 (Cl)^R) for ca. 2 hours. From the mixture
 10 obtained the ion exchange resin is filtrated off and the filtrate obtained is lyophilized. 1-[(1-Benzylideneamino-imidazolidine-2-ylidene-amino)-propyl]-3-methyl-2-methyl-isothiourea in the form of a hydrochloride is obtained in the form of a lyophilisate.

c. A mixture of 1 g of 1-[(1-benzylideneamino-imidazolidine-2-ylidene-amino)-propyl]-3-methyl-2-methyl-isothiourea in the form of a hydrochloride with 0.54 ml of methylamine (33% solution in absolute ethanol) and 30 ml of methanol is refluxed for ca. 7 hours and the solvent is evaporated off. The residue obtained, dissolved in 4 ml of 2 M HCl and 6 ml of H₂O, is poured over a chromatography column (LiChroprep RP-18^R, Merck) and eluted with H₂O/methanol. The fractions containing 2-[3-(N,N'-
 15 dimethylguanidino)-propylamino]-imidazolidine-1-yl-benzylideneamine in the form of a hydrochloride (determination by HPLC) are combined and the combined fractions obtained are lyophilized.

d. Benzylaldehyde is distilled off from a solution of 0.5 g of the derivative of 2-[3-(N,N'-dimethylguanidino)-propylamino]-imidazolidine-1-yl-benzylideneamine in the
 25 form of a hydrochloride in 2.1 ml of 2 M HCl by steam distillation. 2-[3-(N,N'-dimethyl-guanidino)-propylamino]-imidazolidine-1-yl-amine in the form of a dihydrochloride is obtained by solvent evaporation from the remaining residue.

Example H

a. 0.99 ml of N,N'-diisopropylcarbodiimid in 10 ml of dichloromethane are added dropwise to a solution 1 g of 2-amino-1-benzylideneamino-4,5-dihydro-1H-imidazole in 20 ml of dichloromethane within ca. 30 minutes, the mixture obtained is stirred for ca. 6 days at room temperature and the solvent is evaporated off. The residue obtained is dissolved in 6 ml of 2 M HCl and 4 ml of H₂O, poured over a chromatography
 35 column (LiChroprep RP-18^R, Merck) and eluted with water. Fractions containing 1-

benzylideneamino-3-(N,N'-diisopropyl-guanidino)-2-imino- imidazolidine (HPLC determination) are combined and lyophilized.

- b. Solid 1-amino-3-(N,N'-diisopropylguanidino)-2-imino-imidazolidine in the form of a dihydrochloride is obtained by removing benzylaldehyde from 1- benzylideneamino-
5 3-(N,N'-diisopropylguanidino)-2-imino-imidazolidine analogously as described in Example G, d..

Example I

- a. A mixture of 3 g of 2-[(1- benzylideneamino-4,5-dihydro-1H-imidazole-2-
10 yl)amino]-ethanol in 50 ml of methylene chloride with 1.22 ml of thionyl chloride is stirred for ca. 1 hour at room temperature. 2-(2-chloro-ethylimino)-imidazolidine-1-yl- benzylideneamine precipitates, is filtrated off and dried.
- b. A mixture of 3.7 g of 2-(2-chloro-ethylimino)-imidazolidine-1-yl- benzylideneamine in 50 ml of absolute ethanol with 2.25 ml of N-ethyldiisopropylamine is refluxed for
15 ca. 22 hours, the solvent is evaporated off and the residue obtained is treated with acetonitrile. Solid 2,3,5,6-tetrahydro-imidazo[1,2a]imidazole-1-yl- benzylideneamine in the form of a hydrochloride is obtained.
- c. Solid 2,3,5,6-tetrahydro-imidazo[1,2a]imidazole-1-ylamine in the form of a hydrochloride is obtained by removing benzylaldehyde from 2,3,5,6-tetrahydro-
20 imidazo[1,2a]imidazole-1-yl- benzylideneamine in the form of a hydrochloride analogously as described in Example G, d..

Example J

- a. A mixture of 4 g of hydrazino-acetaldehyd diethylacetal in 40 ml of ethanol is
25 stirred with 1.97 g of methylisothiocyanate for ca. 4 hours at room temperature, the solvent is evaporated off and 2-(2,2-diethoxy-ethyl)-4-methyl-thiosemicarbazide is obtained in crystalline form.
- b. A mixture of 4 g of 2-(2,2-diethoxy-ethyl)-4-methyl-thiosemicarbazide and 2.82 g of methyl iodide in 40 ml of methanol is refluxed for ca. 90 minutes and the solvent is
30 evaporated off. 4.53 g of 2-(2,2-diethoxy-ethyl)-3,4-dimethyl-isothiosemicarbazide in the form of a hydroiodide are obtained which are dissolved in water and stirred with a strong basic ion exchange resin in chloride form (Amberlite IRA 400 (Cl)^R) for ca. 2.5 hours. The ion exchange resin is filtrated off and the filtrate obtained is lyophilized. 2-(2,2-Diethoxy-ethyl)-3,4-dimethyl-isothiosemicarbazide in the form of a
35 hydrochloride is obtained in the form of an oil.

c. A mixture of 2 g of 2-(2,2-diethoxy-ethyl)-3,4-dimethyl-isothiosemicarbazide in the form of a hydrochloride in 20 ml of ethanol with 0.91 ml of methylamine (33% solution in absolute ethanol) is stirred for ca. 26 hours at room temperature. To the mixture obtained 0.91 g of benzylaldehyde are added. The mixture obtained is stirred
5 for ca. 21 hours, the solvent is evaporated off and the residue is treated with diethylether. 1-(Benzyldeneamino)-1-(2,2-diethoxy-ethyl)-2,3-dimethyl-guanidine in the form of a hydrochloride in resin-like form is obtained.

d. A mixture of 1.39 g of 1-(benzyldeneamino)-1-(2,2-diethoxy-ethyl)-2,3-dimethyl-guanidine in the form of a hydrochloride with 5 ml of hydrochloric acid conc. is
10 stirred for ca. 30 minutes at room temperature. The pH of the mixture obtained is adjusted to 6.4 with 1 N NaOH. The mixture obtained is extracted with diethylether. The pH of the aqueous phase is adjusted to 12 with 1 N NaOH. The mixture obtained is extracted with dichloromethane. The organic phase is dried over Na₂SO₄, the solvent is evaporated off and benzyldene-(3-methyl-2-methylimino-2,3-dihydro-
15 imidazole-1-yl)-amine is obtained in the form of an oil.

e. Benzylaldehyde is removed from 384 mg of benzyldene-(3-methyl-2-methylimino-2,3-dihydro-imidazole-1-yl)-amine in 10 ml of water and 3.55 ml of 2 N HCl analogously as described in Example G, d. and 3-methyl-2-methylimino-2,3-dihydro-imidazole-1-ylamine in the form of a dihydrochloride is obtained in the form of an oil.
20

Example K

a. 0.6 ml of CS₂ are added dropwise to a solution of 1.7 g of potassium hydroxide in 6 ml of water and 14 ml of ethanol under stirring. The mixture obtained is refluxed for ca. 4 hours with 1.47 g of (R,S)-2,3-diamino-1-propanol in the form of a
25 dihydrochloride. The pH of the mixture obtained is adjusted to 2 with 6 N hydrochloric acid and the solvent is evaporated off. The residue obtained is treated with ethanol and with methanol. KCl precipitates and is filtrated off. The solvent from the filtrate obtained is evaporated off and solid (R,S)-4-hydroxymethyl-imidazolidine-2-thion is obtained.

b. A mixture of 1.4 g of (R,S)-4-hydroxymethyl-imidazolidine-2-thion in 25 ml of methanol with 1.8 g of methyl iodide is refluxed for ca. 2 hours, the solvent is evaporated off and 2.26 g of (R,S)-2-methylthio-4,5-dihydro-1H-imidazole-4-yl)-methanol in the form of a hydroiodide are obtained, are dissolved in 4 ml of water and poured over a column filled with a strong basic ion exchange resin in chloride
35 form (Amberlite IRA 400^R) and are eluted with water. The fractions containing (R,S)-

2-methylthio-4,5-dihydro-1H-imidazole-4-yl)-methanol in the form of a hydrochloride (HPLC determination) are combined and lyophilized.

- c. A mixture of 1.54 g of (R,S)-2-methylthio-4,5-dihydro-1H-imidazole-4-yl)-methanol in the form of a hydrochloride dissolved in methanol with 462 mg of hydrazine hydrate is stirred for ca. one day at room temperature, the solvent is evaporated off and the residue obtained is dissolved in ethanol and treated with etheric hydrochloric acid. (R,S)-2-Hydrazono-imidazolidine-4-yl)-methanol in the form of a dihydrochloride in crystalline form is obtained.

10 Example L

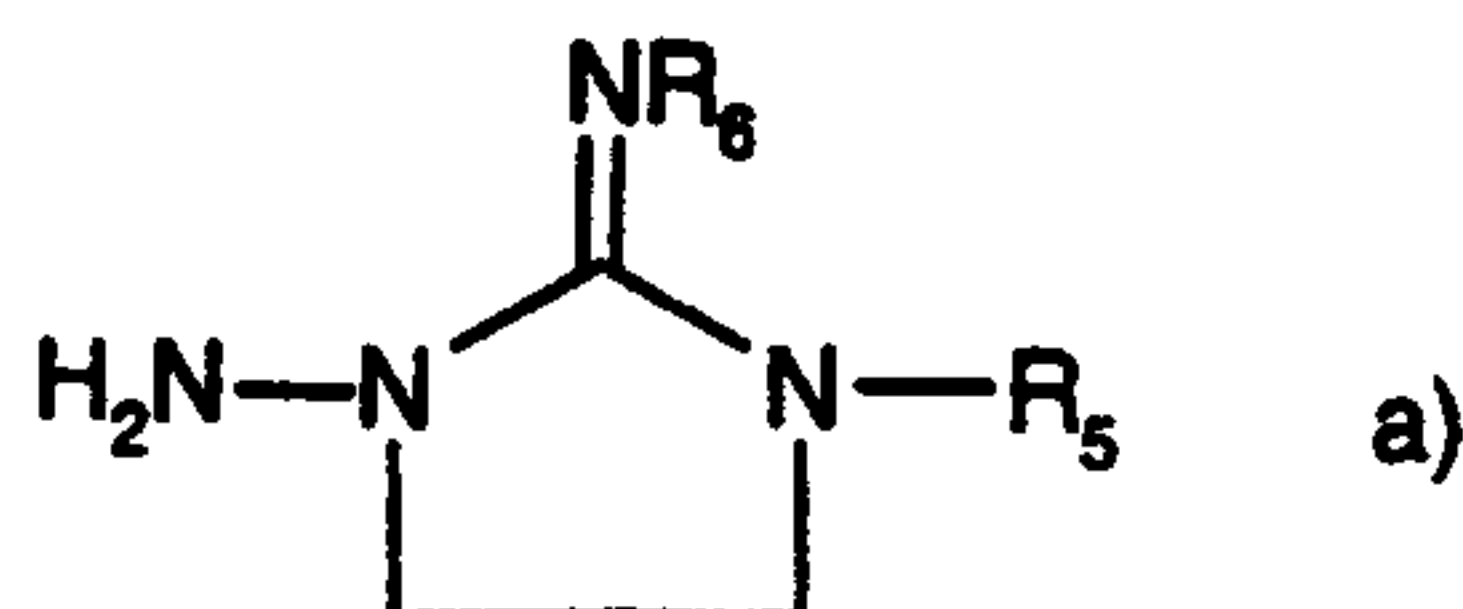
- a. 2.86 ml of CS₂ are added dropwise to a solution of 7.9 g of potassium hydroxide in 30 ml of water and 64 ml of ethanol under stirring. The mixture obtained is refluxed for ca. 4 hours with 6.0 g of DL-2,3-diamino-propionic acid in the form of a hydrochloride. The pH of the mixture obtained is adjusted to 2 with 6 N hydrochloric acid and the solvent is evaporated off. Solid (R,S)-2-thioxo-imidazolidine-4-carboxylic acid is obtained and is stirred overnight with 150 ml of methanol under addition of 5 ml of 1 N etheric hydrochloric acid. KCl precipitates and is filtrated off. The solvent from the filtrate obtained is evaporated off and solid (R,S)-2-thioxo-imidazolidine-4-carboxylic acid methylester is obtained.
- 20 b. A mixture of 6 g of (R,S)-2-thioxo-imidazolidine-4-carboxylic acid methylester in 100 ml of methanol with 4 g of methyl iodide is refluxed for ca. 2 hours, the solvent is evaporated off and 5 g of (R,S)-2-methylthio-4,5-dihydro-1H-imidazole-4-carboxylic acid methylester in the form of a hydroiodide are obtained in solid form, which is dissolved in 30 ml of water. To the solution obtained 3 g of sodium carbonate are added in portions. The aqueous solution obtained is extracted with dichloromethane, the organic phase is dried over Na₂SO₄ and the solvent is evaporated off. Solid (R,S)-2-methylthio-4,5-dihydro-1H-imidazole-4-carboxylic acid methylester is obtained.
- 25 c. A mixture of 1.36 g of (R,S)-2-methylthio-4,5-dihydro-1H-imidazole-4-carboxylic acid methylester in 15 ml of methanol with 710 mg of hydrazine in the form of a monohydrochloride and 1 ml of water is stirred overnight at room temperature and the solvent is evaporated off. Solid (R,S)-2-hydrazono-imidazolidine-4-carboxylic acid methylester in the form of a hydrochloride is obtained.
- 30

Analogously as described in Example A to Example L the compounds described in Example M to Example CZ below are obtained:

35

Example M to Example CK

Compounds of formula

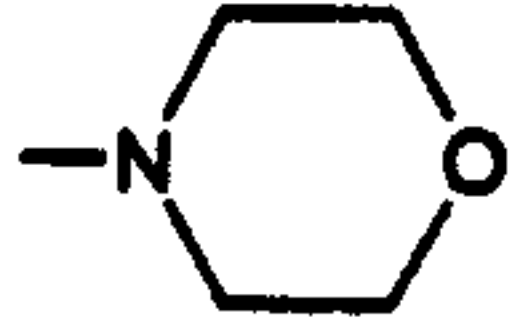
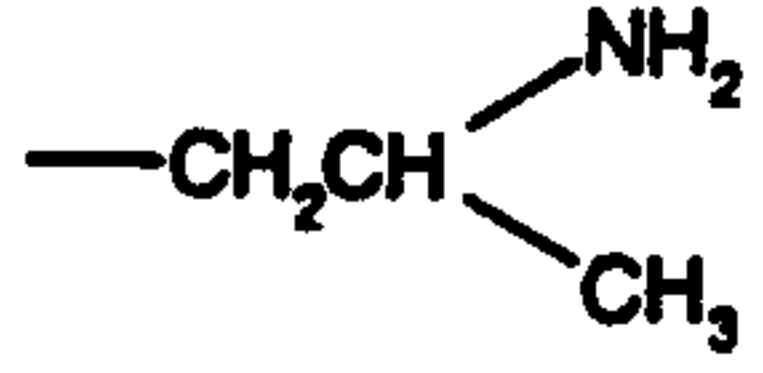
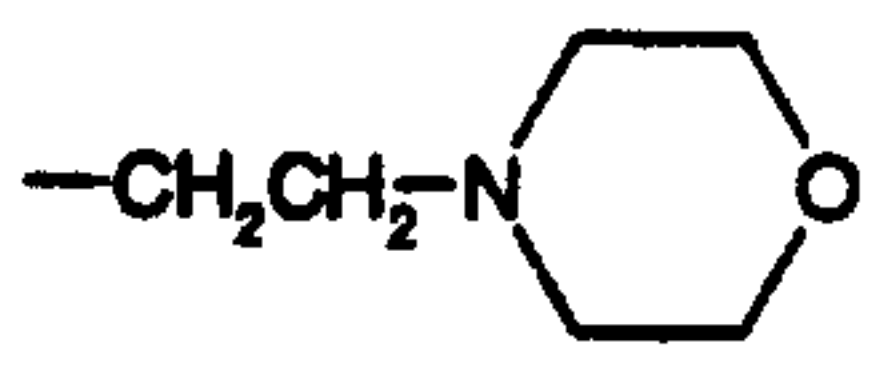
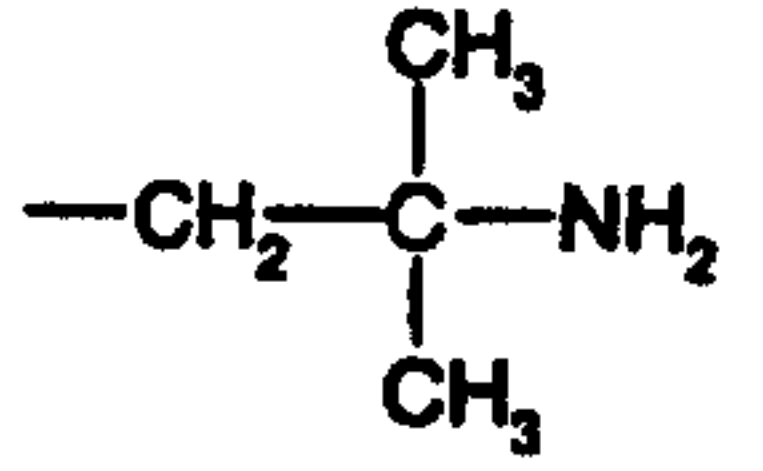
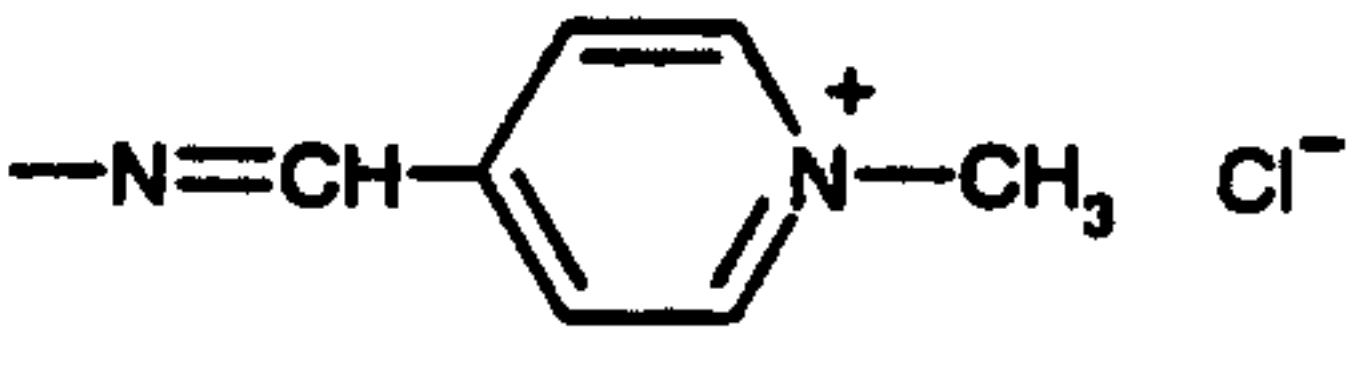
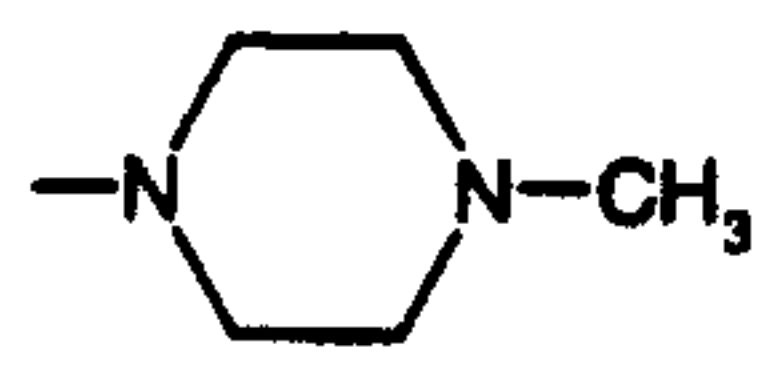
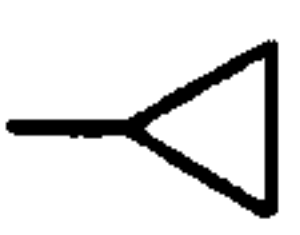


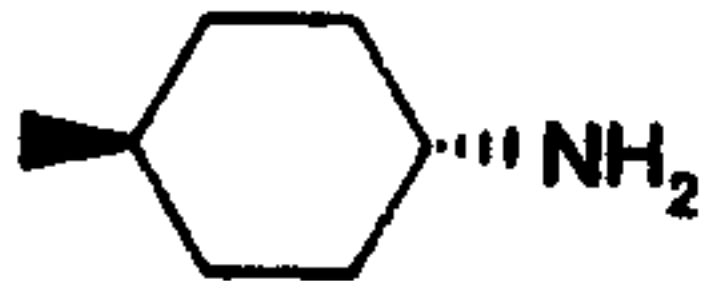
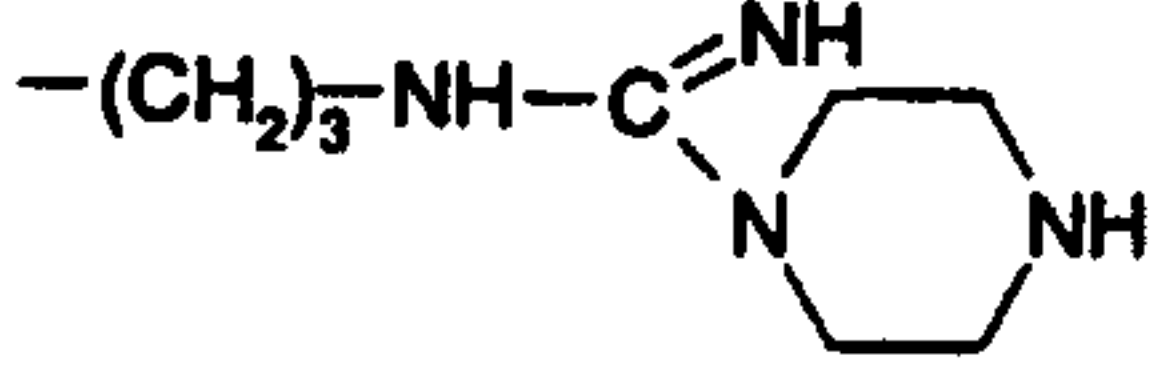
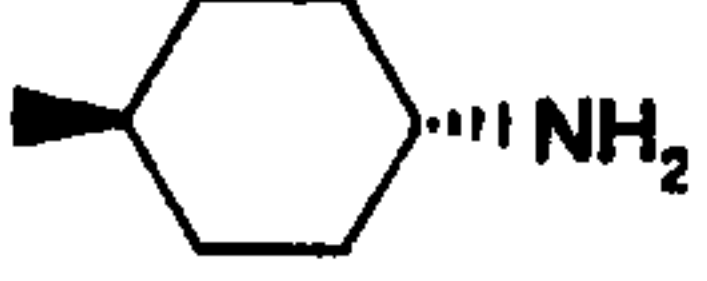
5

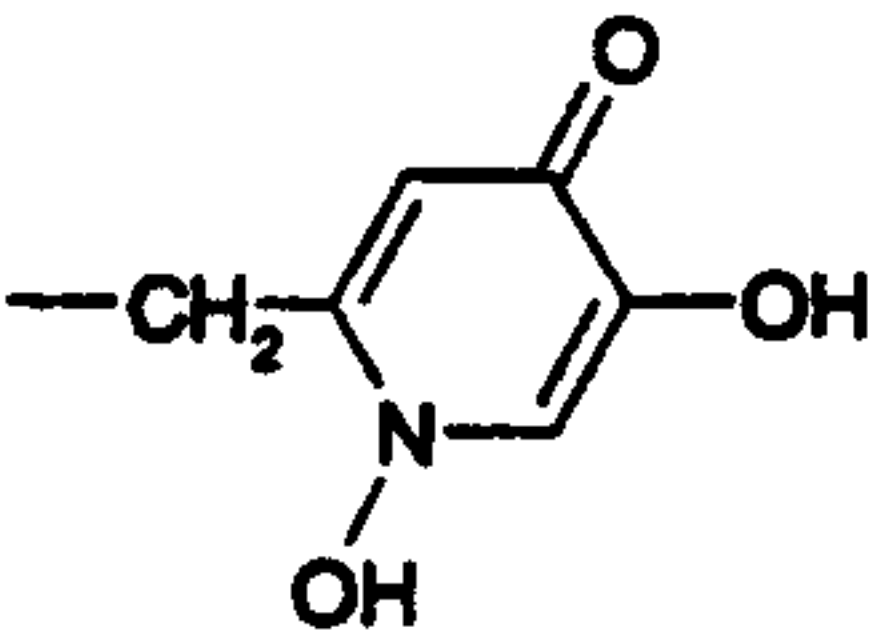
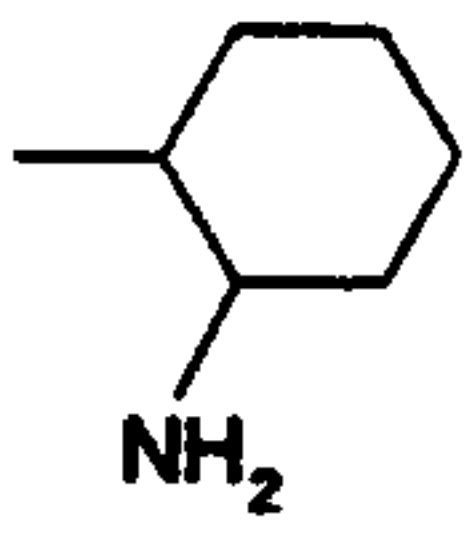
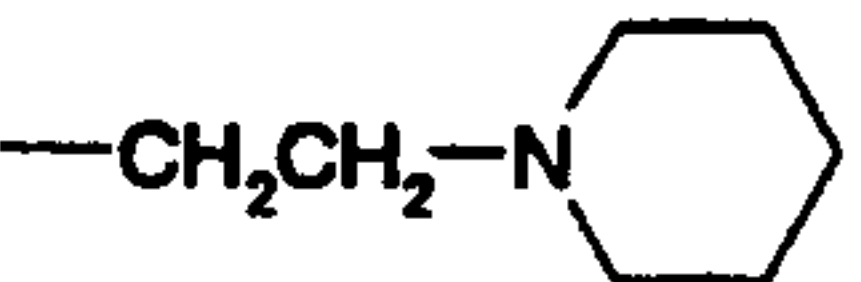
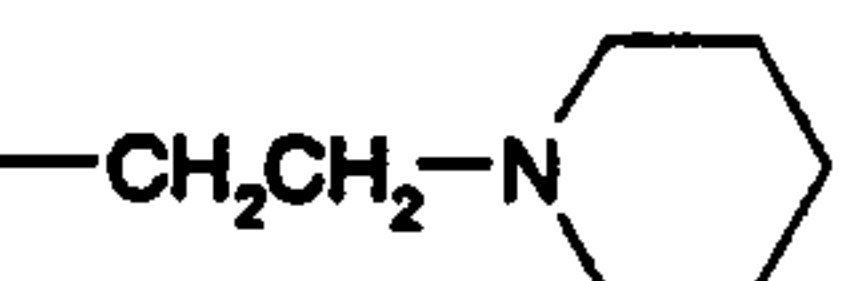
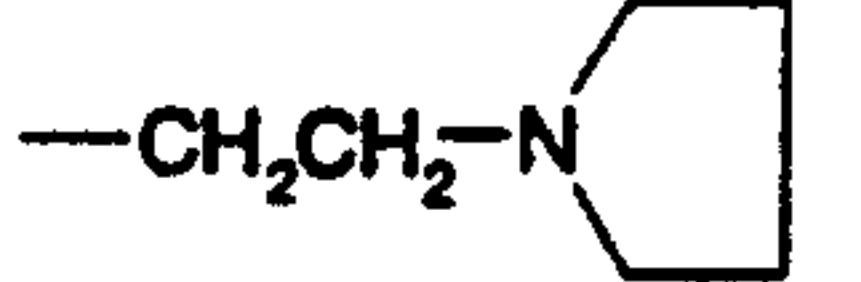
wherein R_5 and R_6 are as defined in TABLE 7 below in the form of a salt as defined in TABLE 7 below (Ex. = Example):

TABLE 7

Ex.	R_5	R_6	Salt
M	H	-NH-CH ₃	HCl
N	H	-NH-C ₆ H ₅	2HCl
O	H	CH ₃	2HCl
P	H		2HCl
Q	-CH ₂ CH ₂ OH	H	2HCl
R	H	-CH ₂ CH ₂ -NH-C ₂ H ₅	2HCl
S	H	-CH ₂ CH ₂ -N(CH ₃) ₂	2HCl
T	H	-CH ₂ CH ₂ -NH ₂	2HCl
U	H	-NH-CH ₂ CH ₂ OH	2HCl
V	H	-(CH ₂) ₃ -NH ₂	2HCl
W	H	-CH ₂ CH ₂ -NH-CH ₂ CH ₂ OH	2HCl
X	-CH ₂ CH ₂ OH		2HCl
Y	H		2HCl
Z	H		2HCl

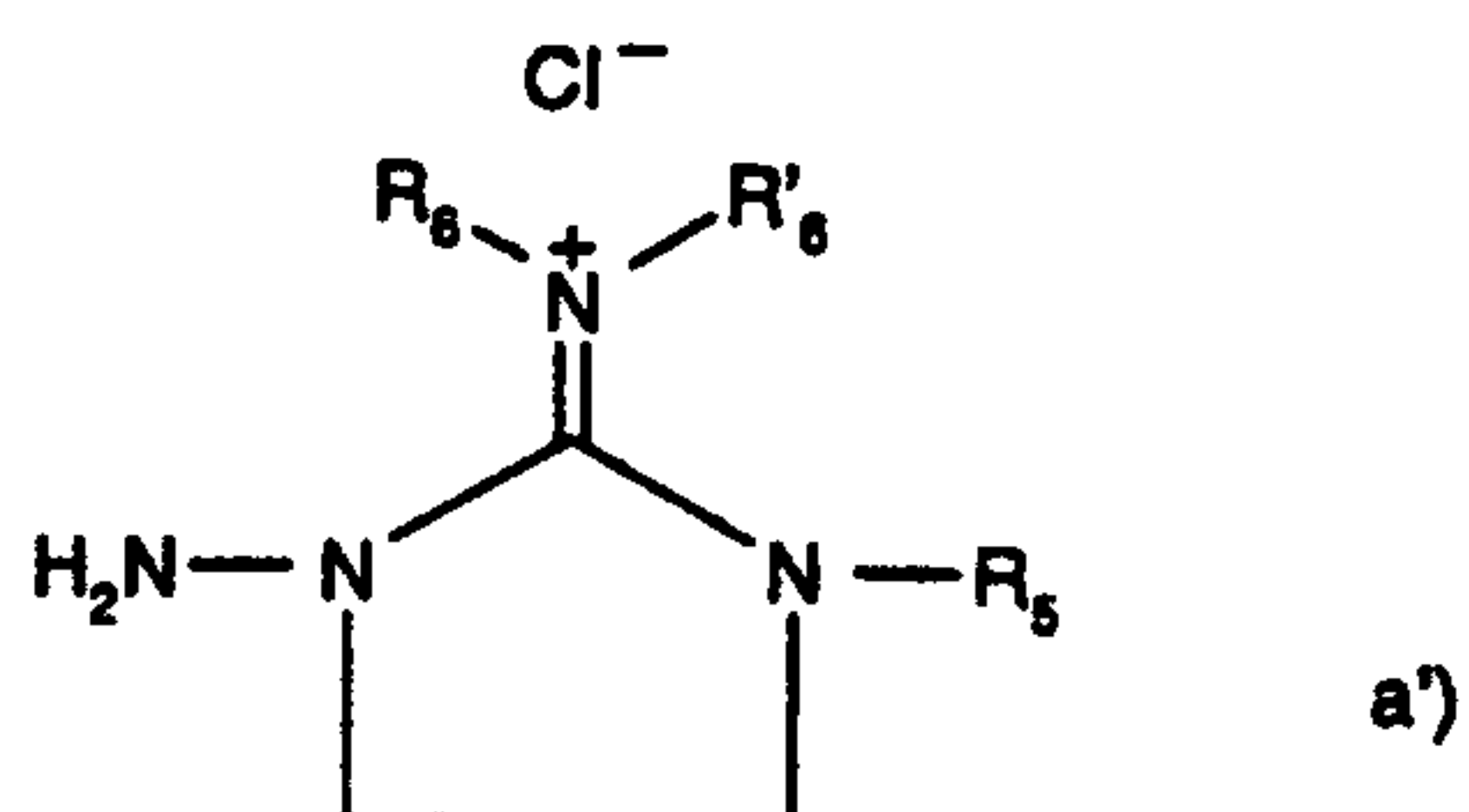
Ex.	R ₅	R ₆	Salt
AA	H	-CH ₂ CH ₂ -O-CH ₂ CH ₂ OH	2HCl
AB	H	OH	2HCl
AC	H		2HCl
AD	H	-(CH ₂) ₄ -NH ₂	2HCl
AE	H	-CH ₂ CH ₂ OH	2HCl
AF	H	-(CH ₂) ₆ -NH ₂	2HCl
AG	H		2HCl
AH	H		2HCl
AI	H		2HCl
AJ		-NH ₂	2HCl
AK	H		2HCl
AL	H		2HCl
AM	H	-C ₂ H ₅	2HCl
AN	H	-C ₃ H ₇	2HCl
AO	H	-CH ₂ CH ₂ -O-CH ₂ CH ₂ -O-CH ₂ CH ₂ -NH ₂	2HCl
AP	H	-(CH ₂) ₃ -NH-CH ₃	2HCl
AQ	H	-(CH ₂) ₃ -NH-CH ₂ CH ₂ OH	2HCl
AR	H	-(CH ₂) ₃ -N(CH ₃) ₂	2HCl
AS	-CH ₂ CH ₂ OH	-(CH ₂) ₃ -NH ₂	2HCl
AT	-CH ₂ CH ₂ OH	-(CH ₂) ₃ -NH-CH ₃	2HCl

Ex.	R ₅	R ₆	Salt
AU	-CH ₂ CH ₂ OH	-(CH ₂) ₃ -NH-CH ₂ CH ₂ OH	2HCl
AV	-CH ₂ CH ₂ OH	-(CH ₂) ₃ -N(CH ₃) ₂	2HCl
AW	-CH ₂ CH ₂ OH	-N(CH ₃) ₂	2HCl
AX	H	-(CH ₂) ₃ -OH	2HCl
AY	-CH ₂ CH ₂ OH	CH ₃	2HCl
AZ	H	-CH ₂ -CH(OH)-CH ₂ -NH ₂	2HCl
BA	H	-CH ₂ CH ₂ -N(CH ₂ CH ₂ NH ₂) ₂	2HCl
BB	-CH ₂ CH ₂ OH	-C ₂ H ₅	2HCl
BC	H	-CH ₂ CH ₂ -NH-(CH ₂) ₃ -NH ₂	3HCl
BD	H		3HCl
BE	-C ₂ H ₅	H	2HCl
BF	H	-CH ₂ -CH(OH)-CH ₂ OH	2HCl
BG	-C ₂ H ₅	CH ₃	2HCl
BH	-C ₂ H ₅	-(CH ₂) ₃ -N(CH ₃) ₂	2HCl
BI	-C ₂ H ₅	-(CH ₂) ₃ -NH ₂	3HCl
BJ	-C ₂ H ₅		3HCl
BK	-CH ₂ CH ₂ OH		3HCl
BL	H		3HCl
BM	CH ₃	H	2HCl
BN	CH ₃	CH ₃	2HCl
BO	CH ₃	-C ₂ H ₅	2HCl
BP	CH ₃		3HCl
BQ	CH ₃	-CH ₂ CH ₂ OH	2HCl

Ex.	R ₅	R ₆	Salt
BR	-CH ₂ CH ₂ OH	-CH ₂ CH ₂ OH	2HCl
BS	-CH ₂ CH ₂ -N(C ₂ H ₅) ₂	H	2HCl
BT	-(CH ₂) ₃ -N(CH ₃) ₂	H	2HCl
BU	H	-CH ₂ CH ₂ -N(C ₂ H ₅) ₂	2HCl
BV	-CH ₂ CH ₂ -N(C ₂ H ₅) ₂	CH ₃	2HCl
BW	-CH ₂ CH ₂ -N(CH ₃) ₂	H	2HCl
BX	H		HCl
BY	H		3HCl
BZ	-CH ₂ CH ₂ CH ₃	H	2HCl
CA	-CH(CH ₃) ₂	H	2HCl
CB		H	2HCl
CC	-(CH ₂) ₃ -CH ₃	CH ₃	2HCl
CD	-(CH ₂) ₃ -CH ₃	H	2HCl
CE		CH ₃	2HCl
CF		H	2HCl
CG	-CH ₂ -COOH	H	2HCl
CH	-(CH ₂) ₄ -CH ₃	H	2HCl
CI	-(CH ₂) ₅ -CH ₃	H	2HCl
CJ	-(CH ₂) ₆ -CH ₃	H	2HCl
CK	-CH ₂ CH ₂ CH ₂ -		2HCl

Example CL to Example CP

Compounds of formula



5

wherein R_5 , R_6 and R'_6 are as defined in TABLE 8 below in the form of a salt as defined in TABLE 8 below (Ex.=Example):

10

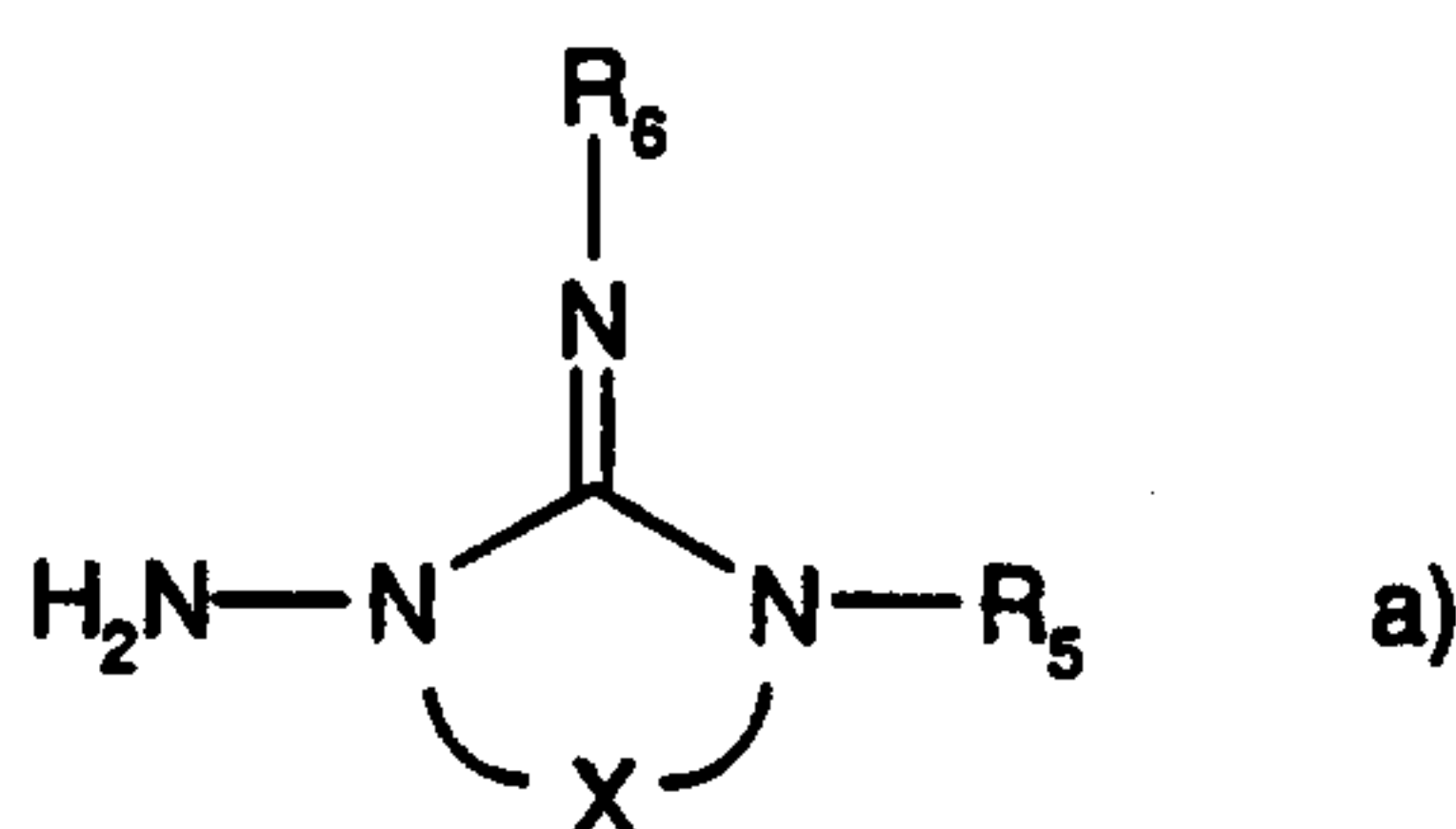
TABLE 8

Ex.	R_5	R_6	R'_6	Salt
Cl	$-C_2H_5$	CH_3	CH_3	HCl
CM	CH_3	CH_3	CH_3	HCl
CN	$-C_2H_5$	$-C_2H_5$	CH_3	HCl
CO	$-CH_2CH_2-$		CH_3	HCl
CP	$-CH_2CH_2CH_2-$		CH_3	HCl

Example CQ to Example CU

Compounds of formula

15



wherein R_5 , R_6 and X are as defined in TABLE 9 below in the form of a salt as defined in TABLE 9 below (Ex.=Example):

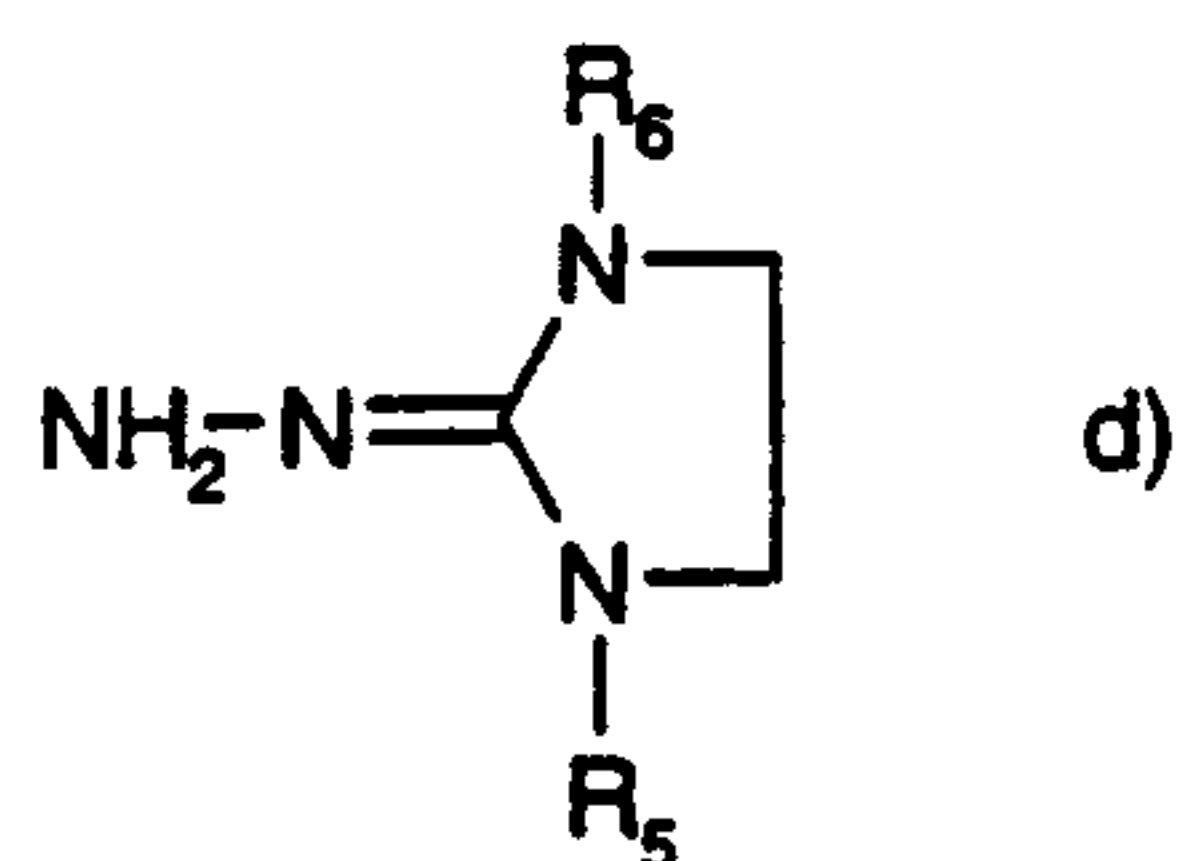
20

TABLE 9

Ex.	R ₅	R ₆	X	Salt
CQ	H	CH ₃	$\text{—CH}_2\text{—CH—}$ CH ₃	2HCl
CR	H	H	$\text{—CH}_2\text{—CH—}$ CH ₃	2HCl
CS	H	-(CH ₂) ₃ -NH ₂	$\text{—CH}_2\text{—CH—}$ CH ₃	3HCl
CT	H	CH ₃	$\text{—CH}_2\text{—C—}$ CH ₃ CH ₃	2HCl
CU	H	H	$\text{—CH}_2\text{—C—}$ CH ₃ CH ₃	2HCl

Example CV to Example CX

5 Compounds of formula



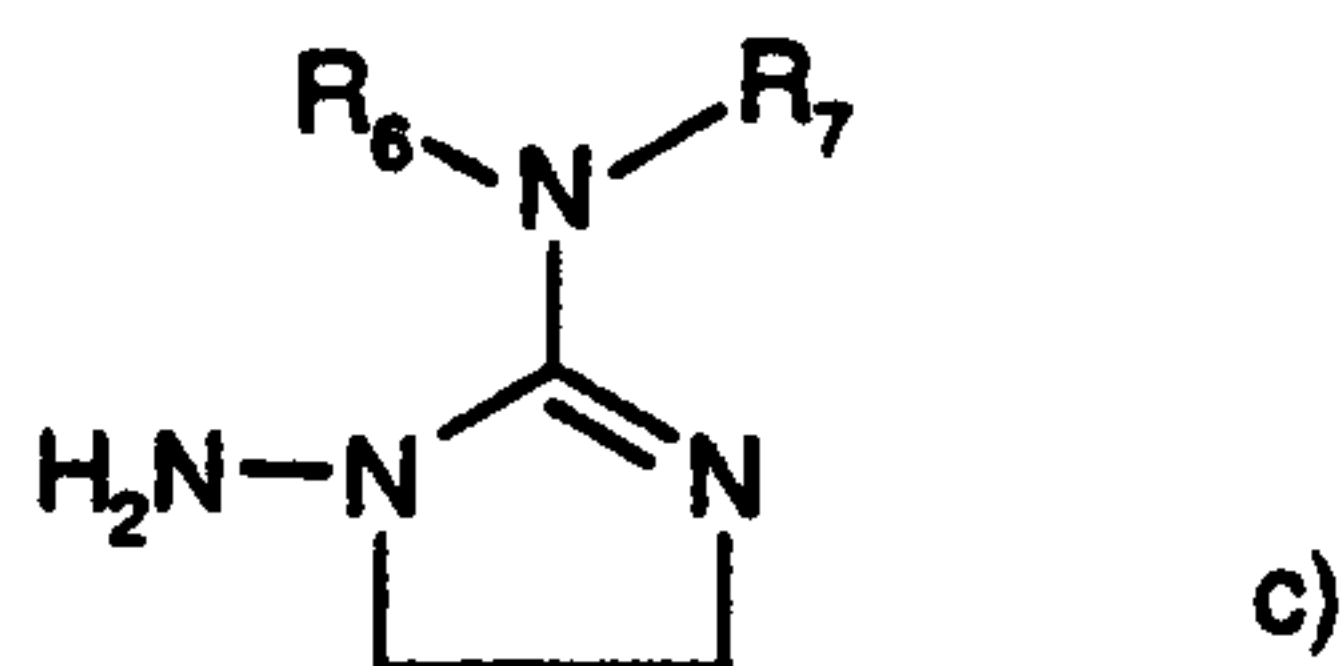
wherein R₅ and R₆ are as defined in TABLE 10 below in the form of a salt as defined
 10 in TABLE 10 below (Ex. = Example):

TABLE 10

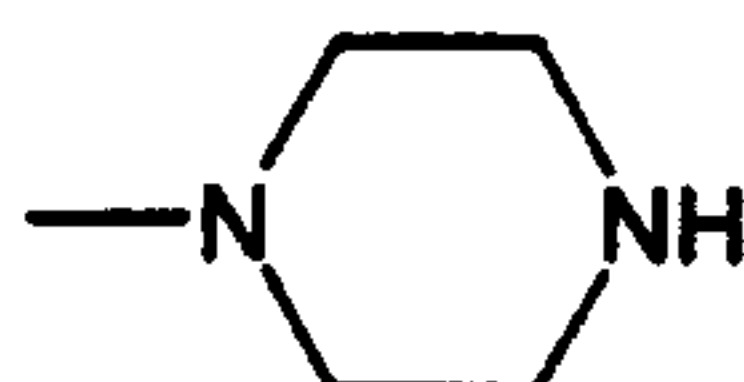
Ex.	R ₅	R ₆	Salt
CV	-CH ₂ CH ₂ CH ₃	H	HCl
CW	-CH(CH ₃) ₂	H	HCl
CX	-CH(CH ₃) ₂	-CH(CH ₃) ₂	HCl

Example CY

A compound of formula



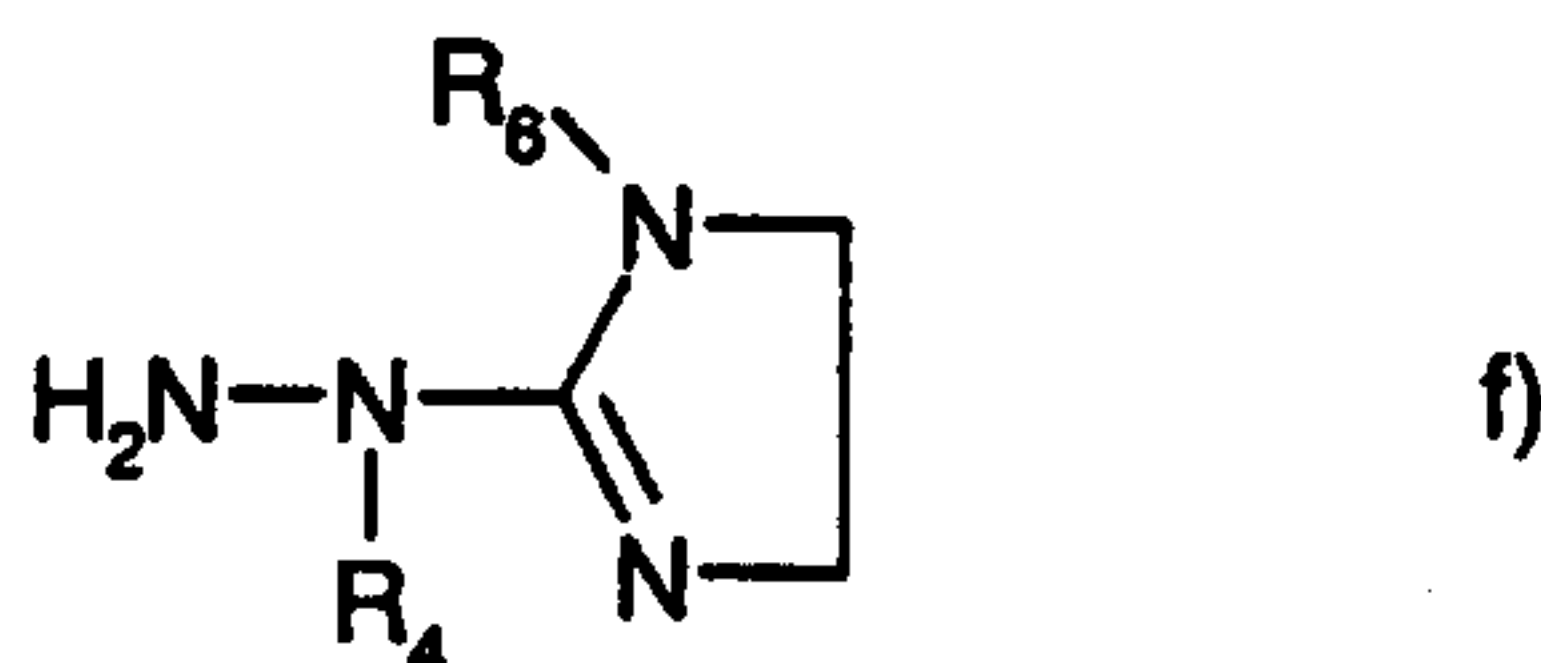
wherein R_6 and R_7 together with the nitrogen atom to which they are attached denote a group of formula



in the form of a dihydrochloride.

Example CZ

15 A compound of formula



wherein $R_4 = \text{CH}_3$ and $R_6 = \text{CH}_3$ in the form of a hydrochloride.

20

Example DA

A cooled mixture of 68.5 ml (ca. -5°) of 2 N H_2SO_4 with 4 g 1-(2-hydroxyethyl)-3-nitrosoimidazolidine-2-thion is treated with 3.42 g of Zn-powder, the mixture obtained is stirred for ca. 15 minutes and filtrated. The filtrate obtained is treated with 2.88 ml of benzylaldehyde and stirred for ca. one hour at room temperature. 1-Benzylideneamino-3-(2-hydroxyethyl)imidazolidine-2-thion precipitates, is filtrated off, washed with diethylether and dried.

25

Analogously as described in Example DA

1-benzylideneamino-3-ethyl-imidazolidine-2-thion is obtained from 1-ethyl-3-nitrosoimidazolidine-2-thion,

1-benzylideneamino-3-methyl-imidazolidine-2-thion is obtained from 1-methyl-3-nitrosoimidazolidine-2-thion,

5 1-benzylideneamino-3-propyl-imidazolidine-2-thion is obtained from 1-propyl-3-nitrosoimidazolidine-2-thion,

1-benzylideneamino-4-methyl-imidazolidine-2-thion is obtained from 1-nitroso-4-methyl-imidazolidine-2-thion, and

10 1-benzylideneamino-4,4-dimethyl-imidazolidine-2-thion is obtained from 4,4-dimethyl-3-nitroso-imidazolidine-2-thion.

Example DB

To an ice-cooled mixture of 6.81 g of 1-ethyl-imidazolidine-2-thion and 3.6 g of NaNO₂ in 440 ml of dichloromethane 63 ml of 1 M HCl are added dropwise and the
15 mixture obtained is stirred for ca 10 minutes. A two phase system is obtained and the phases are separated. The organic phase is washed with H₂O, dried over Na₂SO₄ and the solvent is evaporated off. Solid 1-ethyl-3-nitrosoimidazolidine-2-thion is obtained.

Analogously as described in Example DB

20 1-methyl-3-nitrosoimidazolidine-2-thion is obtained from 1-methyl-imidazolidine-2-thion,

3-nitroso-1-propyl-imidazolidine-2-thion is obtained from 1-propyl-imidazolidine-2-thion,

4-methyl-1-nitroso-imidazolidine-2-thion is obtained from 4-methyl-imidazolidine-2-
25 thion, and

4,4-dimethyl-1-nitroso-imidazolidine-2-thion is obtained from 4,4dimethyl-imidazolidine-2-thion.

30

¹H-NMR-Spectra of compounds (Ex. = Example) in DMSO-d₆ if not otherwise stated

Ex.1: 3.58 and 4.64, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.68 - 4.10, m, 4H, N-CH₂;
5.34, d, J=5 Hz, 1H, β-lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F; 5.95, dd, J=5 Hz and 8
35 Hz, 1H, β-lactam-H; 7.87, s, 1H, CH=N; 9.11, b, 1H, NH; 9.85, d, J=8 Hz, 1H, NH

- Ex.2: 3.20-4.28,m,9H,4H of N-CH₂ and 2H of S-CH₂ and 3H of CH₃;5.30,d, J=5 Hz, 1H,β-lactam-H;5.82,d,J=55 Hz, 2H,CH₂F;5.96,dd,J=5 Hz and J=8 Hz,1H, β-lactam-H;7.92,s,1H,CH=N;8.34,b,2H,NH;8.97,b, 1H, NH; 9.86, d, J=8 Hz, 1H, NH
- 5 Ex.3: 3.52 and 4.54,AB-quartet,J=18 Hz,2H,S-CH₂;3.67-4.25,m, 4H, N-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.93, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 6.85 - 6.92, m, 3H, CH-aromatic; 7.20-7.30, m, 2H, CH-aromatic; 7.93, s, 1H, CH=N; 8.28, b, 2H, NH; 8.51, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH
- 10 Ex.4: 2.97, d, J=5 Hz, 3H, CH₃, 3.56 and 4.55, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.70 - 4.15, m, 4H, N-CH₂; 5.32, d, J=5 Hz, 1H, β-lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F, 5.96, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 7.88, s, 1H, CH=N; 8.33, b, 2H, NH; 8.71, d, J=5 Hz, 1H, NH; 9.75, b, 1H, NH; 9.86, d, J=8 Hz, 1H, NH
- 15 Ex.5: 2.83, s, 3H, CH₃; 3.00 -3.30, m, 6H, N-CH₂; 3.40 - 4.20, m, 7H, 1H of S-CH₂ and 6H of N-CH₂; 4.44, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.82, d, J=55 Hz, 2H, CH₂F; 5.96, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 7.91, s, 1H, CH=N; 8.34, s, 2H, NH; 9.87, d, J=8 Hz, 1H, NH
- 20 Ex.6: 0.60 - 0.92, m, 4H, CH₂-cycloprop.; 2.50 - 2.54, m, 1H, CH-C; 3.51 and 4.59, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.70 - 4.10, m, 4H, N-CH₂; 5.31, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.95, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 7.88, s, 1H, CH=N; 9.85, d, J=8 Hz, 1H, NH
- 25 Ex.7: 3.38 - 4.18, m, 17H, 16H of N-CH₂ and 1H of S-CH₂; 4.60, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.32, d, J=5 Hz, 1H, β-lactam-H; 5.80, d, J=55 Hz, 2H, CH₂F; 5.96, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H;7.92,s,1H, H=N;8.30,b,2H,NH;9.86,d, J=8 Hz, 1H, NH
- 30 Ex.8: 3.45 - 3.70, m, 5H, 4H of N-CH₂ and 1H of S-CH₂; 3.72 - 4.10, m, 4H, N-CH₂ and O-CH₂; 4.59, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.32, d, J=5 Hz, 1H, β-lactam-H; 5.80, d, J=55 Hz, 2H, CH₂F; 5.96, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 7.90, s, 1H, CH=N; 8.33, b, 2H, NH; 9.86, d, J=8 Hz, 1H, NH
- 35 Ex.9: 1.20,t,J=5 Hz,3H,CH₃;2.90-3.20,m,4H,N-CH₂;3.40-4.10,m,7H, 6H von N-CH₂ and 1H of S-CH₂;4.60, part of AB-quartet,J=18 Hz,1H, S-CH₂;5.30,d, J=5 Hz, 1H, β-

lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 7.89, s, 1H, CH=N; 8.28, b, 2H, NH; 9.00, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.10: 2.85, s, 6H, CH₃; 3.35, b, 2H, N-CH₂; 3.48 - 4.15, m, 7H, 6H of N-CH₂ and
5 1H of S-CH₂; 4.61, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.32, d, J=5 Hz, 1H, β-lactam-H; 5.80, d, J=55 Hz, 2H, CH₂F; 5.96, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 7.89, s, 1H, CH=N; 8.31, b, 2H, NH; 9.86, d, J=8 Hz, 1H, NH

Ex.11: 3.05, b, 2H, N-CH₂; 3.45 - 3.68, m, 3H, 2H of N-CH₂ and 1H of S-CH₂;
10 3.70 - 4.15, m, 4H, N-CH₂; 4.52, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.24, d, J=5 Hz, 1H, β-lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F; 5.84, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 8.09, s, 1H, CH=N; 8.30, b, 2H, NH; 9.81, d, J=8 Hz, 1H, NH

Ex.12: 2.90, b, 2H, N-CH₂; 3.40 - 3.61, m, 3H, 2H of O-CH₂ and 1H of S-CH₂;
15 3.63 - 4.20, m, 4H, N-CH₂; 4.50, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.82, d, J=55 Hz, 2H, CH₂F; 5.92, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 8.07, s, 1H, CH=N; 8.23, b, 2H, NH; 9.77, d, J=8 Hz, 1H, NH

Ex.13: 1.72 - 1.92, m, 2H, CH₂; 2.85, b, 2H, N-CH₂; 3.38, b, 2H, N-CH₂; 3.54 and
20 4.51, AB-quartet, J=8 Hz, 2H, S-CH₂; 3.68 - 4.14, m, 4H, N-CH₂; 5.21, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.79, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 8.04, s, 1H, CH=N; 8.26, b, 2H, NH; 9.77, d, J=8 Hz, 1H, NH

Ex.14: 3.10, b, 2H, N-CH₂; 3.20, b, 2H, N-CH₂; 3.55 and 4.64, AB-quartet, J=18 Hz,
25 2H, S-CH₂; 3.62 - 4.15, m, 8H, 6H of N-CH₂ and 2H of OCH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 7.87, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

Ex.15: 3.30 - 4.30, m, 22H, 18H of N-CH₂ and 2H of O-CH₂ and 2H of S-CH₂; 5.25,
30 d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.75, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 8.15, s, 1H, CH=N; 8.26, b, 2H, NH; 9.77, d, J=8 Hz, 1H, NH

Ex.16: 1.18-1.50, m, 2H, CH₂-C; 1.68-1.98, m, 3H, CH₂-C and CH-C; 2.70-2.98, m,
35 2H, N-CH₂; 3.10-3.38, m, 4H, N-CH₂; 3.53 and 4.53, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.62-4.15, m, 4H, N-CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.77, d, J=55 Hz, 2H, CH₂F; 5.93, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 7.88, s, 1H, CH=N; 9.83, d, J=8 Hz, 1H, NH

Ex.17: 3.20 - 4.10, m, 9H, 6H of N-CH₂, 1H of S-CH₂ and 2H of CH₂-C; 4.38, part
of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55
Hz, 2H, CH₂F; 5.90, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 7.87, s, 1H, CH=N;
5 7.90 - 8.20, m, 2H, CH-aromatic; 8.45 - 8.60, m, 1H, CH-aromatic; 8.78 - 8.90, m,
1H, CH-aromatic; 9.83, d, J=8 Hz, 1H, NH; 10.17, b, 1H, OH

Ex.18: 3.40 - 3.70, m, 9H, 6H of O-CH₂ and 2H of N-CH₂ and 1H of S-CH₂; 3.72 -
4.12, m, 4H, N-CH₂; 4.55, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.32, d, J=5 Hz,
10 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.96, dd, J=5 Hz and J=8 Hz, 1H, β-
lactam-H; 7.89, s, 1H, CH=N; 9.63, b, 1H, NH; 9.87, d, J=8 Hz, 1H, NH

Ex.19: 3.50 and 4.45, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.70 - 4.12, m, 4H, N-CH₂;
5.28, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.93, dd, J=5 Hz and
15 J=8 Hz, 1H, β-lactam-H; 7.84, s, 1H, CH=N; 8.30, b, 2H, NH₂; 9.52, b, 1H, NH;
9.83, d, J=8 Hz, 1H, NH; 11.86, b, 1H, OH

Ex.20: 2.80 -3.02, m,4H, O-CH₂;3.42 - 4.18, m,9H, 8H of N-CH₂ and 1H of S-CH₂;
4.50, part of AB-quartet,J=18 Hz,1H, S-CH₂;5.31,d, J=5 Hz, 1H, β-lactam-H; 5.78, d,
20 J=55 Hz,2H, CH₂F; 5.94, dd,J=5 Hz and J=8 Hz, 1H,β-lactam-H; 7.86, s, 1H, CH=N;
8.29, b, 2H,NH; 9.32, b, 1H,NH; 9.85,d, J=8 Hz, 1H, NH; 10.16, b, 1H, OH

Ex.21: 1.59, b, 4H, CH₂-C; 2.80, b, 2H, N-CH₂; 3.32, b, 2H, N-CH₂; 3.53 and 4.53,
AB-quartet, J=18 Hz, 2H, S-CH₂; 3.68 - 4.12, m, 4H, N-CH₂; 5.24, d, J=5 Hz, 1H, β-
25 lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F; 5.80, dd, J=5 Hz and J= 8 Hz, 1H, β-
lactam-H; 8.05, s, 1H, CH=N; 8.31, b, 2H, NH; 9.80, d, J=8 Hz, 1H, NH

Ex.22: 3.35,b,2H, N-CH₂;3.42-3.62,m,3H,2H of OCH₂ and 1H of S-CH₂; 3.65-4.10,
m,4H, N-CH₂;4.46,part of AB-quartet,J=18 Hz,1H, S-CH₂;5.31,d,J=5 Hz, 1H, β-
30 lactam-H;5.80, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H;
7.86, s, 1H, CH=N; 8.30, b, 2H, NH; 9.60, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.23: 1.28,b,4H, C-CH₂;1.52,b,4H,C-CH₂;2.76,b,2H, N-CH₂; 3.25, b, 2H, N-CH₂;
3.50 and 4.45,AB-quartet,J=18 Hz,2H,S-CH₂;3.62 - 4.10, m, 4H, N-CH₂; 5.30, d, J=5
35 Hz, 1H, β-lactam-H;5.80,d,J=55 Hz,2H,CH₂F;5.94,dd,J=5 Hz and J=8 Hz,1H, β-
lactam-H;7.85,s,1H,CH=N;8.10,b,3H,NH;8.30,b, 2H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.24: 1.25,d,J=5 Hz,3H,CH₃;3.35-3.68, m, 4H, 2H of N-CH₂ and 1H of N-CH and
 1H of S-CH₂;3.70-4.20,m,4H, N-CH₂; 4.56, part of AB-quartet, J=18 Hz, 1H, S-CH₂;
 5.24,d,J= 5 Hz,1H, β-lactam-H;5.81,d, J=55 Hz, 2H, CH₂F; 5.84, dd, J=5 Hz and J=8
 5 Hz, 1H, β-lactam-H; 8.09, s, 1H, CH=N; 8.30, b, 2H, NH; 9.81, d, J=8 Hz, 1H, NH

Ex.25: 2.92 - 3.60, m, 5H, 4H of N-CH₂ and 1H of S-CH₂; 3.62 - 4.15, m, 12H, 8H
 of N-CH₂ and 4H of O-CH₂; 4.35, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.16, d,
 J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.72, dd, J=5 Hz and J=8 Hz,
 10 1H, β-lactam-H; 8.10, s, 1H, CH=N; 8.25, b, 2H, NH; 9.76, d, J=8 Hz, 1H, NH

Ex.26: 1.35, s, 6H, CH₃; 3.48 - 4.15, m, 7H, 6H of N-CH₂ and 1H of S-CH₂; 4.74,
 part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.32, d, J=5 Hz, 1H, β-lactam-H; 5.81, d,
 J=55 Hz,. 2H, CH₂F; 5.94, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 7.90, s, 1H,
 15 CH=N; 9.86, d, J=8 Hz, 1H, NH; 10.26, b, 1H, OH

Ex.27: 1.16, t, J=7 Hz, 3H, CH₃; 3.33, q, J=7 Hz, 2H, CH₂; 3.54 and 4.53, AB-
 quartet, J=18 Hz, 2H, S-CH₂; 3.68 - 4.12, m, 4H, N-CH₂; 5.30, d, J=5 Hz, 1H, β-
 lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 and 8 Hz, 1H, β-lactam-H;
 20 7.87, s, 1H, CH=N; 8.28, b, 2H, NH; 8.68, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.28: 0.87,t,J=7 Hz,3H,CH₃;1.55,h, J=7 Hz, 2H, CH₂; 3.24, t, J=7 Hz, N-CH₂; 3.52
 and 4.54,AB-quartet,J=18 Hz,2H, S-CH₂;3.65 - 4.12, m, 4H, N-CH₂; 5.30, d, J=5 Hz,
 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.93, dd, J=5 and 8 Hz, 1H, β-lactam-
 25 H; 7.87, s, 1H, CH=N; 8.29, b, 2H, NH; 8.68, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.29: 2.90-3.05,m,2H,N-CH₂; 3.40 - 4.18, m, 15H, 6H of N-CH₂ and 8H of O-CH₂
 and 1H of S-CH₂; 4.55, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.33, d, J=5 Hz, 1H,
 β-lactam-H; 5.80, d, J=55 Hz, 2H, CH₂F; 5.95, dd, J=5 and 8 Hz, 1H, β-lactam-H;
 30 7.90, s, 1H, CH=N; 8.26, b, 2H, NH; 8.77, b, 1H, NH; 9.82, d, J=5 Hz, 1H, NH

Ex.30: 1.72-2.02, m, 2H, CH₂; 2.54, s, 3H,N-CH₃; 2.94, b, 2H,N-CH₂; 3.34-3.64, m,
 3H, 2H of N-CH₂ and 1H of S-CH₂; 3.70-4.10, m, 4H, N-CH₂; 4.55,part of AB-
 quartet, J=18 Hz, 1H, S-CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.80, d, J=55 Hz, 2H,
 35 CH₂F; 5.92, dd, J=5 and 8 Hz,1H, β-lactam-H; 7.87, s, 1H, CH=N; 8.28, b, 2H, NH;
 8.88, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.31: 1.80-2.05,m,2H,CH₂;2.88-3.12,m,4H,N-CH₂;3.40,b,2H, N-CH₂;3.53 and
 4.51,AB-quartet,J=18 Hz,2H, S-CH₂;3.62-4.12,m,6H,4H of N-CH₂ and 2H of O-
 CH₂;5.30,d,J=5 Hz,1H,β-lactam-H;5.77,d,J=55 Hz,2H, CH₂F; 5.82, dd, J=5 and 8Hz,
 5 1H, β-lactam-H, 8.03, s, 1H, CH=N; 8.30, b, 2H, NH; 9.80, d, J= 8 Hz, 1H, NH

Ex.32: 1.82-2.10,m,2H,CH₂;2.75,s,6H,N-CH₃;3.00-3.18,m, 2H, N-CH₂; 3.32 - 3.48,
 m,2H,N-CH₂;3.54 and 4.54,AB-quartet,J=18 Hz,2H,S-CH₂;3.68-4.12,m,4H,N-CH₂;
 5.30,d,J=5 Hz,1H,β-lactam-H;5.79,d,J=55 Hz,2H,CH₂F;5.92,dd,J=5 and 8 Hz, 1H,
 10 β-lactam-H;7.86,s,1H,CH=N;8.30,b,2H,NH;8.85,b, 1H, NH; 9.84, d, J=8 Hz, 1H,
 NH

Ex.33: 1.78-2.02,m,2H,CH₂;2.95-3-75,m,11H,10H of N-CH₂ and 1H of S-CH₂;
 4.10- 4.35,m,2H,O-CH₂;4.65,part of AB-quartet,J=18 Hz,1H,S-CH₂; 5.27, d, J=5 Hz,
 15 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.82, dd, J=5 u 8 Hz, 1H, β-lactam-H;
 8.24, b, 2H, 1H of CH=N and 1H of NH; 8.32, b, 1H, NH; 9.77, d, J=8 Hz, 1H, NH

Ex.34: 1.82 - 2.02, m, 2H, CH₂; 2.55, s, 3H, N-CH₃; 2.88 - 3.02, m, 2H, N-CH₂;
 3.48 - 4.22, m, 12H, 8H of N-CH₂ and 2H of O-CH₂ and 2H of S-CH₂; 5.27, d, J=5
 20 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.82, dd, J=5 and 8 Hz, 1H, β-
 lactam-H; 8.10, s, 1H, CH=N; 8.28, b, 2H, NH; 9.78, d, J=8 Hz, 1H, NH

Ex.35: 1.82 - 2.08, m, 2H, CH₂; 2.85 - 3.10, m, 4H, N-CH₂; 3.38 - 4.22, m, 14H, 8H
 of N-CH₂ and 4H of O-CH₂ and 2H of S-CH₂; 5.17, d, J=5 Hz, 1H, β-lactam-H; 5.80,
 25 d, J=55 Hz, 2H, CH₂F; 5.82, dd, J=5 and 8 Hz, 1H, β-lactam-H; 8.08, s, 1H, CH=N;
 8.27, b, 2H, NH; 9.75, d, J=8 Hz, 1H, NH

Ex.36: 1.82 - 2.12, m, 2H, CH₂; 2.77, s, 6H, N-CH₃; 3.00 - 3.22, m, 2H, N-CH₂;
 3.45 - 4.12, m, 12H, 8H of N-CH₂ and 2H of O-CH₂ and 2H of S-CH₂; 5.20, d, J=5
 30 Hz, 1H, β-lactam-H; 5.82, d, J=55 Hz, 2H, CH₂F; 5.85, dd, J=5 and 8 Hz, 1H, β-
 lactam-H; 8.09, s, 1H, CH=N; 8.30, b, 2H, NH; 9.78, d, J=8 Hz, 1H, NH

Ex.37: 2.72, s, 6H, N-CH₃; 3.42 - 4.08, m, 9H, 6H of N-CH₂ and 2H of O-CH₂ and
 1H of S-CH₂; 4.56,part of AB quartet, J=18 Hz, 1H, S-CH₂; 5.30, d, J=5 Hz, 1H, β-
 35 lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 and 8 Hz, 1H, β-lactam-H;
 7.84, s, 1H, CH=N; 8.24, b, 2H, NH; 9.77, d, J=8 Hz, 1H, NH

Ex.38: 1.55–1.82, m, 2H, CH₂-C; 3.30–3.65, m, 5H, 2H of N-CH₂ and 2H of O-CH₂ and 1H of S-CH₂; 3.70–4.10, m, 4H, N-CH₂; 4.51, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.32, d, J=5 Hz, 1H, β-lactam-H; 5.8, d, J=55 Hz, 2H, CH₂F; 5.95, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.88, s, 1H, CH=N; 8.32, b, 2H, NH; 8.74, m, 1H, OH; 9.73, b, 1H, NH; 9.87, d, J=8 Hz, 1H, NH

Ex.39: 3.20, d, J=5 Hz, 3H, N-CH₃; 3.45–4.05, m, 9H, 6H of N-CH₂ and 2H of O-CH₂ and 1H of S-CH₂; 4.34, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.95, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.89, s, 1H, CH=N; 8.33, b, 2H, NH; 8.58, d, J=5 Hz, 1H, NH; 9.86, d, J=8 Hz, 1H, NH

Ex.40: 2.65–3.05, m, 2H, N-CH₂; 3.25–3.45, m, 2H, N-CH₂; 3.54 and 4.55, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.65 – 4.12, m, 5H, 4H of N-CH₂ and 1H of O-CH; 5.21, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.80, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.05, s, 1H, CH=N; 8.29, b, 2H, NH; 9.78, d, J=8 Hz, 1H, NH

Ex.41: 2.80–3.20, m, 10H, N-CH₂; 3.40–3.65, m, 3H, 1H of S-CH₂ and 2H of N-CH₂; 3.70–4.05, m, 4H, N-CH₂; 4.45, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.85, d, J=5 Hz, 1H, β-lactam-H; 7.93, s, 1H, CH=N

Ex.42: 1.65–1.92, m, 2H, CH₂-C; 3.12–3.32, m, 2H, N-CH₂; 3.40–3.58, 3H, 2H of N-CH₂ and 1H of S-CH₂; 3.62–4.12, m, 4H, N-CH₂; 4.55, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.92, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.87, s, 1H, CH=N; 9.86, d, J=8 Hz, 1H, NH; 10.01, b, 1H, NH

Ex.43: 1.20, t, J=7 Hz, 3H, CH₃; 3.45 – 4.22, m, 12H, 8H of N-CH₂ and 2H of O-CH₂ and 2H of S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.91, s, 1H, CH=N; 8.29, b, 2H, NH; 8.61, m, 1H, OH; 9.84, d, J=8 Hz, 1H, NH

Ex.44: 1.82–2.08, m, 4H, CH₂-C; 2.82–3.10, m, 6H, N-CH₂; 3.35–3.65, m, 3H, 2H of N-CH₂ and 1H of S-CH₂; 3.70–4.12, m, 4H, N-CH₂; 4.55, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.01, s, 1H, CH=N; 8.30, b, 2H, NH; 9.78, d, J=8 Hz, 1H, NH

Ex.45: 1.30 – 1.70, m, 4H, CH₂-C; 1.85 – 2.10, m, 4H, CH₂-C; 2.85 – 3.10, m, 1H, CH-C; 3.40 – 3.55, m, 2H, 1H of CH and 1H of S-CH₂; 3.56 – 4.10, m, 4H, N-CH₂; 4.59, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.85, s, 1H, CH=N; 8.30, b, 6H, NH; 9.88, d, J=5 Hz, 1H, NH; 10.01, b, 1H, NH

Ex.46: 1.15, t, J=7 Hz, 3H, CH₃; 3.40 – 3.62, m, 3H, 2H of CH₂ and 1H of S-CH₂; 3.70 – 4.10, m, 4H, N-CH₂; 4.55, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.85, s, 1H, CH=N; 8.30, b, 2H, NH; 9.83, d, J=8 Hz, 1H, NH

Ex.47: 3.20–4.10, m, 10H, 6H of N-CH₂ and 2H of O-CH₂ and 1H of O-CH and 1H of S-CH₂; 4.55, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.87, s, 1H, CH=N; 8.28, b, 2H, NH; 8.68, b, 1H, OH; 9.47, b, 1H, OH; 9.84, d, J=8 Hz, 1H, NH

Ex.48: 1.18, t, J=7 Hz, 3H, CH₃; 3.16, d, J=5 Hz, 3H, N-CH₃; 3.45 – 3.68, m, 3H, 2H of N-CH₂ and 1H of S-CH₂; 3.70 – 4.10, m, 4H, N-CH₂; 4.29, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F; 5.96, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.87, s, 1H, CH=N; 8.29, b, 2H, NH; 8.66, d, J=5 Hz, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.49: 1.16, t, J=7 Hz, 3H, CH₃; 1.88 – 2.10, m, 2H, CH₂-C; 2.78, s, 6H, N-CH₃; 3.00 – 3.20, m, 2H, N-CH₂; 3.40 – 4.20, m, 10H, 8H of N-CH₂; 2H of S-CH₂; 5.17, d, J=5 Hz, 1H, β-lactam-H; 5.80, d, J=55 Hz, 2H, CH₂F; 5.82, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.05, s, 1H, CH=N; 8.28, b, 2H, NH; 9.74, d, J=8 Hz, 1H, NH

Ex.50: 1.20, t, J=7 Hz, 3H, CH₃; 1.75 – 2.00, m, 2H, CH₂-C; 2.90 – 3.60, m, 9H, 8H of N-CH₂ and 1H of S-CH₂; 4.08 – 4.38, m, 2H, N-CH₂; 4.65, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.28, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.84, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.24, b, 2H, 1H of CH=N and 1H of NH; 8.37, b, 1H, NH; 9.77, d, J=8 Hz, 1H, NH

Ex.51: 1.14, t, J=7 Hz, 3H, CH₃; 1.30–1.75, m, 4H, CH₂-C; 1.88–2.12, m, 4H, CH₂-C; 2.88–3.10, m, 1H, N-CH; 3.40–4.22, m, 9H, 6H of N-CH₂ and 1H of N-CH and 2H of S-CH₂;

5.28, d, J=5 Hz, 1H, β -lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β -lactam-H; 7.93, s, 1H, CH=N; 8.27, b, 5H, NH; 9.85, d, J=8 Hz, 1H, NH

Ex.52: 1.25–1.70, m, 4H, CH₂-C; 1.85–2.12, m, 4H, CH₂-C; 2.88–3.10, m, 1H, N-CH; 3.45–4.28, m, 11H, 6H of N-CH₂ and 1H of N-CH and 2H of O-CH₂ and 2H of S-CH₂; 5.15, d, J=5 Hz, 1H, β -lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F; 5.74, dd, J=5 Hz and 8 Hz, 1H, β -lactam-H; 8.18, b, 3H, 1H of CH=N and 2H of NH; 8.28, b, 3H, NH; 9.79, d, J=8 Hz, 1H, NH

Ex.53: 2.72 – 2.92, m, 2H, CH₂-C; 3.10 – 3.30, m, 6H, N-CH₂; 3.32 – 3.60, m, 3H, 2H of N-CH₂ and 1 H of S-CH₂; 3.62 – 4.15, m, 8H, N-CH₂; 4.59, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β -lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β -lactam-H; 7.86, s, 1H, CH=N; 8.08, b, 2H, NH; 8.28, b, 2H, NH; 8.59, b, 1H, NH; 8.96, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

15

Ex.54: 1.70 – 1.92, m, 2H, CH₂-C; 2.76, d, J=4 Hz, 6H, N-CH₃; 3.10 – 3.25, m, 2H, N-CH₂; 3.27 – 3.42, m, 2H, N-CH₂; 3.41 and 4.51, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.70 – 4.10, m, 4H, N-CH₂; 5.17, d, J=5 Hz, 1H, β -lactam-H; 5.73, dd, J=5 Hz and 8 Hz, 1H, β -lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 7.72, b, 2H, NH; 8.04, s, 1H, CH=N; 8.26, b, 2H, NH; 8.60, b, 1H, NH; 9.76, d, J=8 Hz, 1H, NH

20

Ex.55: 3.04, s, 3H, N-CH₃; 3.53 and 4.54, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.68–4.04, m, 4H, N-CH₂; 5.29, d, J=5 Hz, 1H, β -lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β -lactam-H; 7.85, s, 1H, CH=N; 8.29, b, 2H, NH; 9.83, d, J=8 Hz, 1H, NH

25

Ex.56: 3.16, s, 3H, N-CH₃; 3.17, s, 3H, N-CH₃; 3.57 and 4.32, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.68 – 4.08, m, 4H, N-CH₂; 5.29, d, J=5 Hz, 1H, β -lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.95, dd, J=5 Hz and 8 Hz, 1H, β -lactam-H; 7.86, s, 1H, CH=N; 8.30, b, 2H, NH; 8.64, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

30

Ex.57: 1.21, t, J=7 Hz, 3H, CH₃; 3.10, s, 3H, N-CH₃; 3.48 – 4.10, m, 7H, 6H of N-CH₂ and 1H of S-CH₂; 4.20, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β -lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.95, dd, J=5 Hz and 8 Hz, 1H, β -lactam-H; 7.89, s, 1H, CH=N; 8.30, b, 2H, NH; 8.69, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

35

5

Ex.58: 1.30–1.75, m, 4H, CH₂-C; 1.88–2.12, m, 4H, CH₂-C; 2.85–3.02, m, 1H, N-CH;
3.07, s, 3H, CH₃; 3.45 – 4.21, m, 7H, 4H of N-CH₂ and 1H of N-CH and 2H of S-CH₂;
5.28, d, J=5 Hz, 1H, β-lactam-H; 5.80, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8
Hz, 1H, β-lactam-H; 7.91, s, 1H, CH=N; 8.31, b, 3H, NH; 9.85, d, J=8 Hz, 1H, NH

10

Ex.59: 3.14, s, 3H, CH₃; 3.50 – 4.10, m, 9H, 6H of N-CH₂ and 2H of O-CH₂ and
1H of S-CH₂; 4.25, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β-
lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H;
7.89, s, 1H, CH=N; 8.23, b, 2H, NH; 9.75, d, J=8 Hz, 1H, NH

15

Ex.60: 3.48 – 4.10, m, 13H, 8H of N-CH₂ and 4H of O-CH₂ and 1H of S-CH₂; 4.20,
part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.13, d, J=5 Hz, 1H, β-lactam-H; 5.72, dd,
J=5 Hz and 8 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 8.16, s, 1H, CH=N;
8.24, b, 2H, NH; 9.76, d, J=8 Hz, 1H, NH

20

Ex.61: 1.24, t, J=7 Hz, 6H, CH₃; 3.05 – 3.45, m, 6H, N-CH₂; 3.54 and 4.55, AB-
quartet, J=18 Hz, 2H, S-CH₂; 3.70 – 4.10, m, 6H, N-CH₂; 5.29, d, J=5 Hz, 1H, β-
lactam-H; 5.80, d, J=55 Hz, 2H, CH₂F; 5.96, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H;
7.86, s, 1H, CH=N; 8.28, b, 2H, NH; 9.83, d, J=8 Hz, 1H, NH; 10.89, b, 1H, NH

25

Ex.62: 1.90 – 2.14, m, 2H, CH₂-C; 2.73, d, J=4 Hz, 6H, N-CH₃; 3.00 – 3.20, m, 2H,
N-CH₂; 3.32 – 4.10, m, 7H, 6H of N-CH₂ and 1H of S-CH₂; 4.60, part of AB-quartet,
J=18 Hz, 1H, S-CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F;
5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.86, s, 1H, CH=N; 8.30, b, 2H, NH;
9.83, d, J=8 Hz, 1H, NH; 10.97, b, 1H, NH

30

Ex.63: 1.24, t, J=7 Hz, 6H, CH₃; 3.05 – 3.40, m, 6H, N-CH₂; 3.53 and 4.56, AB-
quartet, J=18 Hz, 2H, S-CH₂; 3.70 – 4.18, m, 6H, N-CH₂; 5.30, d, J=5 Hz, 1H, β-
lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H;
7.87, s, 1H, CH=N; 8.28, b, 2H, NH; 9.02, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH;
10.26, b, 1H, NH; 10.89, b, 1H, NH

35

Ex.64: 1.21, t, J=7 Hz, 6H, CH₃; 3.08–3.30, m, 7H, 4H of N-CH₂ and 3H of N-CH₃; 3.32
–3.50, m, 2H, N-CH₂; 3.58 and 4.24, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.75–4.10, m, 6H,
N-CH₂; 5.12, d, J=5 Hz, 1H, β-lactam-H; 5.70, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 5.78,
d, J=55 Hz, 2H, CH₂F; 8.15, s, 1H, CH=N; 8.23, b, 2H, NH; 9.75, d, J=8 Hz, 1H, NH

Ex.65: 2.79, d, J=4 Hz, 6H, N-CH₃; 3.32 – 3.48, m, 2H, N-CH₂; 3.53 and 4.56, AB-
quartet, J=18 Hz, 2H, S-CH₂; 3.68 – 4.04, m, 6H, N-CH₂; 5.30, d, J=5 Hz, 1H, β-
lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H;
5 7.86, s, 1H, CH=N; 8.28, b, 2H, NH; 9.84, d, J=8 Hz, 1H, NH; 10.95, b, 1H, NH

Ex.66 (in DMSO-d₆/CF₃COOD): 3.50 and 4.31, AB-quartet, J=18 Hz, 2H, S-CH₂;
3.75 – 4.20, m, 4H, N-CH₂; 5.17, s, 2H, OCH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H;
5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.33, s, 1H,
10 CH; 7.87, s, 1H, CH=N; 8.32, s, 1H, CH; 9.84, d, J=8 Hz, 1H, NH

Ex.67: 1.10 – 2.20, m, 8H, CH₂-C; 3.12 – 3.40, m, 1H, N-CH; 3.55 and 4.55, AB-
quartet, J=18 Hz, 2H, S-CH₂; 3.65 – 4.18, m, 5H, 4 H of N-CH₂ and 1H of N-CH;
5.23, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.84, dd, J=5 Hz and 8
15 Hz, 1H, β-lactam-H; 8.10, s, 1H, CH=N; 8.27, b, 3H, NH; 9.82, d, J=8 Hz, 1H, NH

Ex.68: 1.10 – 2.20, m, 8H, CH₂-C; 3.18 – 3.40, m, 1H, N-CH; 3.55 and 4.59, AB-
quartet, J=18 Hz, 2H, S-CH₂; 3.68 – 4.20, m, 5H, 4H of N-CH₂ and 1H of N-CH;
5.21, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.80, dd, J=5 Hz and 8
20 Hz, 1H, β-lactam-H; 8.07, s, 1H, CH=N; 8.26, b, 3H, NH; 9.77, d, J=8 Hz, 1H, NH

Ex.69: 0.88, t, J=7 Hz, 3H, CH₃; 1.40 – 1.70, m, 2H, CH₂-C; 3.30 – 3.48, m, 2H, N-
CH₂; 3.53 and 4.55, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.65 – 4.08, m, 4H, N-CH₂;
5.29, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.93, dd, J=5 Hz and 8
25 Hz, 1H, β-lactam-H; 7.85, s, 1H, CH=N; 8.29, b, 2H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.70: 0.90, t, J=7 Hz, 3H, CH₃; 1.48 – 1.72, m, 2H, CH₂-C; 3.16, d, J=5 Hz, 3H, N-
CH₃; 3.32 – 3.50, m, 2H, N-CH₂; 3.58 and 4.25, AB-quartet, J=18 Hz, 2H, S-CH₂;
3.70 – 4.10, m, 4H, N-CH₂; 5.28, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H,
30 CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.87, s, 1H, CH=N; 8.29, b, 2H,
NH; 8.71, d, J=5 Hz, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.71: 1.00–1.44, m, 12H, CH₃; 3.54 and 4.59, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.75–
4.30, m, 6H, 4H of N-CH₂ and 2H of N-CH; 5.32, d, J=5 Hz, 1H, β-lactam-H; 5.80, d,
35 J=55 Hz, 2H, CH₂F; 5.98, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.00, s, 1H, CH=N; 8.30,
b, 2H, NH; 9.53, b, 1H, NH; 9.86, d, J=8 Hz, 1H, NH; 10.39, b, 1H, NH; 10.78, b, 1H, NH

Ex.72: 1.19, d, J=7 Hz, 6H, CH₃; 3.53 and 4.55, AB-quartet, J=18 Hz, 2H, S-CH₂;
 3.65 – 4.02, m, 4H, N-CH₂; 4.15 – 4.32, m, 1H, N-CH; 5.29, d, J=5 Hz, 1H, β-
 lactam-H; 5.80, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H;
 5 7.85, s, 1H, CH=N; 8.28, b, 2H, NH; 9.83, d, J=8 Hz 1H, NH

Ex.73: 1.30 – 1.90, m, 6H, CH₂-C; 2.82 – 3.05, m, 2H, N-CH₂; 3.24 – 3.65, 5H, 4H
 of N-CH₂ and 1H of S-CH₂; 3.75 – 4.10, m, 6H, N-CH₂; 4.58, part of AB-quartet,
 J=18 Hz, 1H, S-CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.80, d, J=55 Hz, 2H, CH₂F;
 10 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.85, s, 1H, CH=N; 8.29, b, 2H, NH;
 9.84, d, J=8 Hz, 1H, β-lactam-H; 10.95, b, 1H, NH

Ex.74: 0.90, t, J=7 Hz, 3H, CH₃; 1.25 – 1.42, m, 2H, CH₂-C; 1.50 – 1.70, m, 2H,
 CH₂-C; 3.16, d, J=5 Hz, 3H, N-CH₃; 3.40 – 3.50, m, 2H, N-CH₂; 3.58 and 4.25, AB-
 15 quartet, J=18 Hz, 2H, S-CH₂; 3.70 – 4.12, m, 4H, N-CH₂; 5.29, d, J=5 Hz, 1H, β-
 lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H;
 7.87, s, 1H, CH=N; 8.29, b, 2H, NH; 8.69, d, J=5 Hz, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.75: 0.90, t, J=7 Hz, 3H, CH₃; 1.20–1.40, m, 2H, CH₂-C; 1.45–1.65, m, 2H, CH₂-C; 3.35 –
 20 3.50, m, 2H, N-CH₂; 3.53 and 4.55, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.70–4.10, m, 4H, N-
 CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz. and 8
 Hz, 1H, β-lactam-H; 7.85, s, 1H, CH=N; 8.29, b, 2H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.76: 1.30 – 1.90, m, 6H, CH₂-C; 2.85 – 3.08, m, 2H, N-CH₂; 3.20, d, J=5 Hz, 3H,
 25 N-CH₃; 3.30 – 3.70, m, 5H, 4H of N-CH₂ and 1H of S-CH₂; 3.75 – 4.10, m, 6H, N-
 CH₂; 4.21, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.28, d, J=5 Hz, 1H, β-lactam-H;
 5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.88, s, 1H,
 CH=N; 8.26, b, 2H, NH; 9.11, d, J=5 Hz, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.77: 1.78–2.10, m, 4H, CH₂-C; 3.00–3.20, m, 2H, N-CH₂; 3.40–3.65, m, 5H, 4H of N-
 30 CH₂ and 1H of S-CH₂; 3.80–4.10, m, 6H, N-CH₂; 4.59, part of AB-quartet, J=18 Hz, 1H,
 β-lactam-H; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.80, d, J=55 Hz, 2H, CH₂F; 5.93, dd, J=5 Hz
 and 8 Hz, 1H, β-lactam-H; 7.86, s, 1H, CH=N; 8.28, b, 2H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.78: 3.54 and 4.54, AB-quartet, $J=18$ Hz, 2H, S-CH₂; 3.62–4.18, m, 4H, N-CH₂; 4.34, s, 2H, N-CH₂; 5.33, d, $J=5$ Hz, 1H, β -lactam-H; 5.81, d, $J=55$ Hz, 2H, CH₂F; 5.96, dd, $J=5$ Hz and 8 Hz, 1H, β -lactam-H; 7.93, s, 1H, CH=N; 8.30, b, 2H, NH; 9.86, d, $J=8$ Hz, 1H, NH

5 Ex.79: 0.87, t, $J=7$ Hz, 3H, CH₃; 1.18 – 1.40, m, 4H, CH₂-C; 1.42 – 1.68, m, 2H, CH₂-C; 3.30 – 3.50, 2H, N-CH₂; 3.53 and 4.54, AB-quartet, $J=18$ Hz, 2H, S-CH₂; 3.70 – 4.10, m, 4H, N-CH₂; 5.30, d, $J=5$ Hz, 1H, β -lactam-H; 5.79, d, $J=55$ Hz, 2H, CH₂F; 5.94, dd, $J=5$ Hz and 8 Hz, 1H, β -lactam-H; 7.85, s, 1H, CH=N; 8.26, b, 2H, NH; 8.70, b, 2H, NH; 9.83, d, $J=8$ Hz, 1H, NH

10

Ex.80: 0.86, t, $J=7$ Hz, 3H, CH₃; 1.20 – 1.40, m, 6H, CH₂-C; 1.42 – 1.70, m, 2H, CH₂-C; 3.38 – 3.51, m, 2H, N-CH₂; 3.54 and 4.54, AB-quartet, $J=18$ Hz, 2H, S-CH₂; 3.70 – 4.10, m, 4H, N-CH₂; 5.30, d, $J=5$ Hz, 1H, β -lactam-H; 5.79, d, $J=55$ Hz, 2H, CH₂F; 5.93, dd, $J=5$ Hz and 8 Hz, 1H, β -lactam-H; 7.86, s, 1H, CH=N; 8.25, b, 2H, NH; 8.77, b, 2H, NH; 9.79, d, $J=8$ Hz, 1H, NH

15

Ex.81: 0.85, t, $J=7$ Hz, 3H, CH₃; 1.12 – 1.38, m, 8H, CH₂-C; 1.40 – 1.68, m, 2H, CH₂-C; 3.35 – 3.62, m, 3H, 2H of N-CH₂ and 1H of S-CH₂; 3.70 – 4.10, m, 4H, N-CH₂; 4.55, Part of AB-quartet, $J=18$ Hz, 1H, S-CH₂; 5.30, d, $J=5$ Hz, 1H, β -lactam-H; 5.79, d, $J=55$ Hz, 2H, CH₂F; 5.93, dd, $J=5$ Hz and 8 Hz, 1H, β -lactam-H; 7.85, s, 1H, CH=N; 8.27, b, 2H, NH; 9.84, d, $J=8$ Hz, 1H, NH

20

Ex.82: 3.50 – 3.78, m, 5H, 4H of N-CH₂ and 1H of S-CH₂; 4.00 – 4.48, m, 5H, 4H of N-CH₂ and 1H of S-CH₂; 5.32, d, $J=5$ Hz, 1H, β -lactam-H; 5.79, d, $J=55$ Hz, 2H, CH₂F; 5.94, dd, $J=5$ Hz and 8 Hz, 1H, β -lactam-H; 7.90, s, 1H, CH=N; 8.28, b, 2H, NH; 9.83, d, $J=8$ Hz, 1H, NH; 10.07, b, 1H, NH

25

Ex.83: 1.90 – 2.05, m, 2H, CH₂-C; 3.28 – 3.46, m, 4H, N-CH₂; 3.54 and 4.45, AB-quartet, $J=18$ Hz, 2H, S-CH₂; 3.68 – 4.10, m, 4H, N-CH₂; 5.31, d, $J=5$ Hz, 1H, β -lactam-H; 5.79, d, $J=55$ Hz, 2H, CH₂F; 5.94, dd, $J=5$ Hz and 8 Hz, 1H, β -lactam-H; 7.87, s, 1H, CH=N; 8.30, b, 2H, NH; 9.26, b, 1H, NH; 9.84, d, $J=8$ Hz, 1H, NH

30

Ex.84: 1.10 – 1.30, m, 12H, CH₃; 3.17, d, $J=5$ Hz, 3H, N-CH₃; 3.48 – 3.70, m, 3H, 2H of N-CH₂ and 1H of S-CH₂; 3.75 – 4.00, m, 4H, N-CH₂; 4.37, part of AB-quartet, $J=18$ Hz, 1H, S-CH₂; 5.32, d, $J=5$ Hz, 1H, β -lactam-H; 5.65, part of doublet, 1H,

35

CH₂F; 5.80 – 6.08, m, 4H, 1H of CH₂F and 1H of β-lactam-H and 2H of O-CH₂;
7.79,s,1H,CH=N;8.44,b,1H,NH;8.65,d,J=5 Hz,1H,NH;9.86,d,J=8 Hz,1H,NH

Ex.85: 1.21,t,J=7 Hz,3H,CH₃;3.14,s,6H,N-CH₃;3.30–3.55,q,J=7 Hz,2H,N-CH₂;
5 3.61,part of AB-quartet,J=18 Hz,1H,S-CH₂;3.70–4.20,m,5H,4H of N-CH₂ and 1H of
S-CH₂;5.28,d, J=5 Hz,1H, β-lactam-H;5.79,d,J=55 Hz,2H,CH₂F;5.95,dd,J=5 Hz and
8 Hz,1H,β-lactam-H;7.94,s,1H,CH=N;8.31,b,2H,NH;9.84,d,J=8 Hz,1H,NH

Ex.86: 3.12, s 3H, N-CH₃, 3.14, s, 6H, N-CH₃; 3.61, Part of AB-quartet, J=18 Hz,
10 1H, S-CH₂; 3.70 – 4.18, m, 5H, 4H of N-CH₂ and 1H of S-CH₂; 5.29, d, J=5 Hz, 1H,
β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H;
7.92, s, 1H, CH=N; 8.32, b, 2H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.87: 1.12–1.30,m,6H,CH₃;3.09,s,3H,N-CH₃;3.32–4.20,m,10H,8H of N-CH₂ and
15 2H of S-CH₂;5.28,d, J=5 Hz,1H,β-lactam-H;5.78,d,J=55 Hz,2H,CH₂F;5.95,dd, J=5
Hz and 8 Hz,1H,β-lactam-H;7.95,s,1H,CH=N;8.31,b,2H,NH;9.84,d,J=8 Hz, 1H,NH

Ex.88: 0.92, t, J=7 Hz, 3H, CH₃; 1.50 – 1.75, m, 2H, CH₂-C; 3.14, s, 6H, N-CH₃;
3.30 – 3.50, m, 2H, N-CH₂; 3.61, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 3.72 –
20 4.18, m, 5H, 4H of N-CH₂ and 1H of S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.80,
d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.94, s, 1H,
CH=N; 8.30, b, 2H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.89: 3.28, s, 3H, N-CH₃; 3.42 – 3.72, m, 5H, 4H of N-CH₂ and 1H of S-CH₂;
25 3.90 – 4.50, m, 5H, 4H of N-CH₂ and 1H of S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H;
5.80, d, J=55 Hz, 2H, CH₂F; 5.95, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.91, s, 1H,
CH=N; 8.30, b, 2H, NH; 9.85, d, J=8 Hz, 1H, NH

Ex.90: 1.90 – 2.12, m, 2H, CH₂-C; 3.20 – 3.60, m, 8H, 4H of N-CH₂ and 3H of N-
30 CH₃ and 1H of S-CH₂; 3.62 – 4.15, m, 5H, 4H of N-CH₂ and 1H of S-CH₂; 5.27, d,
J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz,
1H, β-lactam-H; 7.91, s, 1H, CH=N; 8.31, b, 2H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.91 (diaisostereomeric mixture): 1.20–1.40, m,3H,CH₃;3.30–3.65,m,2H,1H of N-
35 CH and 1H of S-CH₂;3.95–4.30,m,2H,N-CH₂;4.53,part of AB-quartet,J=18 Hz,1H,S-

CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.93, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.83, s, 1H, CH=N; 9.27, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.92 (diaisostereomeric mixture): 1.20 – 1.40, m, 3H, CH₃; 2.94, d, J=5 Hz, 3H, N-CH₃; 3.30 – 3.70, m, 2H, 1H of N-CH and 1H of S-CH₂; 3.90 – 4.30, m, 2H, N-CH₂; 4.49, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.31, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.83, s, 1H, CH=N; 8.30, b, 2H, NH; 8.65, d, J=5 Hz, 1H, NH; 9.84, d, J=8 Hz, 1H, NH

Ex.93: 1.32, d, J=6 Hz, 3H, CH₃; 1.70 – 1.98, m, 2H, CH₂-C; 2.75 – 2.98, m, 2H, N-CH₂; 3.25 – 3.65, m, 4H, 2H of N-CH₂ and 1H of N-CH and 1H of S-CH₂; 4.05 – 4.35, m, 2H, N-CH₂; 4.53, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.22, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.80, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.01, s, 1H, CH=N; 8.28, b, 2H, NH; 9.78, d, J=8 Hz, 1H, NH

15

Ex.94: 1.28, d, J=6 Hz, 3H, CH₃; 1.70 – 1.92, m, 2H, CH₂-C; 2.72 – 3.00, m, 2H, N-CH₂; 3.22 – 3.72, m, 4H, 2H of N-CH₂ and 1H of N-CH and 1H of S-CH₂; 3.90 – 4.35, m, 2H, N-CH₂; 4.49, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.19, d, J=5 Hz, 1H, β-lactam-H; 5.76, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 8.07, s, 1H, CH=N; 8.27, b, 2H, NH; 9.77, d, J=8 Hz, 1H, NH

20

Ex.95 (in CDCl₃/CD₃OD = 1/1): 1.46, s, 3H, CH₃; 1.48, s, 3H, CH₃; 3.55 and 4.32, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.71, AB-system, J=4 Hz and 10 Hz, 2H, N-CH₂; 5.18, d, J=5 Hz, 1H, β-lactam-H; 5.75, d, J=55 Hz, 2H, CH₂F; 5.94, d, J=5 Hz, 1H, β-lactam-H; 8.10, s, 1H, CH=N

25

Ex.96 (in CDCl₃/CD₃OD = 1/1): 1.46, s, 3H, CH₃; 1.48, s, 3H, CH₃; 2.84, s, 3H, N-CH₃; 3.56 and 4.36, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.76, b, 2H, N-CH₂; 5.19, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.92, d, J=5 Hz, 1H, β-lactam-H; 8.06, s, 1H, CH=N

30

Ex.97: 3.17, s, 3 H, N-CH₃; 3.58, s, 3 H, N-CH₃; 3.65 and 4.25, AB-quartet, J=18.2 Hz, 2H, S-CH₂; 5.28, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=58 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8.1 Hz, 1H, β-lactam-H; 7.05, d, J=2.8 Hz, 1H, imidazole-H; 7.61, d, J=2.8 Hz, 1H, imidazole-H; 8.61, s, 1H, CH=N; 9.90, d, J=8.1 Hz, 1H, NH

35

Ex.98 (in D₂O): 1.84,b,2H,CH₂-C;2.84,b,2H,N-CH₂;3.34,b,2H,N-CH₂;3.56 and 4.40,AB-quartet,J=18 Hz,2H, S-CH₂;3.68-4.10,m,4H,N-CH₂;5.13,d,J=5 Hz,1H, β-lactam-H;5.71,d,J=5 Hz,1H,β-lactam-H;6.64,s,1H,thiazole-H; 7.97, s, 1H, CH=N.

- 5 Ex.99 (in D₂O): 3.45-3.68,m,3H,2H of N-CH₂ and 1H of S-CH₂;3.70-4.10,m,4H, N-CH₂;4.40,part of AB-quartet,J=18 Hz,1H,S-CH₂;5.16,d,J=5 Hz, 1H, β-lactam-H; 5.75, d, J=5 Hz, 1H, β-lactam-H; 6.65, s, 1H, thiazole-H; 7.95, s, 1H, CH=N

- 10 Ex.100: 1.18,t,J=7 Hz,3H,CH₃;3.15,s,3H,N-CH₃;3.42-3.68,m,3H,2H of N-CH₂ and 1H of S-CH₂;3.70-4.10,m,4H,N-CH₂;4.25,part of AB-quartet,J=18 Hz,1H,S-CH₂; 5.12,d,J=5 Hz,1H,β-lactam-H,5.69,dd,J=5 Hz and 8 Hz,1H,β-lactam-H;6.65,s,1H, thiazole-H;7.14,b,2H,NH;8.14,s,1H,CH=N;8.42,b,1H,NH;9.45,d,J=8 Hz,1H,NH

- 15 Ex.101: 3.58 and 4.47, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.85 - 4.00, m, 2H, N-CH₂; 4.15 - 4.30, m, 2H, N-CH₂; 5.35, d, J=5 Hz, 1H, β-lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F; 5.98, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 7.37 - 7.56, m, 3H, CH-aromatic; 7.85 - 7.95, m, 2H, CH-aromatic; 7.99, s, 1H, aromatic-CH=N; 8.34, b, 2H, NH; 8.74, s, 1H, CH=N; 9.82, s, 1H, NH; 9.88, d, J=8 Hz, 1H, NH

- 20 Ex.102: 3.45-3.97, m, 9H, 6H of N-CH₂ and 2H of O-CH₂ and 1H of S-CH₂; 4.43, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.32, d, J=5 Hz; 1H, β-lactam-H;5.8, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.62, s, 1H, CH=N; 8.81, s, 1H, NH; 9.86, d, 1H, NH

- 25 Ex.103: 3.51 and 4.36, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.71, b, 4H, N-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.95, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.26, b, 2H, 1H of CH=N and 1H NH; 9.83, d, J=8 Hz, 1H, NH.

- 30 Ex.104: 1.90, m, 2H, CH₂-C; 3.33, b, 4H, N-CH₂; 3.50 and 4.45, AB-quartet, J=18 Hz, 2H, S-CH₂; 5.28, d, J=5 Hz, 1H, β-lactam-H; 5.77, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.30, b, 3H, 1H of CH=N and 2H of NH; 8.42, b, 2H, NH; 9.85, d, J= 8 Hz, 1H, NH

- 35 Ex.105: 3.11, b, 2H, N-CH₂; 3.51 and 4.39, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.60 - 3.95, m, 6H, N-CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.77, d, J=55 Hz, 2H,

CH₂F; 5.96, dd, 5 Hz and 8 Hz, 1H, β-lactam-H; 8.12, b, 2H, NH; 8.28, b, 2H, 1H of NH and 1H of CH=N; 8.70, b, 2H, NH; 9.82, d, J=8 Hz, 1H, NH

Ex.106: 3.56 and 4.45, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.75-4.25, m, 4H, N-CH₂; 4.30, s, 3H, CH₃; 5.33, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.98, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.18, s, 1H, pyrid.-CH=N; 8.30, b, 2H, NH; 8.66 and 9.07, m, each 2H, CH-aromatic; 8.95, s, 1H, CH=N; 9.85, d, J=8 Hz, 1H, NH

Ex.107: 3.15, s, 6H, N-CH₃; 3.55-3.82, m, 5H, 4H of N-CH₂ and 1H of S-CH₂; 3.95, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F; 5.92, dd, J=5 and 8 Hz, 1H, β-lactam-H; 8.73, s, 1H, CH=N; 9.87, d, J=8 Hz, 1H, NH.

Ex.108: 1.12, t, J=7 Hz, 3H, CH₃; 3.42, q, J=7 Hz, 2H, N-CH₂; 3.51 and 4.38, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.60-3.90, m, 4H, N-CH₂; 5.32, d, J=5 Hz, 1H, β-lactam-H; 5.81, d, J=55 Hz, 2H, CH₂F; 5.95, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.31, b, 2H, NH; 8.64, s, 1H, CH=N; 8.80, b, 1H, NH; 9.86, d, J=8 Hz, 1H, NH; 12.83, s, 1H, OH

Ex.109: 2.98, s, 3H, N-CH₃; 3.51 and 4.38, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.60-3.88, m, 4H, N-CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 8.30, b, 2H, NH; 8.61, s, 1H, CH=N; 8.79, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH; 12.83, s, 1H, OH

Ex.110: 0.87, t, J=7 Hz, 3H, CH₃; 1.45-1.70, m, 2H, CH₂-C; 3.25-3.40, m, 2H, N-CH₂; 3.51 and 4.39, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.60-3.90, m, 4H, N-CH₂; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.28, b, 2H, NH; 8.61, s, 1H, CH=N; 8.77, b, 1H, NH; 9.84, d, J=8 Hz, 1H, NH; 12.76, s, 1H, OH

Ex.111: 1.00-1.32, m, 6H, CH₃; 3.51 and 4.39, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.60-3.90, m, 4H, N-CH₂; 4.08-4.30, m, 1H, N-CH; 5.30, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and J=8 Hz, 1H, β-lactam-H; 8.32, b, 2H, NH; 8.66, s, 1H, CH=N; 8.78, b, 1H, NH; 9.86, d, J=8 Hz, 1H, NH; 12.84, s, 1H, OH

Ex.112: 1.16, d, 12H, CH₃; 3.40-3.90, m, 6H, 4H of N-CH₂ and 2H of S-CH₂; 4.67, h, 2H, N-CH; 5.21, d, J=5 Hz, 1H, β-lactam-H; 5.82, d, J=55 Hz, 2H, CH₂F; 5.84, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.26, b, 2H, NH; 8.54, s, 1H, CH=N; 9.80, d, J=8 Hz, 1H, NH

Ex.113 (diaisostereomeric mixture): 1.27, d, J=6 Hz, 3H, CH₃; 3.20 – 3.38, m, 1H, N-CH; 3.52 and 4.37, AB-quartet, J=18 Hz, 2H, S-CH₂; 3.75 – 3.92, m, 1H, 1H of N-CH₂; 4.08 – 4.30, m, 1H, 1H of N-CH₂; 5.29, d, J=5 Hz, 1H, β-lactam-H; 5.79, d, J=55 Hz, 2H, CH₂F; 5.93, dd, J=5 Hz and 8 Hz, 1H, β-lactam-H; 8.29, b, 2H, NH; 8.38, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

Ex.114: 3.52 and 4.42, AB-quartet, J=18.2 Hz, 2H, S-CH₂; 3.79, s, 3H, O-CH₃; 3.83 and 4.02, q, 1H, J=5.5 Hz and 10.0 Hz and broad triplet, 1H, J=10.4 Hz, N-CH₂; 4.79, q, 1H, J=5.5 Hz and 10.4 Hz, N-CH; 5.32, d, J=5 Hz, 1H, β-lactam-H; 5.80, d, J=58 Hz, 2H, CH₂F; 5.94, dd, J=5 Hz and 8.2 Hz, 1H, β-lactam-H; 8.44, s, 1H, CH=N; 9.87, d, J=8.2 Hz, 1H, NH.

Ex.115: 3.4 – 3.9, m, 5H, 1H of NCH and 1H of NCH₂ and 2H of O-CH₂ and 1H of SCH₂, 4.40, m, 1H, N-CH₂; 4.43, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.31 d, J=4.6 Hz, 1H, β-lactam-H; 5.80, d, J=55 Hz, 2H, CH₂F; 5.94, dd, J=4.6 Hz and 8.1 Hz, 1H, β-lactam-H; 8.40, s, 1H, CH=N; 9.86, d, J=8.1 Hz, 1H, NH

Ex.116 (in D₂O): 3.11, s, 3H, N-CH₃; 3.28, s, 3H, N-CH₃; 3.58 - 3.71, m, 3H, 2H of N-CH₂ and 1H of S-CH₂; 3.78 - 3.89, m, 2H, N-CH₂; 3.96, s, 3H, O-CH₃; 3.97, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.22, d, J=5 Hz, 1H, β-lactam-H; 5.76, d, J=5 Hz, 1H, β-lactam-H; 7.04, s, 1H, thiazole-H; 7.98, s, 1H, CH=N

Ex.117 (in D₂O): 3.10, s, 3H, N-CH₃; 3.29, s, 3H, N-CH₃; 3.50 - 3.72, m, 3H, 2H of N-CH₂ and 1H of S-CH₂; 3.75 - 3.89, m, 2H, N-CH₂; 3.97, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.22, d, J=5 Hz, 1H, β-lactam-H; 5.78, d, J=5 Hz, 1H, β-lactam-H; 7.02, s, 1H, thiazole-H; 7.98, s, 1H, CH=N

Ex.118 (in DMSO-d₆/D₂O): 3.12, s, 3H, N-CH₃; 3.30, s, 3H, N-CH₃; 3.52 - 3.72, m, 3H, 2H of N-CH₂ and 1H of S-CH₂; 3.76 - 3.91, m, 2H, N-CH₂; 4.01, part of AB-quartet, J=18 Hz, 1H, S-CH₂; 5.22, d, J=5 Hz, 1H, β-lactam-H; 5.77, d, J=55 Hz, 2H, CH₂F; 5.83, d, J=5 Hz, 1H, β-lactam-H; 8.06, s, 1H, CH=N

Ex.119: 3.31, b, 4H, N-CH₂-piperazine; 3.52 - 4.30, m, 10H, 4H of N-CH₂-piperazine and 4H of N-CH₂-imidazole and 2H of S-CH₂; 5.29, d, J=5 Hz, 1H, β-

lactam-H; 5.82, d, $J=55$ Hz, 2H, CH_2F ; 5.90, dd, $J=5$ Hz and $J=8$ Hz, 1H, β -lactam-H; 7.98, s, 1H, $\text{CH}=\text{N}$; 8.30, b, 2H, NH; 9.82, d, $J=8$ Hz, 1H, NH

Ex.120: (diastereomeric mixture): 1.15–1.60, m, 4H, $\text{CH}_2\text{-C}$; 1.62–1.85, m, 2H, $\text{CH}_2\text{-C}$;
 5 1.88 – 2.22, m, 2H, $\text{CH}_2\text{-C}$; 3.20 – 3.40, m, 2H, N-CH; 3.52 and 4.31 bzw. 3.55 and 4.39, AB-quartet, $J=18$ Hz, 2H, S- CH_2 ; 5.31, d, $J=5$ Hz, 1H, β -lactam-H; 5.78, d, $J=55$ Hz, 2H, CH_2F ; 5.94, dd, $J=5$ Hz and 8 Hz, 1H, β -lactam-H; 8.28, b, 2H, NH; 8.41, s, 1H, $\text{CH}=\text{N}$; 8.78, b, 1H, NH; 9.15, b, 1H, NH; 9.84, d, $J=8$ Hz, 1H, NH

10 Ex. A: 3.38 - 3.58 and 3.60 - 3.80, m, 4H, N- CH_2

Ex. B (in CDCl_3): 3.60 - 3.75 and 3.76 - 3.92, m, 4H, N- CH_2 ; 7.22 - 7.48, m, 4H, 3H of CH-aromatic and 1H of $\text{CH}=\text{N}$; 7.52 - 7.68, m, 2H, CH-aromatic

15 Ex. C: 1.39, b, 9H, CH_3 ; 2.98-3.20 and 3.22-3.40 and 3.42-3.55 and 3.57-3.78, m, 8H, N- CH_2

Ex. D (in D_2O): 0.80, t, $J=7$ Hz, 3H, CH_3 ; 1.53, hex, $J=7$ Hz, 2H, $\text{CH}_2\text{-C}$; 2.99, s, 3H, N- CH_3 ; 3.25, t, $J=7$ Hz, 2H, N- CH_2 ; 3.40 – 3.65, m, 4H, N- CH_2

20

Ex. E (in D_2O): 0.79, t, $J=7$ Hz, 3H, CH_3 ; 1.52, hex, $J=7$ Hz, 2H, $\text{CH}_2\text{-C}$; 2.97, s, 6H, N- CH_3 ; 3.15, t, $J=7$ Hz, 2H, N- CH_2 ; 3.48 – 3.75, m, 4H, N- CH_2

Ex. F (in D_2O): 1.68 – 1.90, m, 2H, $\text{CH}_2\text{-C}$; 3.08 – 3.32, m, 4H, N- CH_2 ; 3.42 – 3.70, m, 4H, N- CH_2

25

Ex. G (in D_2O): 1.70 – 1.90, m, $\text{CH}_2\text{-C}$; 2.73, s, 6H, N- CH_3 ; 3.10 – 3.30, m, 4H, N- CH_2 ; 3.40 – 3.70, m, 4H, N- CH_2

30 Ex. H (in D_2O): 1.21, d, $J=7$ Hz, 12H, CH_3 ; 3.70 – 3.96, m, 4H, N- CH_2 ; 3.98 – 4.18, m, 2H, N-CH

Ex. I (in D_2O): 3.28 – 3.48, m, 4H, N- CH_2 ; 3.82 – 4.00, m, 4H, N- CH_2

35 Ex. J (in CDCl_3): 3.12, s, 3H, N- CH_3 ; 3.57, s, 3H, N- CH_3 ; 6.95 and 6.99, AB-quartet, $J=2$ Hz, 2H, N-CH

Ex. K (in D₂O): 3.30-3.60, m, 3H, 2H of O-CH₂ and 1H v N-CH₂; 3.78, t, J=10 Hz, 1H, N-CH₂; 4.14, m, 1H, N-CH

- 5 Ex. L: 3.61, q, J=5.4 Hz and 10.3 Hz, 1H, N-CH; 3.87, s, 3H, O-CH₃, 4.10, t, J=10.3 Hz, 1H, N-CH₂; 4.56, q, J=5.4 Hz and 10.6 Hz, 1H, N-CH₂

Ex. M: 3.33-3.50, m, 5H, 3H of N-CH₃ and 2H of N-CH₂; 3.66-3.78, m, 2H, N-CH₂

- 10 Ex. N: 3.40 - 3.64 and 3.66 - 3.92, m, 4H, N-CH₂; 6.75 - 6.92, m, 3H, CH-aromatic; 7.15 - 7.40, m, 2H, CH-aromatic

Ex. O: 2.85, d, J=5 Hz, 3H, CH₃; 3.40 - 3.56 and 3.58 - 3.72, m, 4H, N-CH₂; 8.18, d, J=5 Hz, 1H, NH

15

Ex. P (in D₂O): 3.41 - 3.81, m, 16H, 8H of N-CH₂-piperazine and 4H of N-CH₂-imidazole and 4H of N-CH₂

- 20 Ex. Q: 3.35 - 3.58, m, 4H, N-CH₂-imidazole; 3.60 - 3.72, m, 4H, 2H of N-CH₂ and 2H of O-CH₂; 7.14, b, 2H, NH₂

Ex. R: 1.24, t, J=7 Hz, 3H, CH₃; 2.85 - 3.15, m, 4H, N-CH₂; 3.42 - 3.78, m, 6H, 4H of N-CH₂-imidazole and 2H of N-CH₂; 8.30, t, J=6 Hz, 1H, NH; 9.20, b, 1H, NH; 9.46, b, 2H, NH₂

25

Ex. S (in D₂O): 2.87, s, 6H, CH₃; 3.28 - 3.40, m, 2H, N-CH₂; 3.51 - 3.75, m, 6H, 4H of N-CH₂-imidazole and 2H of N-CH₂

- 30 Ex. T (in D₂O): 3.08 - 3.26, m, 2H, N-CH₂; 3.43 - 3.76, m, 6H, 4H of N-CH₂-imidazole and 2H of N-CH₂

Ex. U: 2.68 - 2.91, m, 2H, N-CH₂; 3.30 - 3.76, m, 6H, 4H of N-CH₂-imidazole and 2H of O-CH₂

- 35 Ex. V (in D₂O): 1.78 - 2.00, m, 2H, CH₂-C; 2.89 - 3.14, m, 2H, N-CH₂; 3.25 - 3.32, m, 2H, N-CH₂; 3.45 - 3.71, m, 4H, N-CH₂-imidazole

Ex. W (in D₂O): 3.07 - 3.29, m, 4H, N-CH₂; 3.45 - 3.69, m, 6H, 4H of N-CH₂-imidazole and 2H of N-CH₂; 3.70 - 3.79, m, 2H, O-CH₂

5 Ex. X (in D₂O): 3.15 - 3.80, m, 20H, N-CH₂ and O-CH₂

Ex. Y (in D₂O): 1.20 - 1.50, m, 2H, CH₂-C; 1.72 - 2.00, m, 3H, CH₂-C and CH-C; 2.71 - 3.72, m, 10H, N-CH₂

10 Ex. Z: 3.12 - 3.41, m, 2H, N-CH₂; 3.43 - 3.90, m, 6H, N-CH₂; 7.88 - 8.08, m, 1H, pyr.-H; 8.10 - 8.20, m, 1H, CH-aromatic; 8.40, b, 1H, NH; 8.50 - 8.68, m, 1H, CH-aromatic; 8.71 - 8.90, m, 1H, CH-aromatic; 9.38, b, 1H, NH

15 Ex. AA: 3.28-3.72,m,12H,N-CH₂ and O-CH₂;8.09,t,J=6 Hz,1H,NH,8.86,b,1H,NH

Ex. AB (in D₂O): 3.40 - 3.78, m, 4H, N-CH₂-imidazole

Ex. AC: 2.66 - 2.90, m, 4H, O-CH₂; 3.38 - 3.88, m, 8H, N-CH₂

20 Ex. AD (in D₂O): 1.46 - 1.76, m, 4H, C-CH₂-C; 2.82 - 3.02, m, 2H, N-CH₂; 3.08 - 3.30, m, 2H, N-CH₂; 3.40 - 3.74, m, 4H, N-CH₂-imidazole

Ex. AE: 3.20 - 3.40, m, 2H, N-CH₂; 3.42 - 3.78, m, 6H, N-CH₂-imidazole and O-CH₂; 8.14, t, J=6 Hz, 1H, NH; 8.99, b, 1H, NH

25

Ex. AF (in D₂O): 1.13 - 1.38, m, 4H, CH₂-C; 1.40 - 1.68, m, 4H, CH₂-C; 2.78 - 2.98, m, 2H, N-CH₂; 3.02 - 3.22, m, 2H, N-CH₂; 3.40 - 3.68, m, 4H, N-CH₂-imidazole

Ex. AG (in D₂O): 1.22, d, J=6 Hz, 3H, CH₃; 3.25 - 3.75, m, 7H, N-CH₂ and N-CH

30

Ex. AH: 2.95 - 4.18, m, 16H, N-CH₂ and O-CH₂; 8.43, b, 1H, NH; 9.42, b, 1H, NH

Ex. AI (in D₂O): 1.37, s, 6H, CH₃; 3.48, s, 2H, N-CH₂; 3.50 - 3.95, m, 4H, N-CH₂-imidazole; 7.35 - 7.51, m, 3H, CH-aromatic; 7.66, s, 1H, CH=N; 7.70 - 7.82, m, 2H,

35 CH-aromatic

Ex. AJ (in DMSO- d_6 /D₂O): 4.00 - 4.22 and 4.28 - 4.48, m, 4H, N-CH₂; 4.53, s, 3H, CH₃; 8.14, s, 1H, CH=N; 8.48 - 8.62 and 8.92 - 9.10, m, 4H, CH-aromatic

- 5 Ex. AK (in D₂O): 2.87, s, 3H, CH₃; 2.90 - 3.80, m, 12H, 8H of N-CH₂-piperazine and 4H of N-CH₂-imidazole

Ex. AL: 0.58-0.82, m, 4H, CH₂-C; 2.55-2.72, m, 1H, CH-C; 3.50-3.82, m, 4H, N-CH₂

- 10 Ex. AM: 1.10, t, J=7 Hz, 3H, CH₃; 3.27, p, J=7 Hz, 2H, N-CH₂; 3.42 - 3.78, m, 4H, N-CH₂; 8.30, t, J=7 Hz, 1H, NH; 9.06, b, 1H, NH

Ex. AN: 0.86, t, J=7 Hz, 3H, CH₃; 1.48, h, J=7 Hz, 2H, CH₂; 3.16, p, J=7 Hz, 2H, N-CH₂; 3.40 - 3.72, m, 4H, N-CH₂; 8.30, t, J=7 Hz, 1H, NH; 9.03, b, 1H, NH

15

Ex. AO (in D₂O): 3.08, t, J=5 Hz, 2H, N-CH₂; 3.33, t, J=5 Hz, 2H, N-CH₂; 3.42 - 3.71, m, 12H, 4H of N-CH₂ and 8H of O-CH₂

- 20 Ex. AP (in D₂O): 1.89, p, J=7.5 Hz, 2H, CH₂; 2.61, s, 3H, N-CH₃; 3.00, t, J=7.5 Hz, 2H, N-CH₂; 3.25, t, J=7.5 Hz, 2H, N-CH₂; 3.42 - 3.72, m, 4H, N-CH₂

Ex. AQ (in D₂O): 1.89, p, J=7.5 Hz, 2H, CH₂; 2.92 - 3.15, m, 4H, N-CH₂; 3.23, t, J=7.5 Hz, 2H, N-CH₂; 3.42 - 3.68, m, 4H, N-CH₂; 3.71, t, J=5 Hz, 2H, O-CH₂

- 25 Ex. AR (in D₂O): 1.82 - 2.02, m, 2H, CH₂; 2.79, s, 6H, N-CH₃; 3.04 - 3.18, m, 2H, N-CH₂; 3.24, t, J=7 Hz, 2H, N-CH₂; 3.43 - 3.69, m, 4H, N-CH₂

Ex. AS (in D₂O): 1.84, p, J=6 Hz, 2H, CH₂; 3.13 - 3.43, m, 8H, 6H of N-CH₂ and 2H of O-CH₂; 3.68 - 3.84, m, 4H, N-CH₂

30

Ex. AT (in D₂O): 1.85-2.12, m, 2H, CH₂; 2.64, s, 3H, CH₃; 2.95 - 3.12, m, 2H, N-CH₂; 3.30 - 3.42, m, 2H, N-CH₂; 3.50 - 3.78, m, 8H, 6H of N-CH₂ and 2H of O-CH₂

- 35 Ex. AU (in D₂O): 1.84 - 2.08, m, 2H, CH₂; 2.98 - 3.18, m, 4H, N-CH₂; 3.30 - 3.42, m, 2H, N-CH₂; 3.48 - 3.82, m, 10H, 6H of N-CH₂ and 4H of O-CH₂

- Ex. AV (in D₂O): 1.95-2.20, m, 2H, CH₂; 2.88, s, 6H, N-CH₃; 3.12-3.28, m, 2H, N-CH₂; 3.38 - 3.50, m, 2H, N-CH₂; 3.58 - 3.83, m, 8H, 6H of N-CH₂ and 2H of O-CH₂
- 5 Ex. AW (in D₂O): 2.67, s, 6H, N-CH₃; 3.49-3.80, m, 8H, 6H of N-CH₂ and 2H of O-CH₂
- Ex. AX (in D₂O): 1.69, p, J=7 Hz, 2H, CH₂-C; 3.19, t, J=7 Hz, 2H, N-CH₂; 3.40 - 3.64, m, 6H, 4H of N-CH₂ and 2H of O-CH₂
- 10 Ex. AY (in D₂O): 3.03, s, 3H, N-CH₃; 3.48, t, J=5 Hz, 2H, N-CH₂; 3.52 - 3.62, m, 4H, N-CH₂; 3.70, t, J=5 Hz, 2H, O-CH₂
- Ex. AZ (in D₂O): 2.70 - 3.40, m, 4H, N-CH₂; 3.42 - 3.75, m, 4H, N-CH₂; 3.85 - 4.10, m, 1H, O-CH
- 15 Ex. BA (in D₂O): 3.20 - 3.75, m, 16H, N-CH₂
- Ex. BB (in D₂O): 1.10, t, J=7 Hz, 3H, CH₃; 3.30 - 3.80, m, 10H, 8H of N-CH₂ and 2H of O-CH₂
- 20 Ex. BC (in D₂O): 1.78 - 2.18, m, 4H, CH₂-C; 2.85 - 3.18, m, 6H, N-CH₂; 3.20 - 3.38, m, 2H, N-CH₂; 3.40 - 3.78, m, 4H, N-CH₂
- Ex. BD (in D₂O): 1.20 - 1.60, m, 4H, CH₂-C; 1.80 - 2.20, m, 4H, CH₂-C; 2.98 - 3.40, m, 2H, N-CH; 3.42 - 3.72, m, 4H, N-CH₂
- 25 Ex. BE (in D₂O): 1.05, t, J=7 Hz, 3H, CH₃; 3.22, q, J=7 Hz, 2H, N-CH₂; 3.40 - 3.68, m, 4H, N-CH₂
- 30 Ex. BF (in D₂O): 3.06 - 3.34, m, 2H, N-CH₂; 3.36 - 3.66, m, 6H, 4H of N-CH₂ and 2H of O-CH₂; 3.68 - 3.82, m, 1H, O-CH
- Ex. BG (in D₂O): 1.07, t, J=7 Hz, 3H, CH₃; 2.98, s, 3H, N-CH₃; 3.34, q, J=7 Hz, 2H, N-CH₂; 3.42 - 3.58, m, 4H, N-CH₂
- 35

Ex. BH (in D₂O): 1.05, t, J=7 Hz, 3H, CH₃; 1.88 – 2.12, m, 2H, CH₂-C; 2.78, s, 6H, N-CH₃; 2.98 – 3.35, m, 4H, N-CH₂; 3.40 – 3.70, m, 6H, N-CH₂

Ex. BI (in D₂O): 1.22, t, J=7 Hz, 3H, CH₃; 1.72 – 1.95, m, 2H, CH₂-C; 2.95 – 3.18, m, 2H, N-CH₂; 3.20 – 3.40, m, 6H, N-CH₂; 3.60 – 3.80, m, 2H, N-CH₂

Ex. BJ (in D₂O): 1.10, t, J=7 Hz, 3H, CH₃; 1.25 – 1.60, m, 4H, CH₂-C; 1.82 – 2.20, m, 4H, CH₂-C; 3.00 – 3.20, m, 1H, N-CH; 3.29, q, J=7 Hz, 2H, N-CH₂; 3.42 – 3.68, m, 4H, N-CH₂; 3.85 – 4.10, m, 1H, N-CH

10

Ex. BK (in D₂O): 1.25 – 1.60, m, 4H, CH₂-C; 1.85 – 2.20, m, 4H, CH₂-C; 2.96 – 3.25, m, 1H, N-CH; 3.30 – 3.40, m, 2H, N-CH₂; 3.50 – 3.78, m, 6H, 4H of N-CH₂ and 2H of O-CH₂; 4.02 – 4.22, m, 1H, N-CH

Ex. BL (in D₂O): 1.65 – 1.95, m, 2H, CH₂-C; 3.05 – 3.38, m, 8H, N-CH₂; 3.40 – 3.82, m, 8H, N-CH₂

Ex. BM (D₂O): 2.84, s, 3H, N-CH₃; 3.40 – 3.65, m, 4H, N-CH₂

Ex. BN (in D₂O): 2.98, s, 3H, N-CH₃; 3.0, s, 3H, N-CH₃; 3.42 – 3.58, m, 4H, N-CH₂

Ex. BO (in D₂O): 1.13, t, J=7 Hz, 3H, CH₃; 2.96, s, 3H, N-CH₃; 3.40 – 3.60, m, 6H, N-CH₂

Ex. BP (D₂O): 1.25 – 1.60, m, 4H, CH₂-C; 1.85 – 2.18, m, 4H, CH₂-C; 2.93, s, 3H, N-CH₃; 3.02 – 3.25, m, 1H, N-CH; 3.40 – 3.68, m, 4H, N-CH₂; 3.88 – 4.10, m, 1H, N-CH

25

Ex. BQ (D₂O): 2.95, s, 3H, N-CH₃; 3.42 – 3.70, m, 8H, 6H of N-CH₂ and 2H of O-CH₂

Ex. BR (D₂O): 3.25 – 3.82, m, 12H, 8H of N-CH₂ and 4H of O-CH₂

30

Ex. BS (D₂O): 1.22, t, J=7 Hz, 6H, CH₃; 3.10 – 3.28, m, 4H, N-CH₂; 3.30 – 3.42, m, 2H, N-CH₂; 3.50 – 3.75, m, 6H, N-CH₂

Ex. BT (in D₂O): 1.88 – 2.08, m, 2H, CH₂-C; 2.83, s, 6H, N-CH₃; 3.05 – 3.20, m, 2H, N-CH₂; 3.25 – 3.38, m, 2H, N-CH₂; 3.46 – 3.70, m, 4H, N-CH₂

35

- Ex. BU (in D₂O): 1.20, t, J=7 Hz, 6H, CH₃; 3.22, q, J=7 Hz, 4H, N-CH₂; 3.26 – 3.38, m, 2H, N-CH₂; 3.48 – 3.74, m, 6H, N-CH₂
- 5 Ex. BV (in D₂O): 1.24, t, J=7 Hz, 6H, CH₃; 3.07, s, 3H, N-CH₃; 3.12–3.92, m, 12H, N-CH₂
- Ex. BW (in D₂O): 2.87, s, 6H, N-CH₃; 3.30 – 3.48, m, 2H, N-CH₂; 3.50 – 3.78, m, 6H, N-CH₂
- 10 Ex. BX (in D₂O): 3.55 – 3.82, m, 4H, N-CH₂; 5.00, s, 2H, O-CH₂; 7.10, s, 1H, CH; 7.99, s, 1H, CH
- Ex. BY (in D₂O): 1.10 – 1.54, m, 4H, CH₂-C; 1.56 – 1.84, m, 2H, CH₂-C; 1.86 – 2.18, m, 2H, CH₂-C; 3.10 – 3.46, m, 2H, N-CH; 3.48 – 3.70, m, 4H, N-CH₂
- 15 Ex. BZ (in D₂O): 0.79, t, J=7 Hz, 3H, CH₃; 1.51, hex, J=7 Hz, 2H, CH₂-C; 3.15, t, J=7 Hz, 2H, N-CH₂; 3.40 – 3.70, m, 4H, N-CH₂
- Ex. CA (in D₂O): 1.11, d, J=7 Hz, 6H, CH₃; 3.40 – 3.62, m, 4H, N-CH₂; 3.72 – 3.92, m, 1H, N-CH
- 20 Ex. CB (in D₂O): 1.22 – 2.00, m, 6H, CH₂-C; 2.80 – 3.08, m, 2H, N-CH₂; 3.20 – 3.82, m, 10H, N-CH₂
- 25 Ex. CC (in D₂O): 0.80, t, J=7 Hz, 3H, CH₃; 1.10–1.38, m, 2H, CH₂-C; 1.40–1.58, m, 2H, CH₂-C; 3.00, s, 3H, N-CH₃; 3.20 – 3.38, m, 2H, N-CH₂; 3.40 – 3.68, m, 4H, N-CH₂
- Ex. CD (in D₂O): 0.80, t, J=7 Hz, 3H, CH₃; 1.08 – 1.32, m, 2H, CH₂-C; 1.36 – 1.62, m, 2H, CH₂-C; 3.08 – 3.30, m, 2H, N-CH₂; 3.40 – 3.70, m, 4H, N-CH₂
- 30 Ex. CE (in D₂O): 1.10 – 1.90, m, 6H, CH₂-C; 2.78 – 3.04, m, 5H, 2H of N-CH₂ and 3H of N-CH₃; 3.20 – 3.90, m, 10H, N-CH₂
- Ex. CF (in D₂O): 1.75 – 2.22, m, 4H, CH₂-C; 2.92 – 3.18, m, 2H, N-CH₂; 3.32 – 3.48, m, 2H, N-CH₂; 3.48 – 3.78, m, 8H, N-CH₂
- 35

- Ex. CG (D₂O): 3.48 – 3.72, m, 4H, N-CH₂; 4.11, s, 2H, CH₂
- Ex. CH (D₂O): 0.79, t, J=7 Hz, 3H, CH₃; 1.08 – 1.40, m, 4H, CH₂-C; 1.42 – 1.68, m,
 5 2H, CH₂-C; 3.10 – 3.32, m, 2H, N-CH₂; 3.40 – 3.70, m, 4H, N-CH₂
- Ex. CI (D₂O): 0.75, t, J=7 Hz, 3H, CH₃; 1.08 – 1.32, m, 6H, CH₂-C; 1.48 – 1.60, m,
 2H, CH₂-C; 3.10 – 3.25, m, 2H, N-CH₂; 3.40 – 3.68, m, 4H, N-CH₂
- 10 Ex. CJ (D₂O): 0.90, t, J=7 Hz, 3H, CH₃; 1.20 – 1.48, m, 8H, CH₂-C; 1.52 – 1.75, m
 2H, CH₂-C; 3.25 – 3.40, m, 2H, N-CH₂; 3.52 – 3.80, m, 4H, N-CH₂
- Ex. CK (D₂O): 1.80 – 2.02, m, 2H, CH₂-C; 3.10 – 3.38, m, 4H, N-CH₂; 3.40 – 3.65,
 m, 4H, N-CH₂
- 15 Ex. CL (in D₂O): 1.09, t, J=7 Hz, 3H, CH₃; 2.98, s, 6H, N-CH₃; 3.26, q, J=7 Hz, 2H,
 N-CH₂; 3.48 – 3.75, m, 4H, N-CH₂
- Ex. CM (in D₂O): 2.90, s, 3H, N-CH₃; 2.99, s, 6H, N-CH₃; 3.45 – 3.75, m, 4H, N-CH₂
- 20 Ex. CN (in D₂O): 1.00 – 1.22, m, 6H, CH₃; 2.94, s, 3H, N-CH₃; 3.12 – 3.45, m, 4H,
 N-CH₂; 3.50 – 3.72, m, 4H, N-CH₂
- Ex. CO (in D₂O): 3.1, s, 3H, N-CH₃; 3.20 – 3.42, m, 4H, N-CH₂; 3.75 – 4.02, m, 4H, N-CH₂
- 25 Ex. CP (in D₂O): 1.72 – 2.02, m, 2H, CH₂-C; 2.95 – 3.30, m, 7H, 3H of N-CH₃ and
 4H of N-CH₂; 3.32 – 3.70, m, 4H, N-CH₂
- Ex. CQ (in D₂O): 1.17, d, J=6 Hz, 3H, CH₃; 2.75, s, 3H, N-CH₃; 3.05 – 3.28, m, 1H,
 30 N-CH; 3.60 – 4.10, m, 2H, N-CH₂
- Ex. CR (in D₂O): 1.17, d, J=6 Hz, 3H, CH₃; 3.12 – 3.30, m, 1H, N-CH; 3.68 – 4.05,
 m, 2H, N-CH₂
- 35 Ex. CS (in D₂O): 1.2, d, J=6 Hz, 3H, CH₃; 1.72 – 2.12, m, 2H, CH₂-C; 2.88 – 3.10, m, 2H, N-
 CH₂; 3.12 – 3.45, m, 3H, 2H of N-CH₂ and 1H of N-CH; 3.68 – 4.15, m, 2H, N-CH₂

Ex. CT (in $\text{CDCl}_3/\text{CD}_3\text{OD} = 1/1$): 1.40, s, 6H, CH_3 ; 2.90, s, 3H, N- CH_3 ; 3.58, s, 2H, N- CH_2

5 Ex. CU (in $\text{CDCl}_3/\text{CD}_3\text{OD} = 1/1$): 1.40, s, 6H, CH_3 ; 3.54, s, 2H, N- CH_2

Ex. CV: 0.84, t, $J=7$ Hz, 3H, CH_3 ; 1.49, hex, $J=7$ Hz, 2H, $\text{CH}_2\text{-C}$; 3.16, t, $J=7$ Hz, 2H, N- CH_2 ; 3.42 – 3.72, m, 4H, N- CH_2

10 Ex. CW (in D_2O): 1.14, d, $J=7$ Hz, 6H, CH_3 ; 3.50 – 3.92, m, 5H, 4H of N- CH_2 and 1H of N-CH

Ex. CX: 1.12, d, 12H, CH_3 ; 3.50, b, 4H, N- CH_2 ; 4.88, h, 2H, N-CH

15 Ex. CY: 3.17, b, 4H, N- CH_2 -piperazine; 3.40 - 3.58 and 3.68 - 3.88, m, 4H, N- CH_2 -imidazole; 3.98, b, 4H, N- CH_2 ; 9.16, b, 1H, NH; 10.01, b, 2H, NH_2

Ex. CZ (in D_2O): 3.05, s, 3H, N- CH_3 ; 3.20, s, 3H, N- CH_3 ; 3.45 - 3.54, m, 2H, N- CH_2 ; 3.66 - 3.76, m, 2H, N- CH_2

20

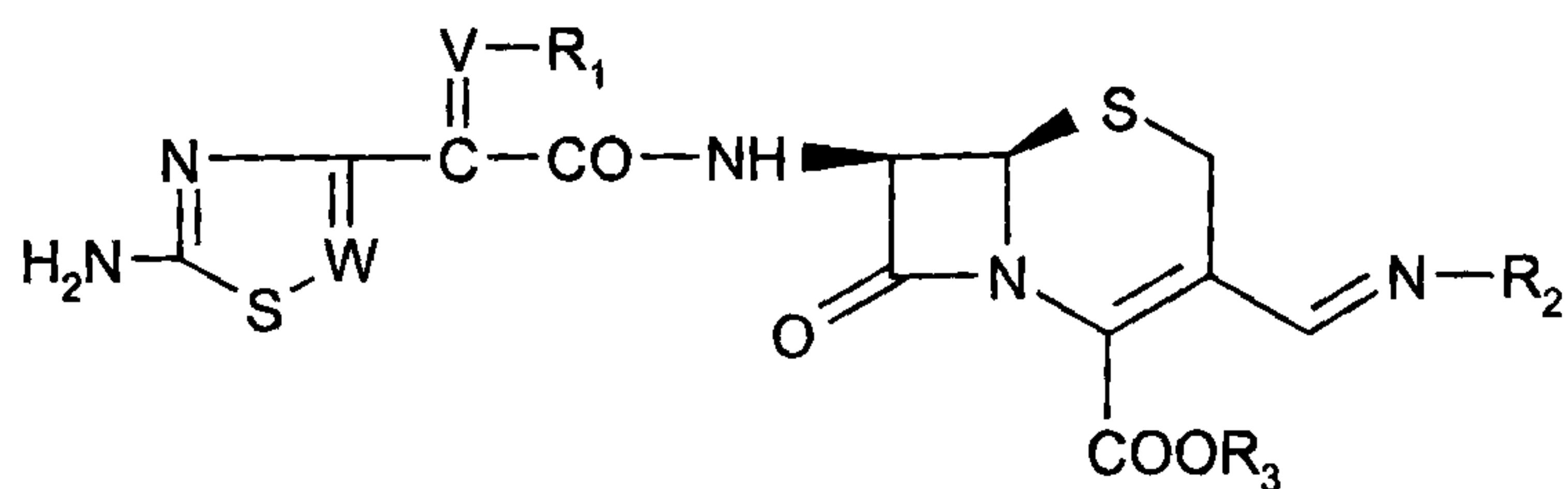
Ex. DB (in CDCl_3): 1.26, t, $J=7$ Hz, 3H, CH_3 ; 3.70 – 4.00, m, 6H, N- CH_2

28565-27

65

CLAIMS:

1. A compound of formula



wherein

5

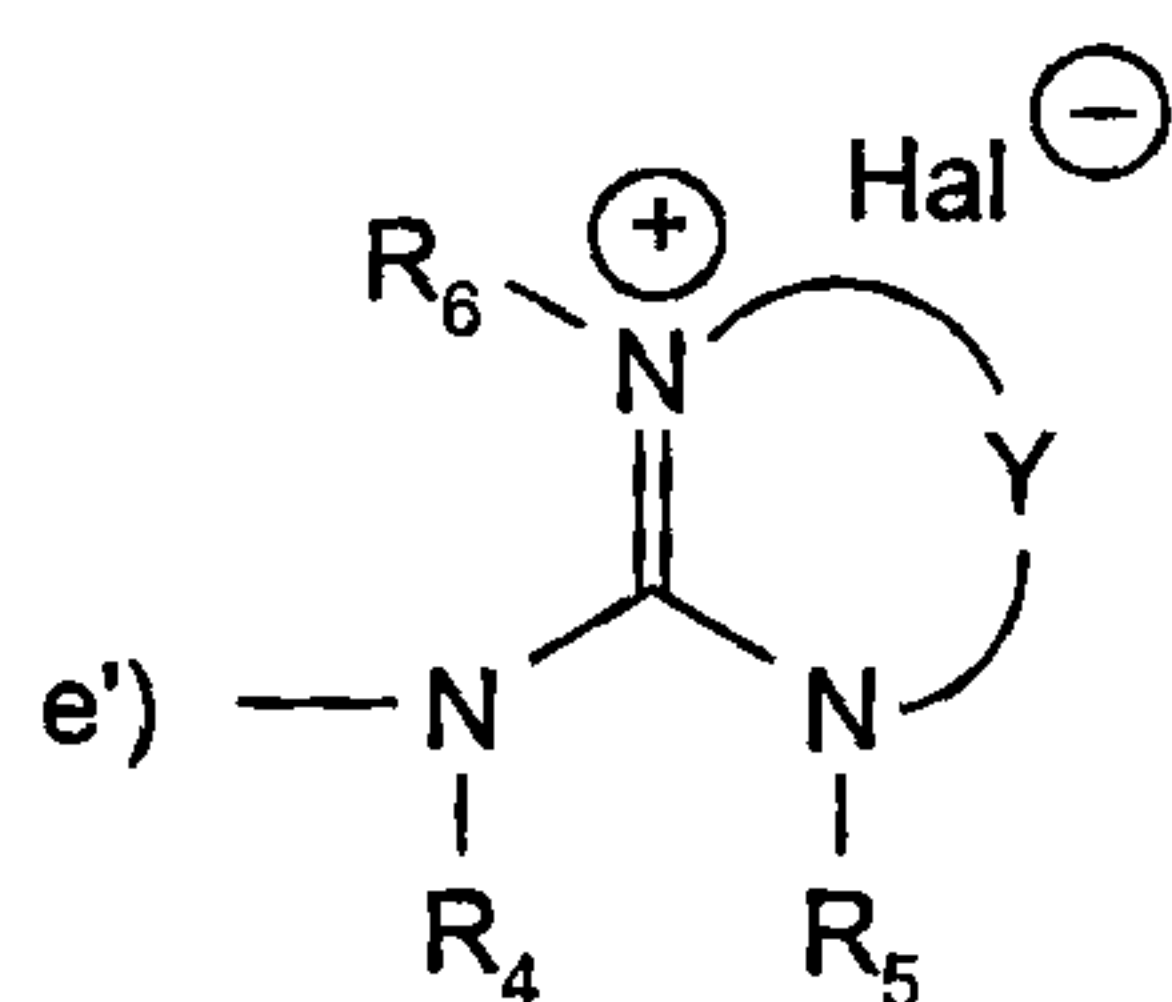
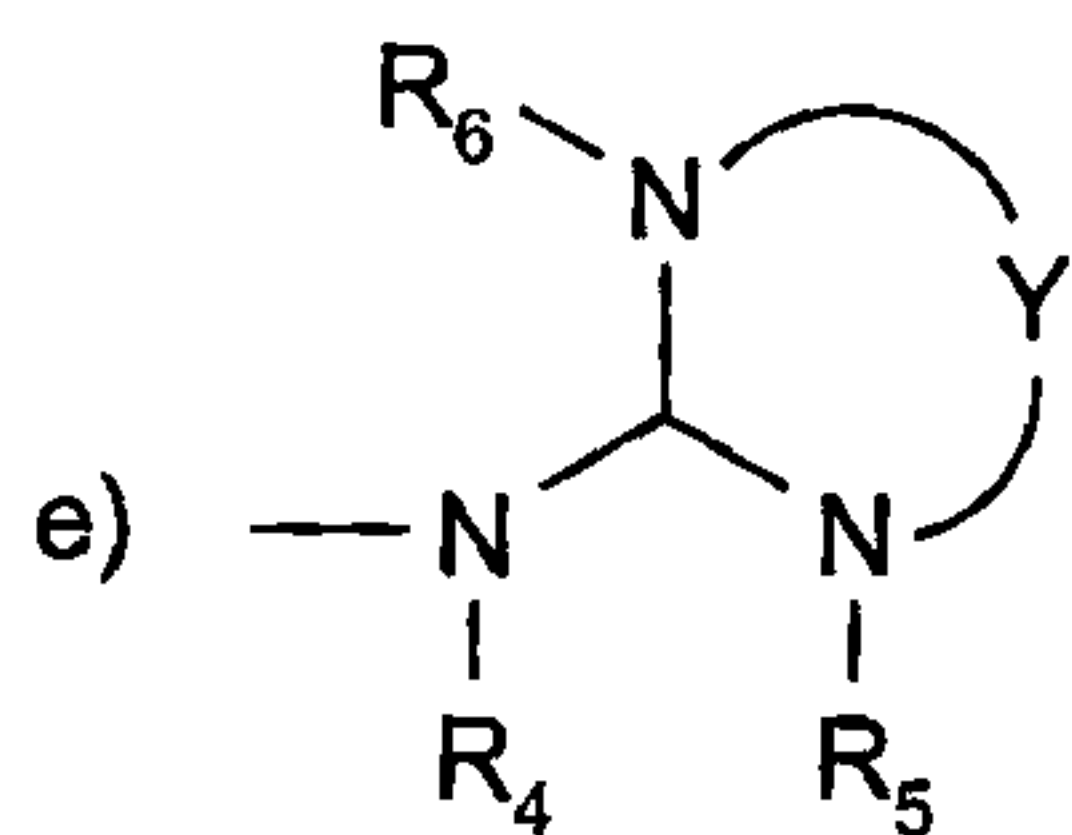
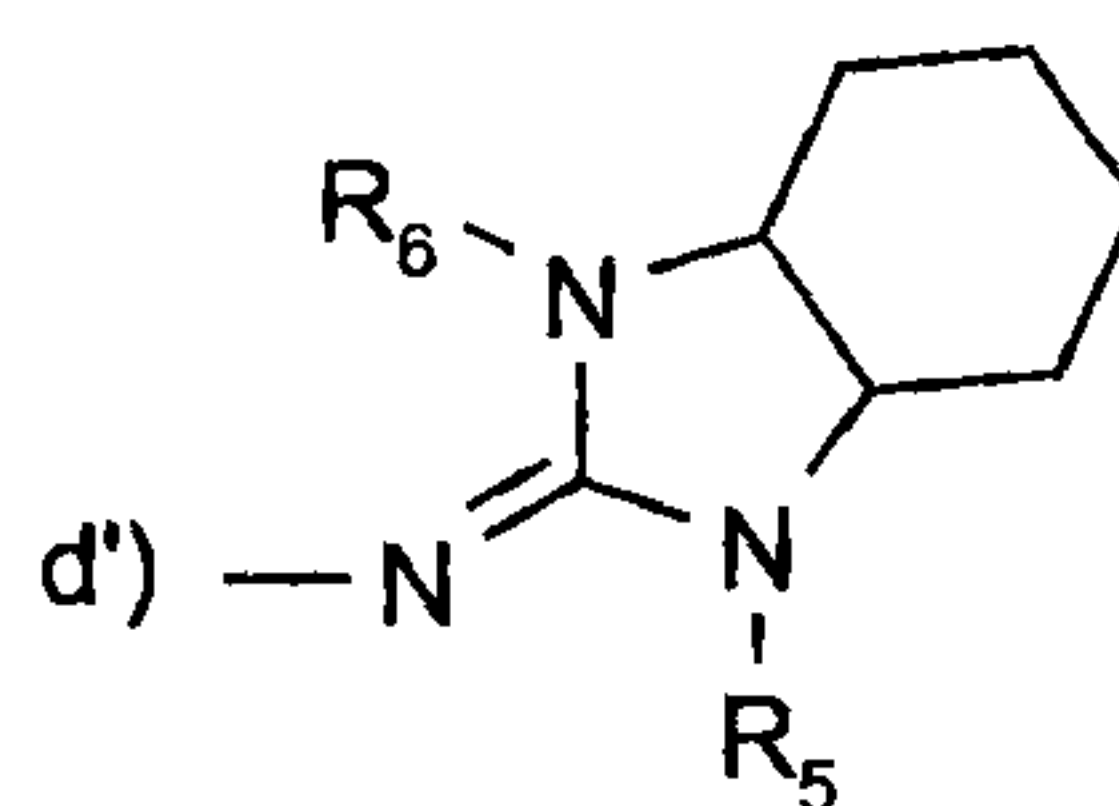
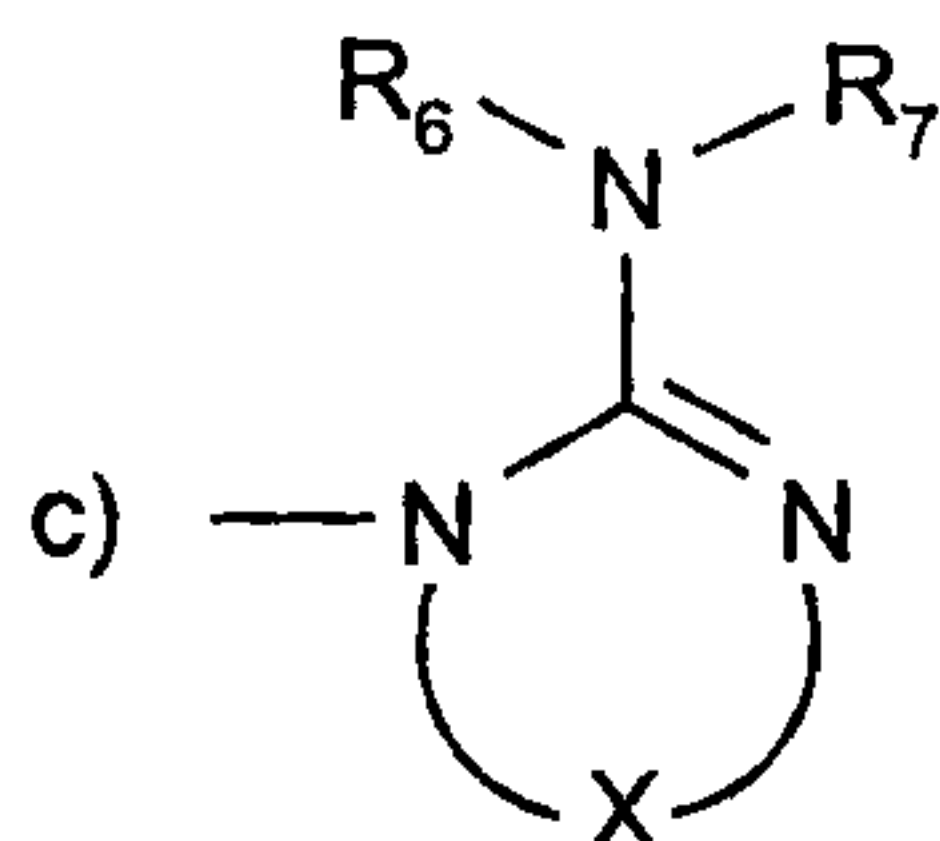
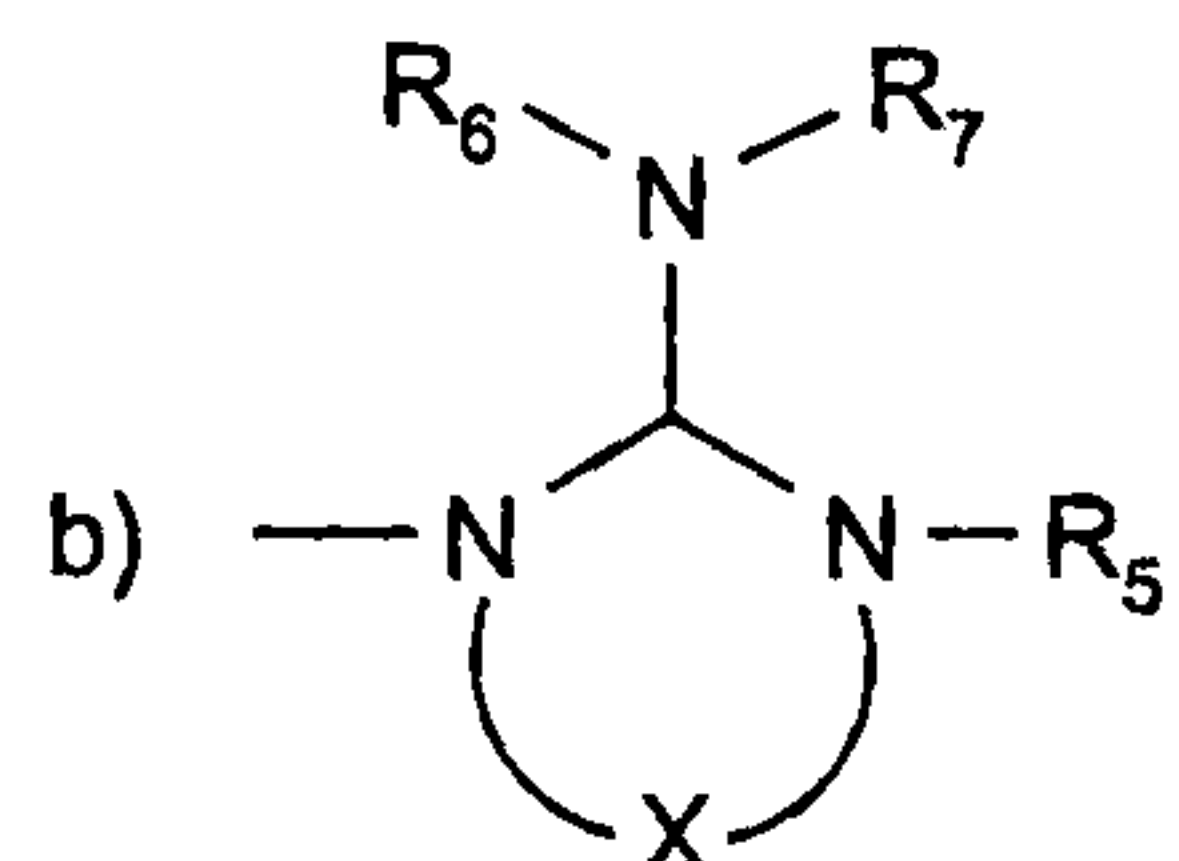
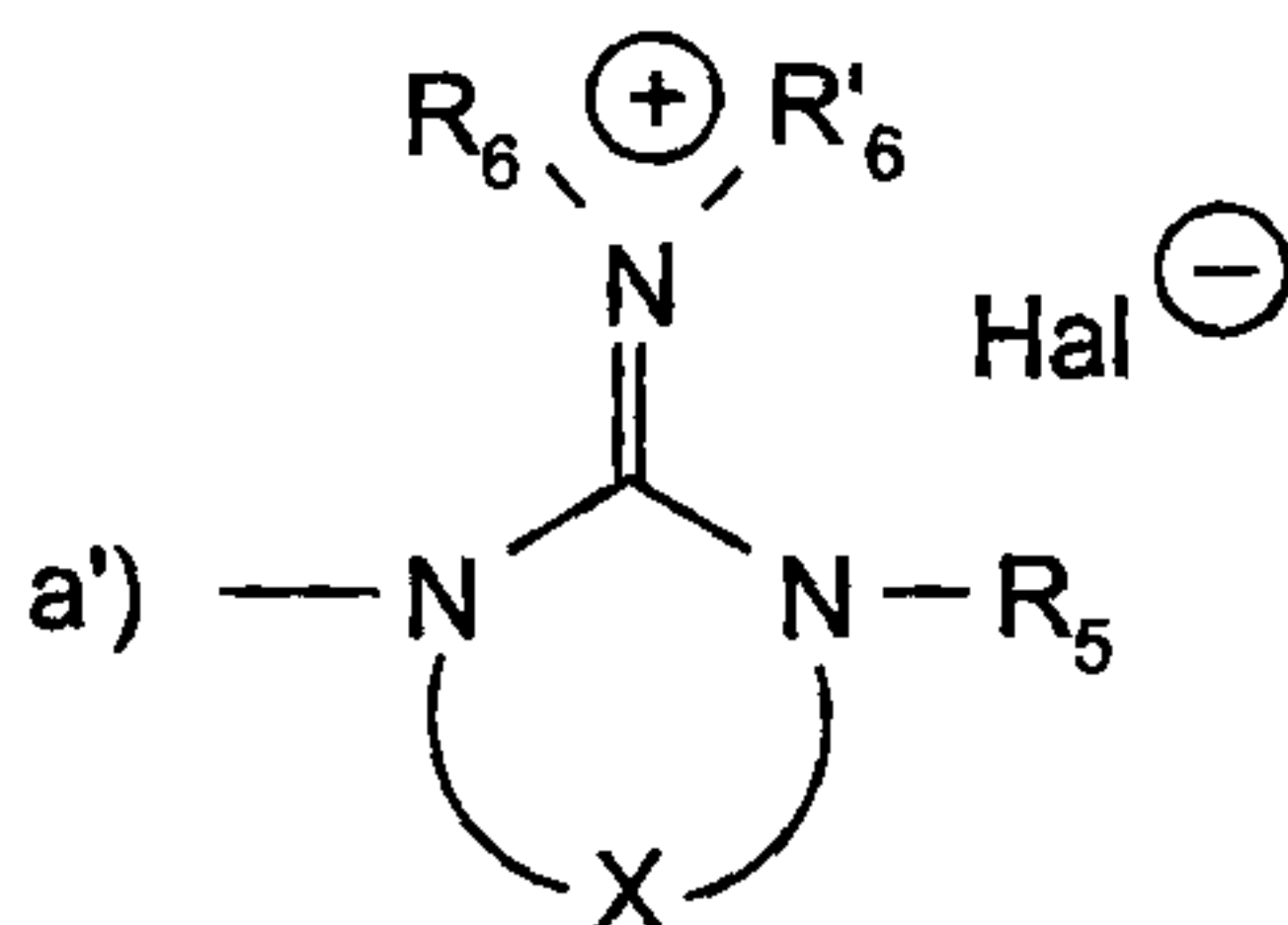
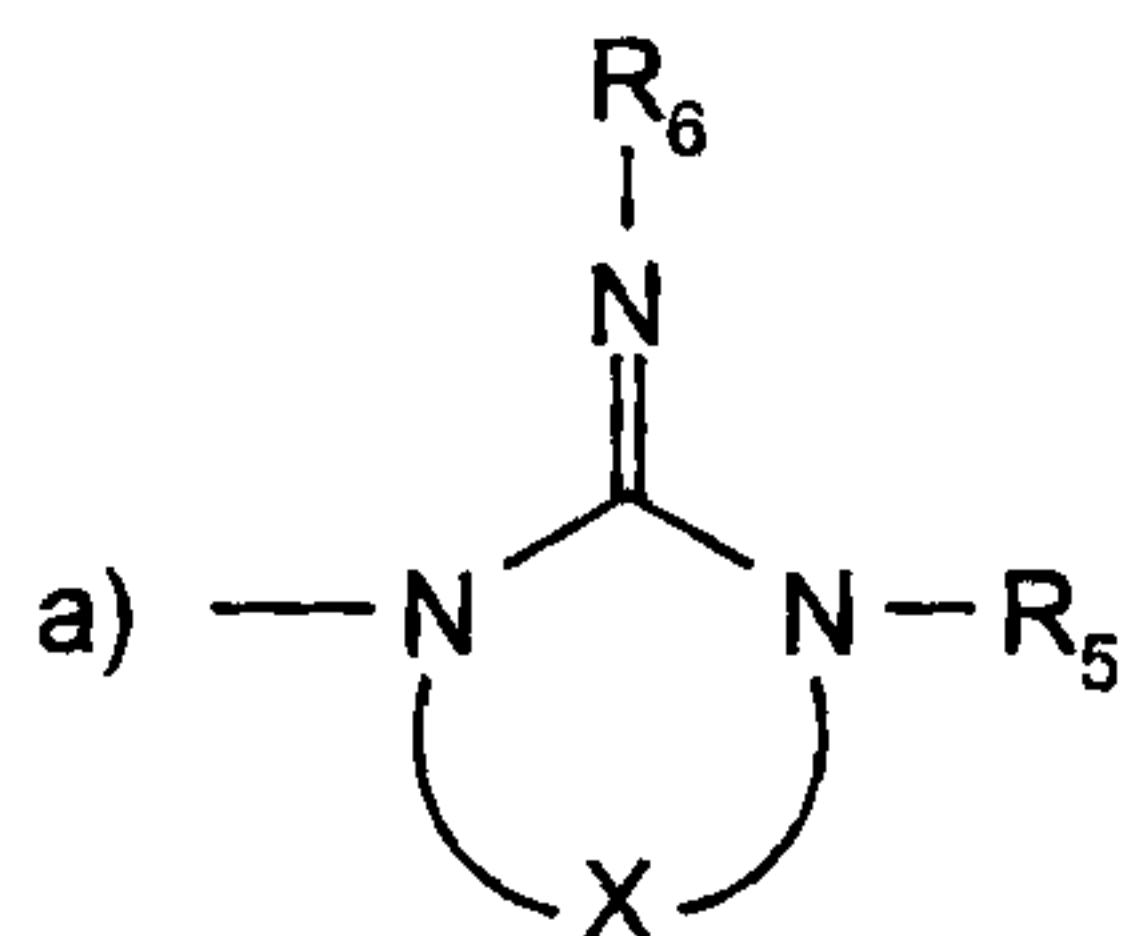
W denotes CH or N,

V denotes CH or NO,

R₁ denotes hydrogen, C₁₋₁₂acyl, carboxyl or alkyl,

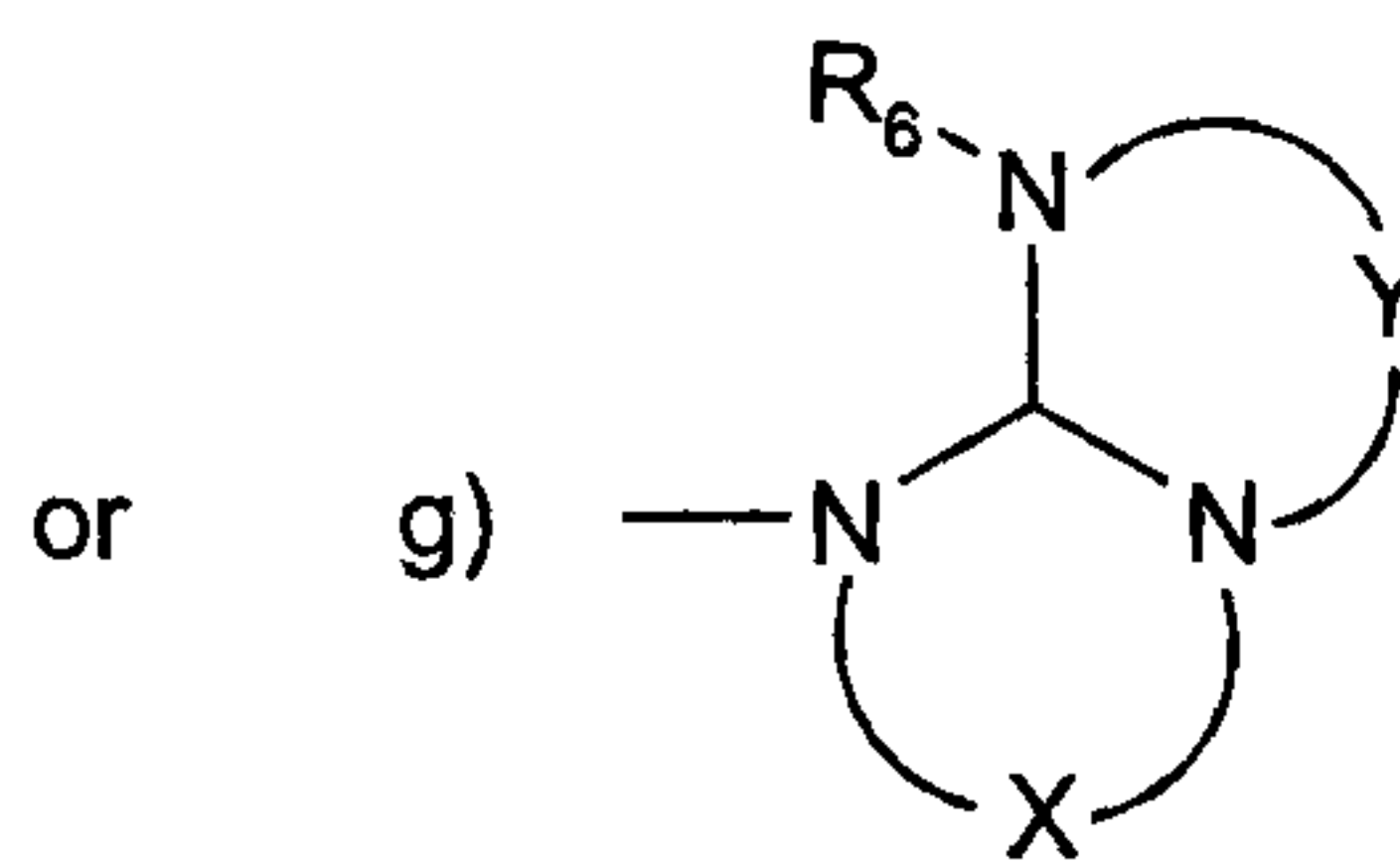
R₃ denotes hydrogen or an ester moiety or a cation,

R₂ denotes a group of formula



28565-27

66



wherein

X and Y independently of each other each denote

5 C₂₋₅alkylene, or

(C₂₋₅)alkenylene wherein one -C=C- double bond is present, or, in case of at least C₄-alkenylene, wherein two -C=C- double bonds are present,

R₄ denotes hydrogen or alkyl,

10 R₅ denotes hydrogen, alkyl, or aminoiminomethyl,

R₆ denotes hydrogen, alkyl, cycloalkyl, amino, hydroxy, alkoxy, unsaturated or saturated heterocyclyl having 5 or 6 ring members and 1 or 2 hetero atoms and being unsubstituted or substituted by alkyl, aryl, alkoxy, 15 halogen, hydroxy, carboxyl, -SO₃H, C₁₋₁₂-acyl, amino, guanidino, oxo, thiono, mercapto, alkylthio, arylthio, imino or alkylimino, or R₆ denotes a group of formula -N=CHR₈, wherein

R₈ denotes alkyl, aryl or unsaturated or saturated 20 heterocyclyl having 5 or 6 ring members and 1 or 2 hetero atoms and being unsubstituted or substituted by alkyl, aryl, alkoxy, halogen, hydroxy, carboxyl, -SO₃H, C₁₋₁₂-acyl, amino, guanidino, oxo, thiono, mercapto, alkylthio, arylthio, imino or alkylimino, or

25 R₅ and R₆ together with the nitrogen atoms to which they are attached denote unsaturated or saturated

28565-27

67

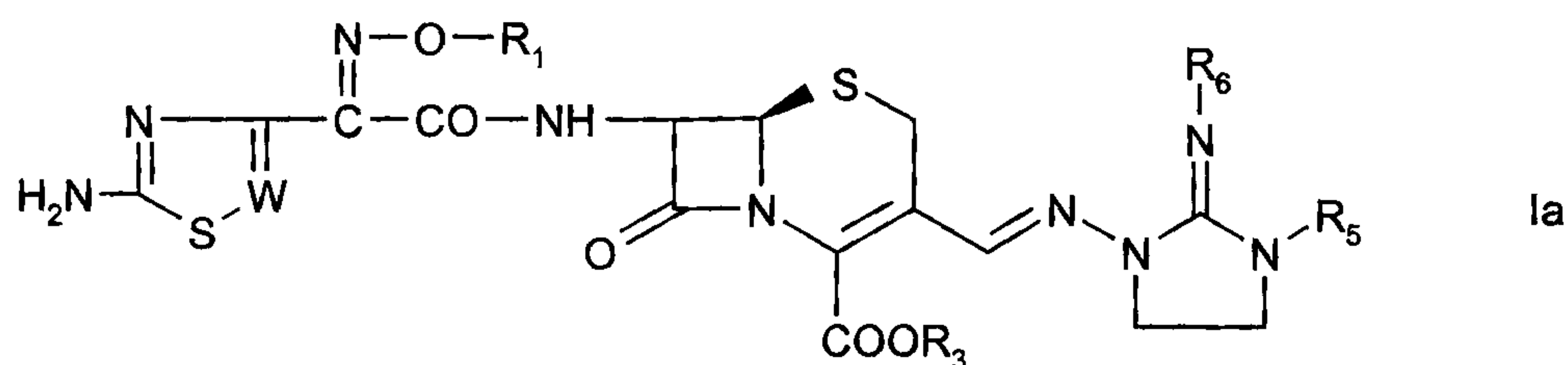
heterocyclyl having 5 or 6 ring members and 1 or 2 hetero atoms and being unsubstituted or substituted by alkyl, aryl, alkoxy, halogen, hydroxy, carboxyl, $-\text{SO}_3\text{H}$, C_{1-12} -acyl, amino, guanidino, oxo, thiono, mercapto, alkylthio, arylthio, imino or alkylimino,

R'_6 denotes alkyl,

R_7 denotes hydrogen, or

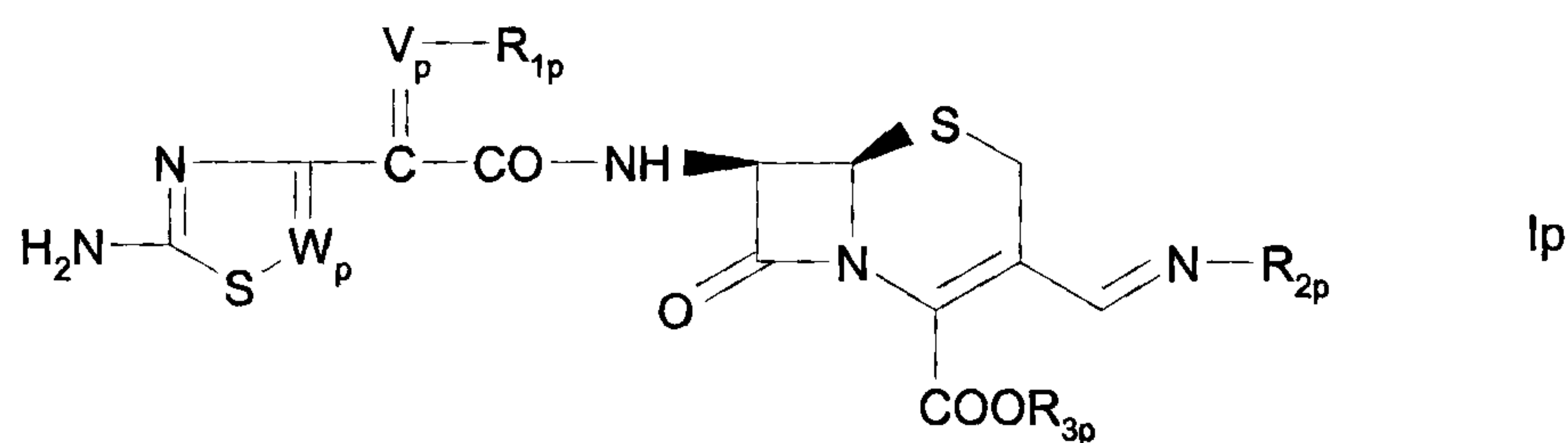
R_6 and R_7 together with the nitrogen atom to which they are attached form unsaturated or saturated heterocyclyl having 5 or 7 ring members and 1 or 2 hetero atoms and being unsubstituted or substituted by alkyl, aryl, alkoxy, halogen, hydroxy, carboxyl, $-\text{SO}_3\text{H}$, C_{1-12} -acyl, amino, guanidino, oxo, thiono, mercapto, alkylthio, arylthio, imino or alkylimino; or a salt, solvate or hydrate thereof.

2. A compound of formula



wherein W , R_1 , R_3 , R_5 and R_6 are as defined in claim 1; or a salt, solvate or hydrate thereof.

3. A compound of formula



wherein

28565-27

68

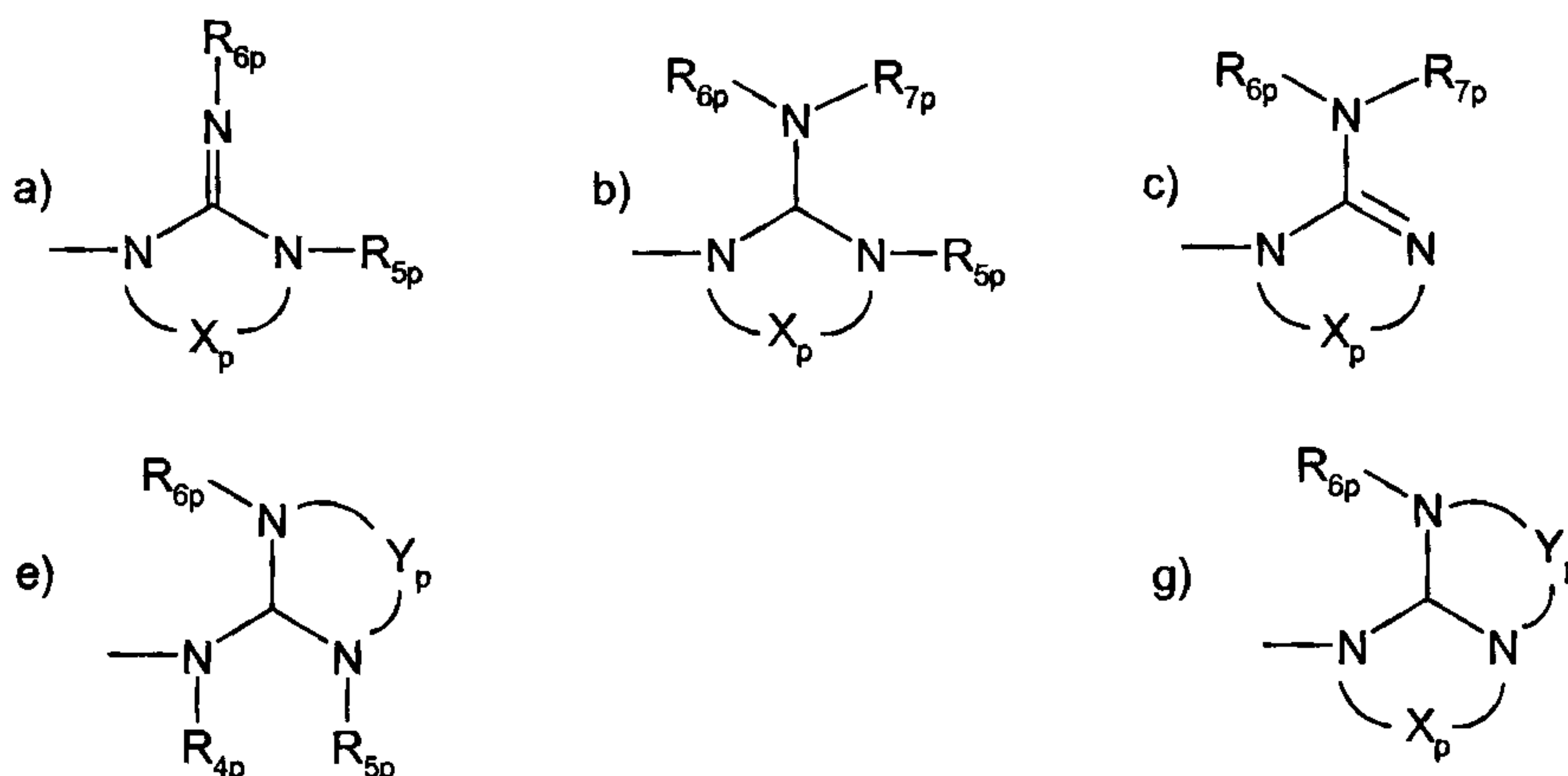
W_p denotes CH or N,

V_p denotes =CH- or =N-O-,

R_{1p} denotes hydrogen, C_{1-12} acyl, carboxyl, unsubstituted alkyl, or alkyl substituted by halogen or
5 carboxyl,

R_{3p} denotes hydrogen, an ester forming group or a cation,

R_{2p} denotes a group of formula



10 wherein X_p and Y_p are the same or different and each denote a $-(CH_2)_n$ -group, wherein n denotes a number from 2 to 5, and optionally two CH_2 -groups are replaced by a $-CH=CH-$ group and optionally one or more hydrogen atoms are replaced by halogen, alkyl, cycloalkyl, hydroxyalkyl,
15 aminoalkyl, carboxyl or ethoxycarbonyl,

R_{4p} denotes hydrogen, alkyl or hydroxyalkyl,

R_{5p} denotes hydrogen, alkyl, (poly)hydroxyalkyl or aminoalkyl, wherein optionally the alkyl groups are additionally substituted by $-COOH$, $-SO_3H$, or $-OPO_3H_2$,

20 R_{6p} denotes hydrogen, alkyl, hydroxyalkyl, aminoalkyl, amino, hydroxy, alkoxyalkyl, cycloalkyl, a group $N=CHR_{8p}$, wherein

28565-27

69

R_{8p} denotes aryl or heteroaryl, or a group $-NR_{9p}R_{10p}$,
wherein

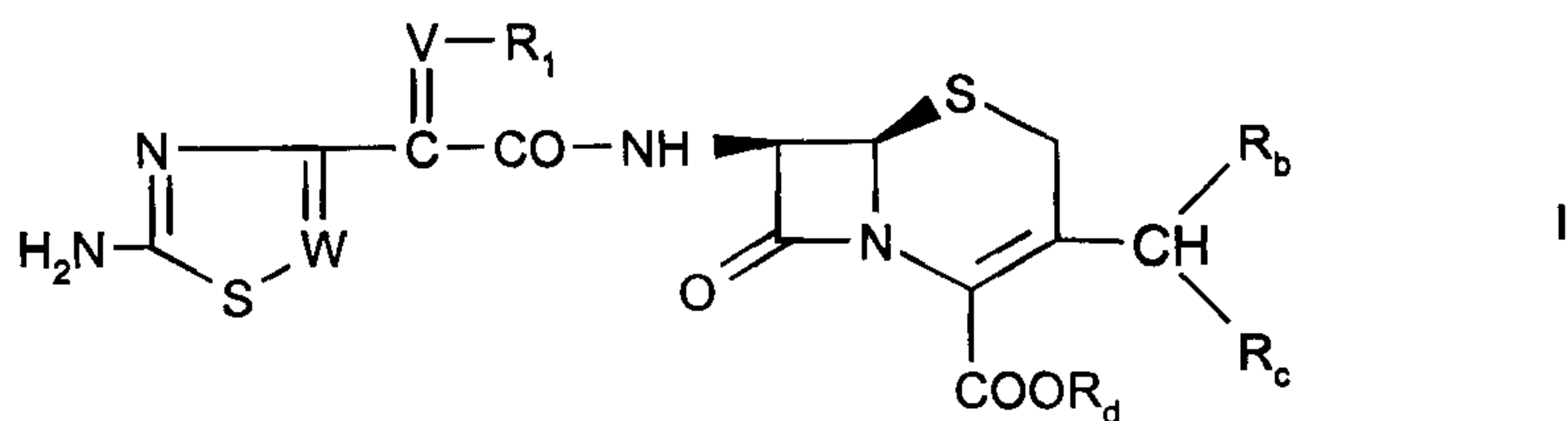
R_{9p} and R_{10p} are the same or different and each
denote hydrogen, alkyl, hydroxyalkyl or aryl or denote
5 together with the nitrogen atom a saturated, unsubstituted
heterocycle with 5 or 6 ring members with one or two
nitrogen and/or oxygen atoms, and

R_{7p} denotes hydrogen, or

R_{7p} and R_{6p} denote together with the nitrogen atom a
10 heterocycle with 5 to 7 ring members containing one or two
nitrogen and/or oxygen atoms; or a salt, solvate or hydrate
thereof.

4. 7-{[(5-Amino-1,2,4-thiadiazole-3-yl)-(Z)-
(fluoromethoxyimino)acetyl]amino}-3-{[(3-ethyl-2-
15 methylimino-imidazolidine-1-yl)imino]methyl}-3-cephem-4-
carboxylic acid; or a salt, solvate or hydrate thereof.

5. A process for the production of a compound of
formula I as defined in claim 1, comprising reacting a
compound of formula



20

wherein W, V and R_1 are as defined in claim 1 and
either

α) R_b denotes hydroxy and R_c and R_d together denote
a bond, or

28565-27

70

β) R_d denotes hydrogen, a cation, an ester forming group or a silyl group, and R_b and R_c together denote an oxo group,

in free form or in the form of an acid addition
5 salt thereof, with an amine of formula



wherein R₂ is as defined in claim 1.

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4 or a pharmaceutically
10 acceptable salt, solvate or hydrate thereof and a pharmaceutically acceptable carrier or diluent.

7. A pharmaceutical composition according to claim 6 for treatment of a bacterial disease in a subject in need thereof.

15 8. A pharmaceutical composition according to claim 7, wherein the bacterial disease is caused by a bacteria genus selected from the group consisting of *Pseudomonas*, *Escherichia*, *Enterobacter*, *Klebsiella*, *Moraxella*, *Enterococcus*, *Streptococcus* and *Staphylococcus*.

20 9. A use of a compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt, solvate or hydrate thereof, in preparation of a pharmaceutical composition for treating a bacterial infection in a subject in need thereof.

25 10. A use according to claim 9, wherein the bacterial disease is caused by a bacteria genus selected from the group consisting of *Pseudomonas*, *Escherichia*, *Enterobacter*, *Klebsiella*, *Moraxella*, *Enterococcus*, *Streptococcus* and *Staphylococcus*.

28565-27

71

11. A use of a compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt, solvate or hydrate thereof, for treating a bacterial infection in a subject in need thereof.

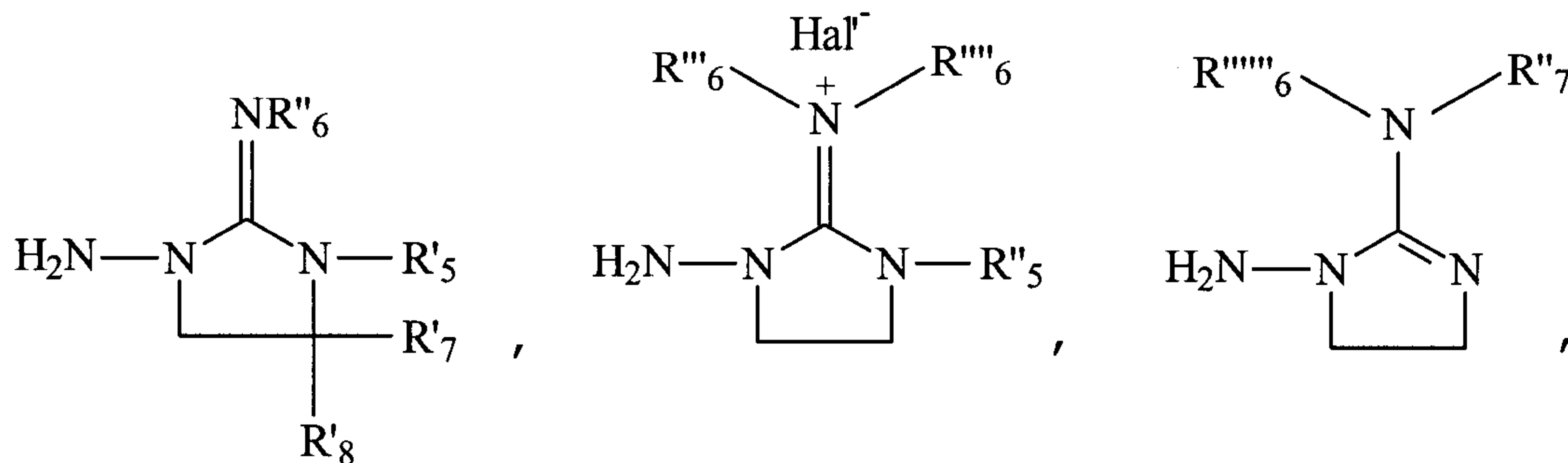
5 12. A use according to claim 11, wherein the bacterial disease is caused by a bacteria genus selected from the group consisting of *Pseudomonas*, *Escherichia*, *Enterobacter*, *Klebsiella*, *Moraxella*, *Enterococcus*, *Streptococcus* and *Staphylococcus*.

10 13. A compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt, solvate or hydrate thereof, for treating a bacterial infection in a subject in need thereof.

14. A compound, salt, solvate or hydrate according to
15 claim 13, wherein the bacterial disease is caused by a bacteria genus selected from the group consisting of *Pseudomonas*, *Escherichia*, *Enterobacter*, *Klebsiella*, *Moraxella*, *Enterococcus*, *Streptococcus* and *Staphylococcus*.

15. A compound of formula

20

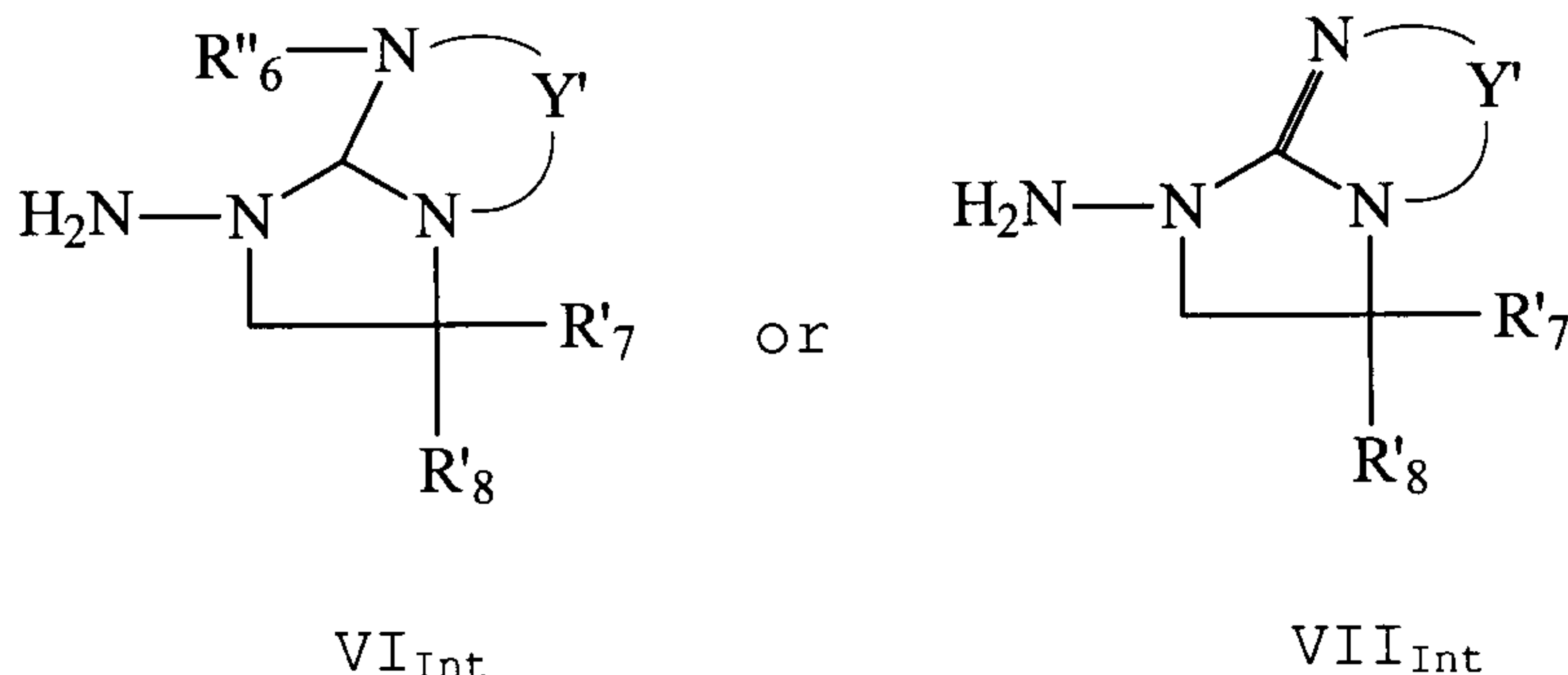


25

I_{Int}II_{Int}IV_{Int}

28565-27

72



wherein

Y' denotes alkylene;

R'₅ denotes hydrogen, alkyl or alkylimino;

R''₆ denotes hydrogen, alkyl, hydroxy, alkoxy,
 10 cycloalkyl, amino or heterocyclyl;

R'₇ and R'₈ independently of each other denote
 hydrogen, carboxyl, alkoxycarbonyl or alkyl;

R'''₆ and R''''₆ independently of each other denote
 alkyl, or,

15 R'''₆ and R''''₆ together with the nitrogen atom to
 which they are attached denote heterocyclyl;

R''₅ denotes alkyl, or

R''₅ and R'''₆ together denote alkylene,

R''''''₆ and R''₇ together with the nitrogen atom to
 20 which they are attached form heterocyclyl; and

Hal' denotes halogen,

with the proviso that a compound of formula I_{Int}

28565-27

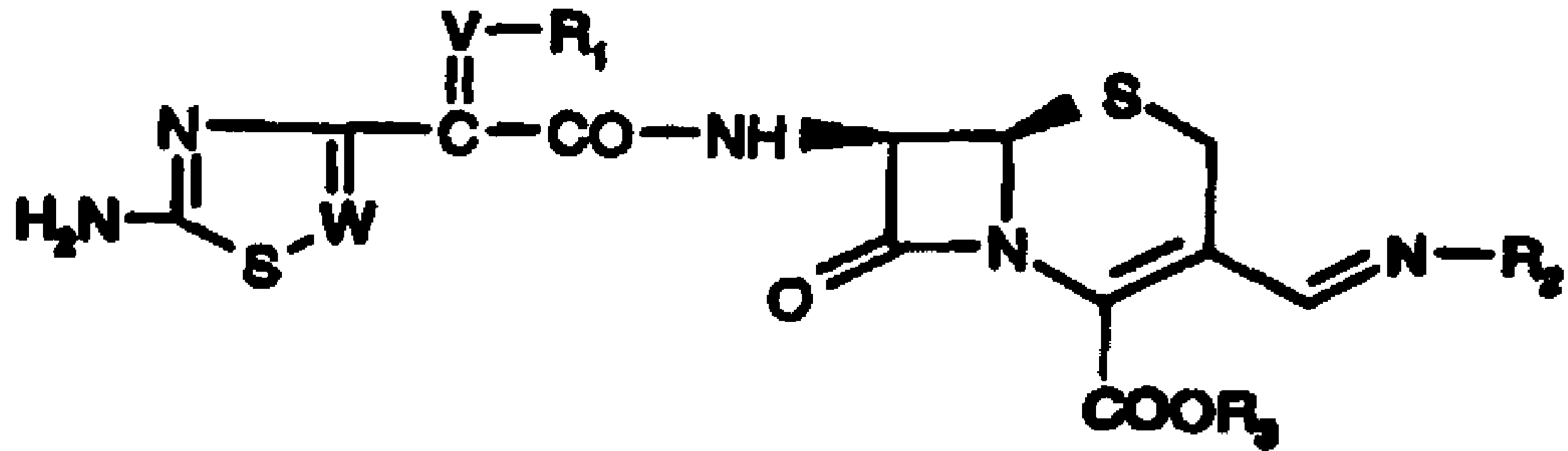
73

wherein R'_5 , R'_7 and R'_8 are hydrogen and R''_6 is hydrogen, 2-(N-morpholino)ethyl, 3-(N,N-dimethyl-amino)-propyl; (2-hydroxyethyl)amino or 2-hydroxyethyl, is excluded.

FETHERSTONHAUGH & CO.

OTTAWA, CANADA

PATENT AGENTS



(1)