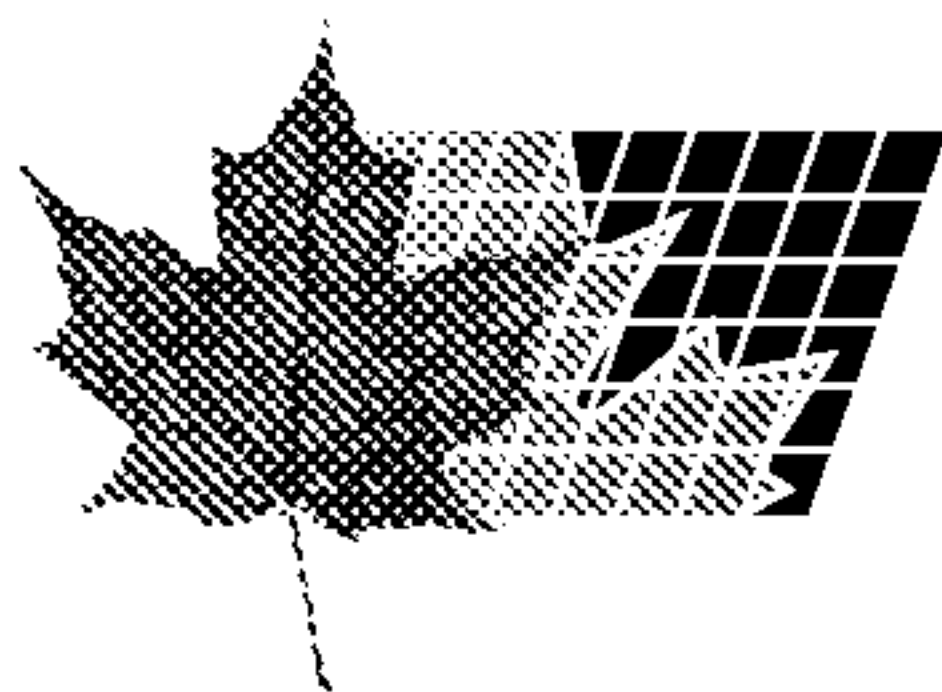




(72) DODEY, PIERRE, FR

(72) BONDOUX, MICHEL, FR

(72) HOUZIAUX, PATRICK, FR

(72) BARTH, MARTINE, FR

(72) OU, KHAN, FR

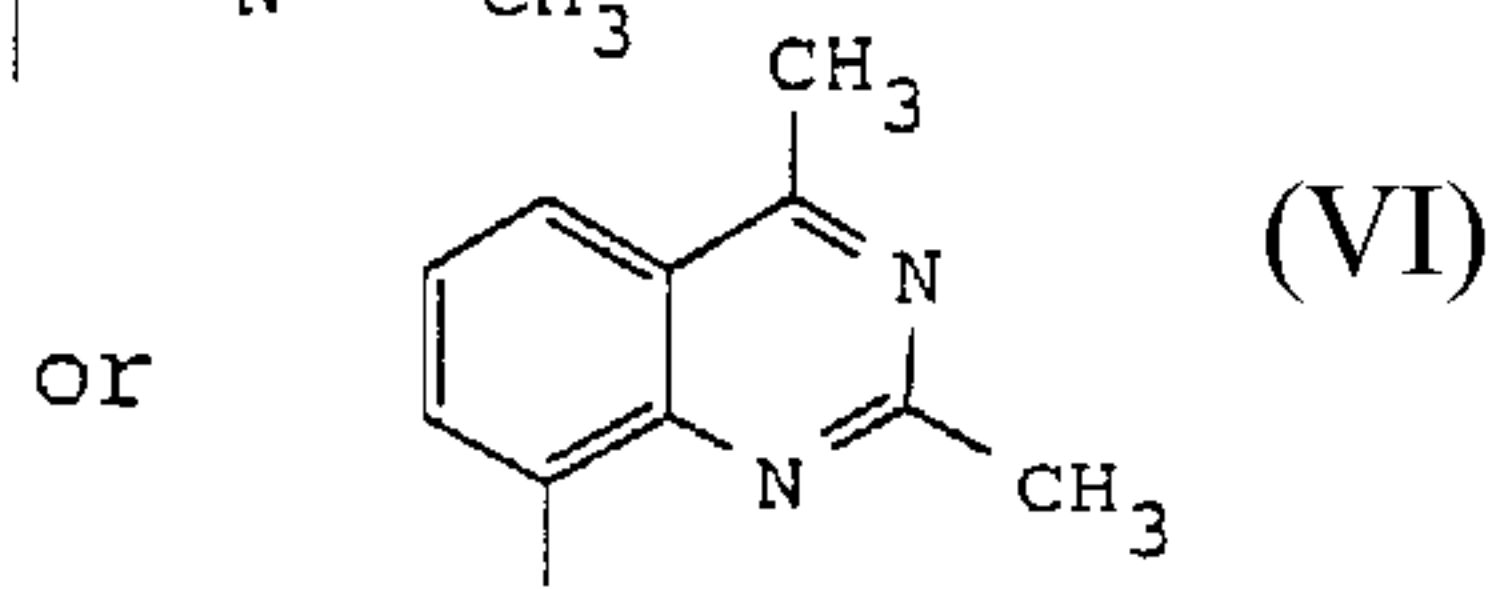
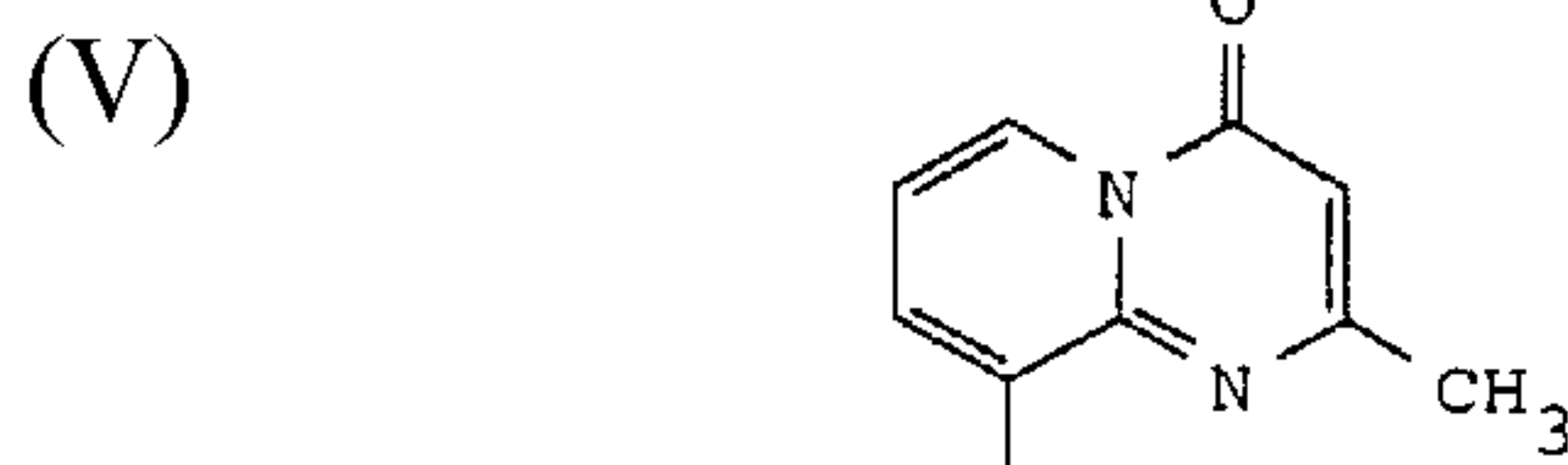
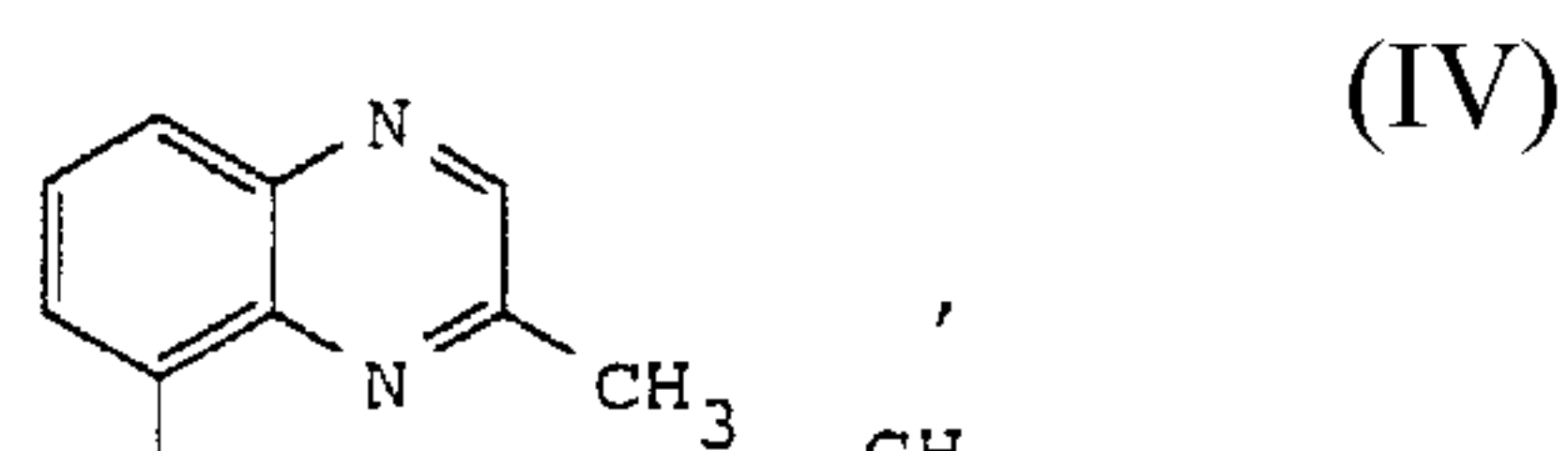
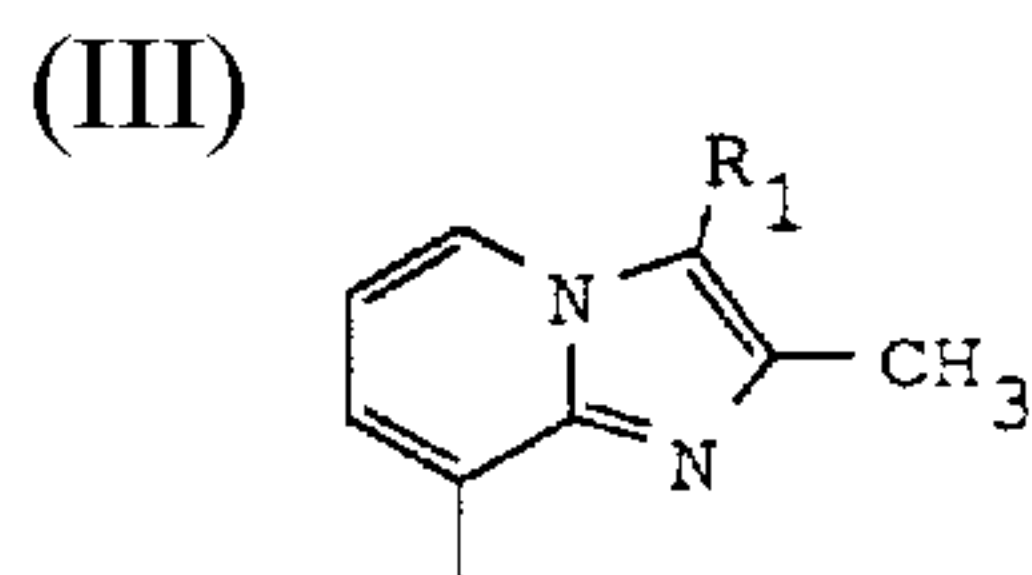
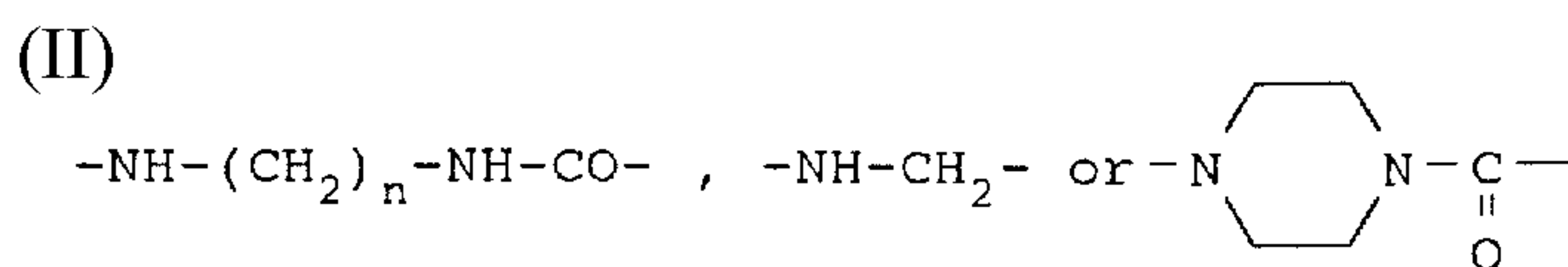
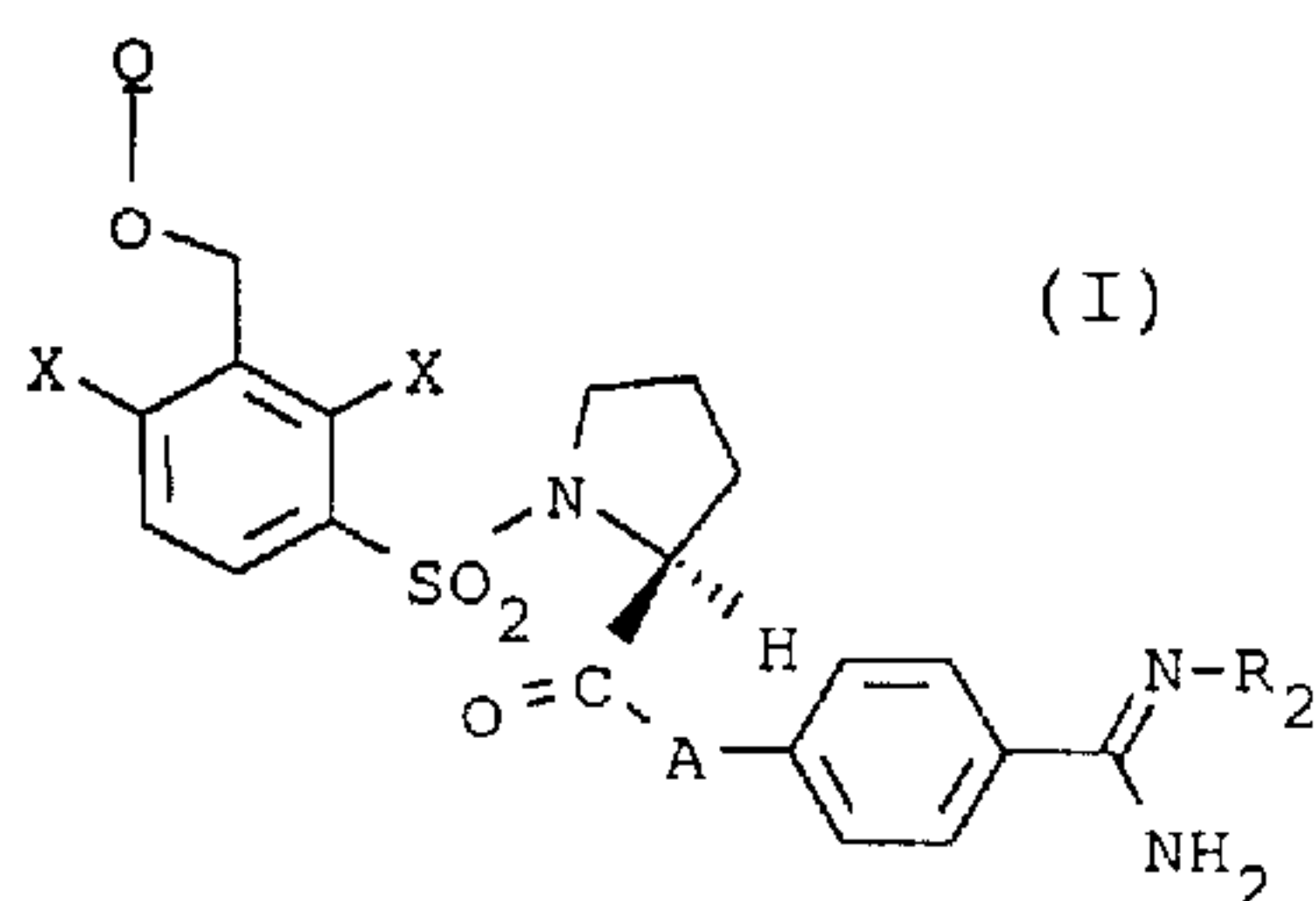
(71) FOURNIER INDUSTRIE ET SANTE, FR

(51) Int.Cl.⁷ C07D 471/04, A61K 31/495, A61K 31/40, C07D 403/12

(30) 1997/06/27 (97 08 114) FR

(54) **NOUVEAUX COMPOSES DE N-BENZENESULFONYL-L-PROLINE, PROCEDE DE PREPARATION ET UTILISATION EN THERAPEUTIQUE**

(54) **NOVEL N-BENZENESULPHONYL-L-PROLINE COMPOUNDS, PREPARATION METHOD AND USE IN THERAPY**



(57) La présente invention concerne des composés choisis parmi l'ensemble constitué par (i) les composés de formule (I), dans laquelle X représente un atome d'halogène, A représente un groupe (voir formule II); Q représente un groupe (voir formules III, IV, V et VI); R₁ est hydrogène, halogène, alkyle en C₁-C₃ ou 1-oxoalkyle en C₁-C₅; R₂ est H ou OH; et n est 2, 3, ou 4; et (ii) leurs sels d'addition. Elle concerne également leur procédé de préparation et leur utilisation en thérapeutique, notamment vis-à-vis des pathologies mettant en cause la bradykinine.

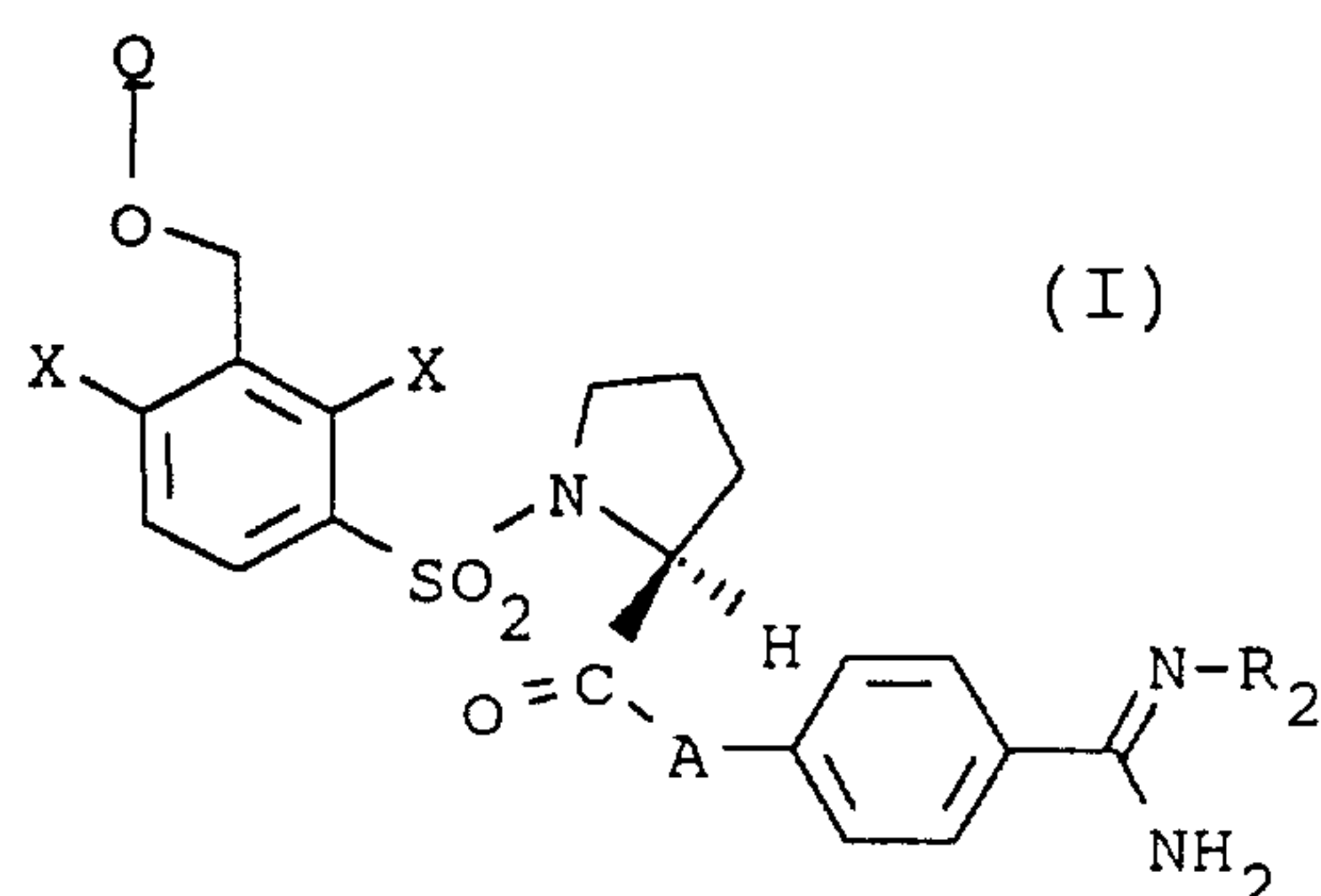
(57) The invention concerns compounds selected among the set consisting of (i) compounds of formula (I) in which X represents a halogen atom; A represents a group (see above formula II); Q represents a group (see above formulas III, IV, V and VI); R₁ is hydrogen, halogen, C₁-C₃ alkyl or C₁-C₅ 1-oxoalkyl; R₂ is H or OH; and n is 2, 3, or 4; and (ii) their addition salts. The invention also concerns their preparation method and their use in therapy, in particular for treating pathologies involving bradykinin.

ABSTRACT OF THE DISCLOSURE

The present invention relates to compounds selected from the group consisting of:

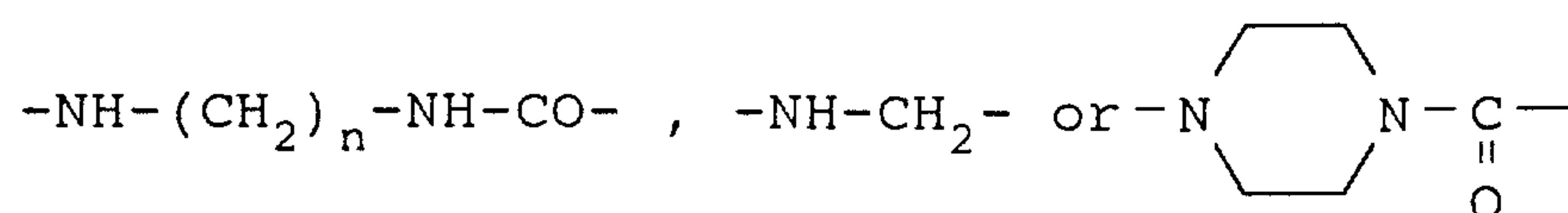
(i) the compounds of the formula

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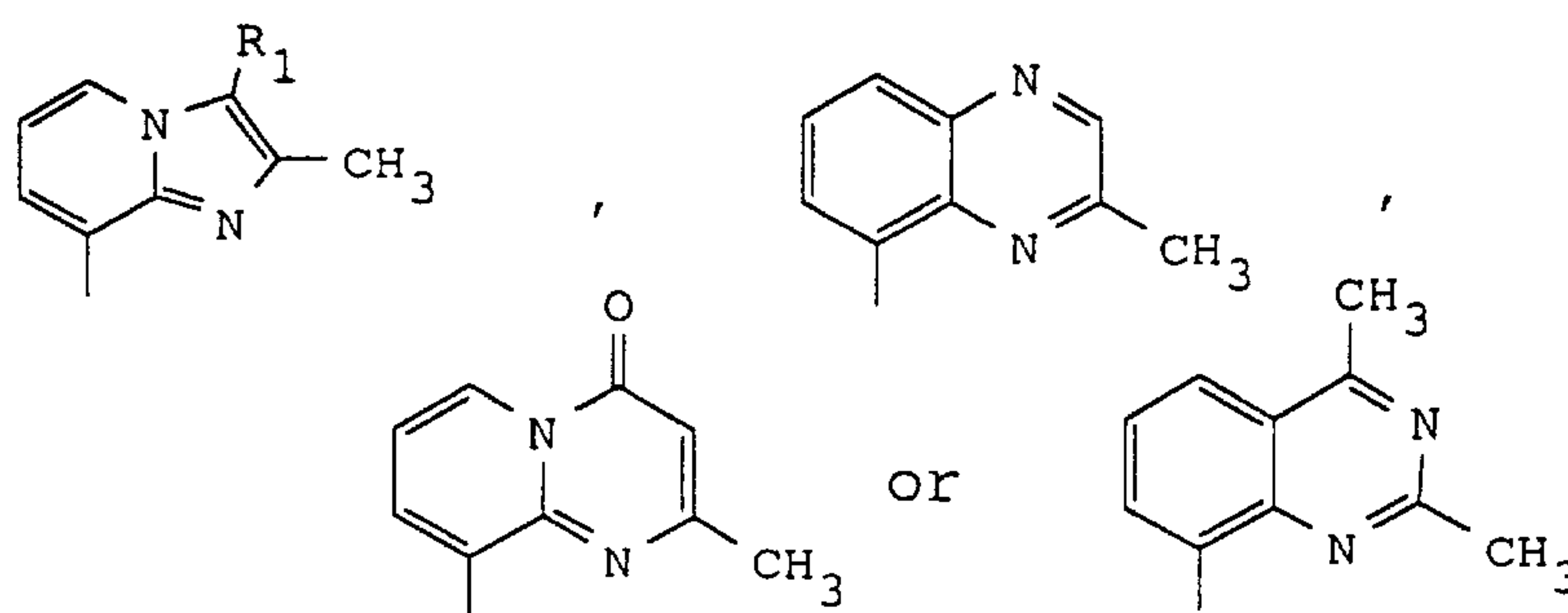


in which X is a halogen atom, A is a group

10



Q is a group



15

R_1 is hydrogen, halogen, C_1 - C_3 alkyl or C_1 - C_5 1-oxoalkyl, R_2 is H or OH and n is 2, 3 or 4; and

(ii) their addition salts.

It further relates to the process for their preparation and to their use in therapeutics, especially for combating pathological conditions involving bradykinin.

20

NOVEL N-BENZENESULFONYL-L-PROLINE COMPOUNDS, PROCESS FOR THEIR PREPARATION AND USE IN THERAPEUTICS

5 **Field of the invention**

The present invention relates to novel compounds derived from N-(benzenesulfonyl)-(L)-proline, to the process for their preparation and to their use in therapeutics.

10 These novel compounds have an antagonistic action towards bradykinin and are useful in therapeutics, particularly for the treatment of pain and inflammation and especially for the treatment of asthma, cerebral traumatic shock and allergic rhinitis.

Prior art

15 It is known that one of the possible treatments for certain pathological conditions of a painful and/or inflammatory nature (such as asthma, rhinitis, septic shock, toothache, etc.) is to inhibit the action of certain hormones such as bradykinin or kallidin. These peptide hormones are in fact involved in a large number of physiological processes, some of which are closely associated with these pathological conditions.

20 Although no product possessing this mode of action has yet been marketed, numerous studies have been undertaken in order to understand the mode of action of kinins, particularly bradykinin and its homologs, and then create compounds capable of antagonizing the bradykinin receptors. Pharmacological Reviews, vol. 44, no. 1, pages 1 - 80 (1992) and Biopolymers (Peptide Science), vol. 37, pages 25 143 - 155 (1995) may be mentioned among the numerous publications relating to this work.

30 Bradykinin is a peptide hormone consisting of 9 amino acids (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) and kallidin is a peptide hormone (Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) which contains an additional amino acid (Lys) compared with bradykinin. It is known that earlier studies made it possible to obtain peptides which interact with the bradykinin receptors: some of them, like bradycor (CP.0127 from Cortech), icatibant (HOE 140 from Hoechst) ["bradycor" and "icatibant" are international non-proprietary names (INN)] or NPC 17761 (from Scios-Nova), have an inhibitory action on the binding of bradykinin to its B₂ receptor. Recent 35 publications refer to other peptides capable of having an antagonistic action on bradykinin in respect of its B₂ receptor; examples of these publications which may

be mentioned are WO-A-97/09347, WO-A-97/09346, US-A-5610140, US-A-5620958, US-A-5610142 and US-A-5597803. Furthermore, non-peptide compounds have been proposed as antagonists towards the binding of bradykinin to its B₂ receptor, especially in EP-A-0596406, EP-A-0622361, US-A-5578601, FR-A-2735128, JP-A-09 040662, FR-A-2737892 and WO-A-97/11069. It is also known that certain compounds whose structure is more or less related to those of the compounds referred to in the present patent application have already been described for their possible antithrombotic properties, especially in the publications DE-A-3617183 and EP-A-0261539.

10 **Object of the invention**

There is a need for reducing or eliminating pain and inflammation in mammals and particularly in man.

To meet this need, a novel technical solution has been sought which is effective in the treatment of pain, irrespective of its origin, and especially in the treatment of pain associated with inflammatory phenomena or traumatisms.

According to the invention, it is proposed to provide a novel technical solution which involves competitive binding, at the bradykinin B₂ receptor, between (i) bradykinin and related or analogous hormones, and (ii) an antagonist, and utilizes compounds of the benzenesulfonamide type which are structurally different from the known products mentioned above and which are capable of limiting or substantially inhibiting the binding of bradykinin and analogous hormones to said bradykinin B₂ receptor.

According to this technical solution, the novel compounds bind competitively to the bradykinin B₂ receptor without causing the effects of bradykinin on this receptor (these novel compounds are said to be antagonists). This results in the appearance of a state analogous to that observed in the absence of bradykinin, namely a reduction in pain and in inflammatory reactions.

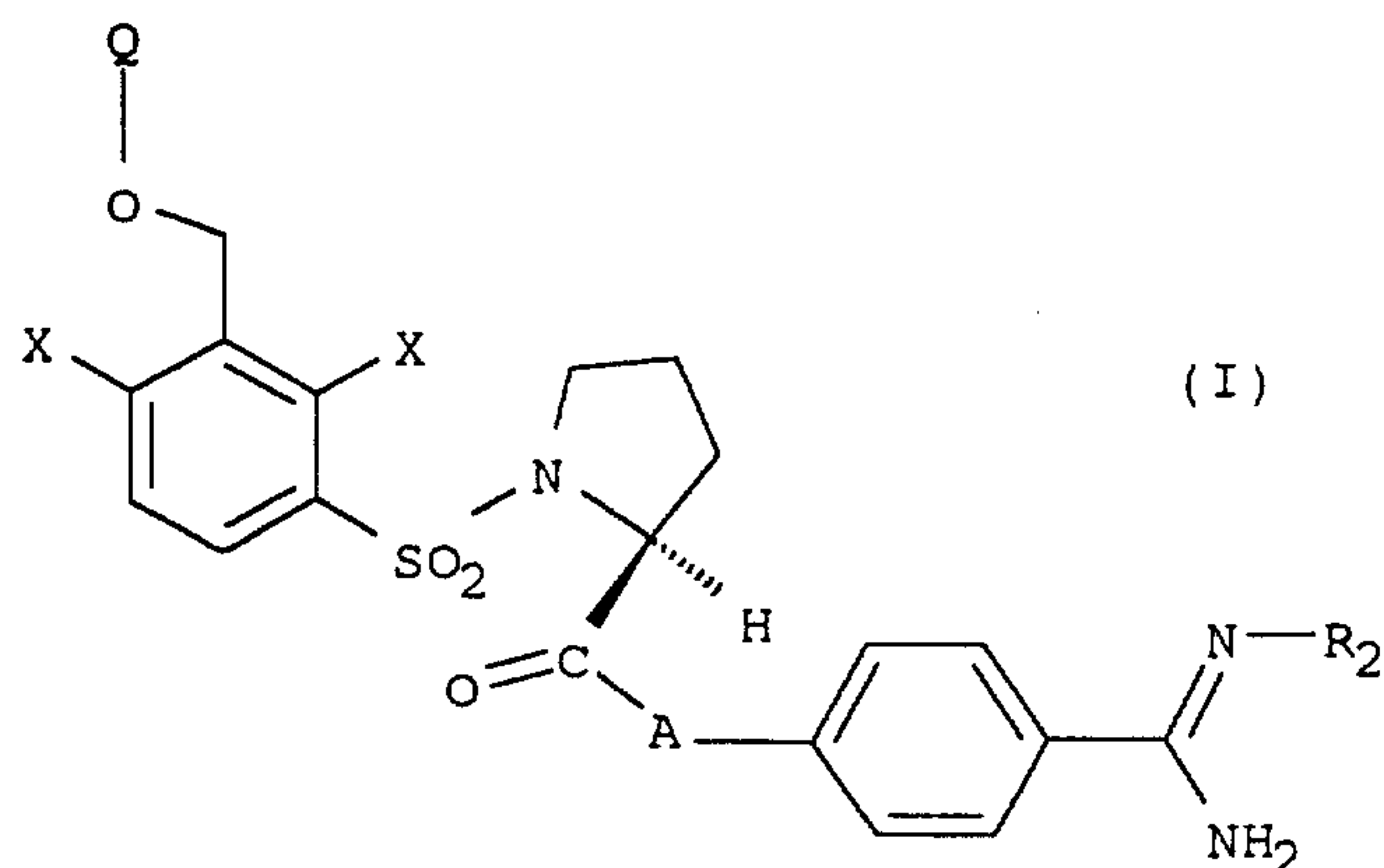
In accordance with this novel technical solution, it is proposed according to a first aspect of the invention to provide compounds derived from N-(benzenesulfonyl)-(L)-proline as novel industrial products, according to a second aspect of the invention to provide a process for the preparation of these compounds, and according to a third aspect of the invention to provide the use of these compounds, especially in therapeutics, as analgesics and/or anti-inflammatories.

Subject of the invention

In accordance with the novel technical solution of the invention, an N-(benzenesulfonyl)-L-proline compound is recommended as a novel industrial

product, said compound being selected from the group consisting of:

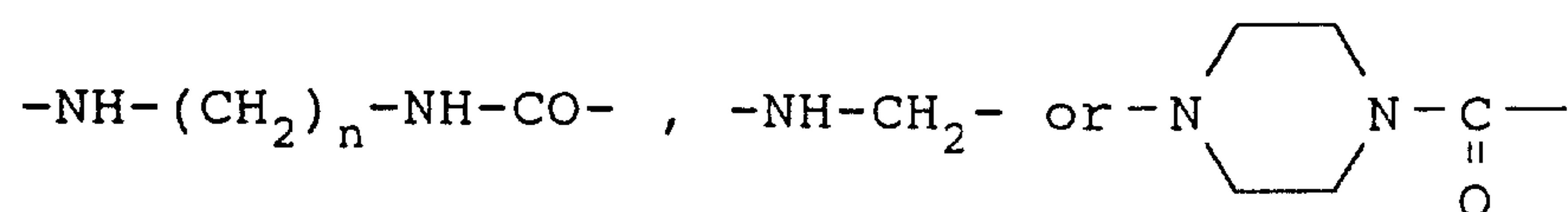
(i) the compounds of formula I:



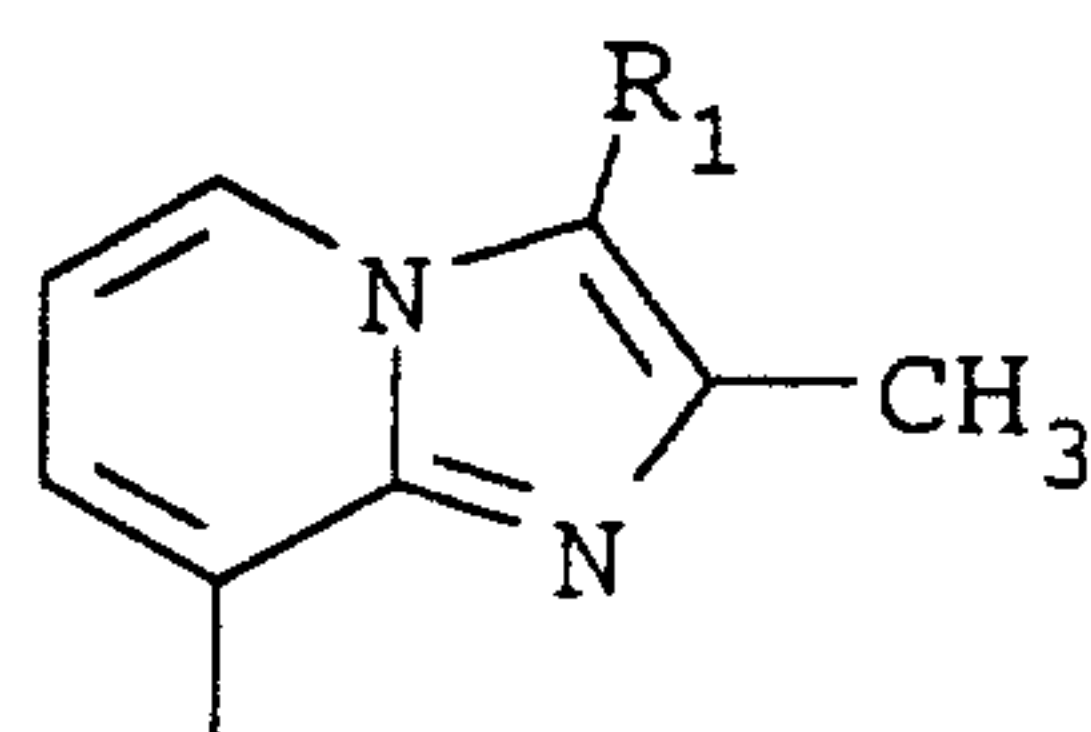
5 in which:

X is a halogen atom,

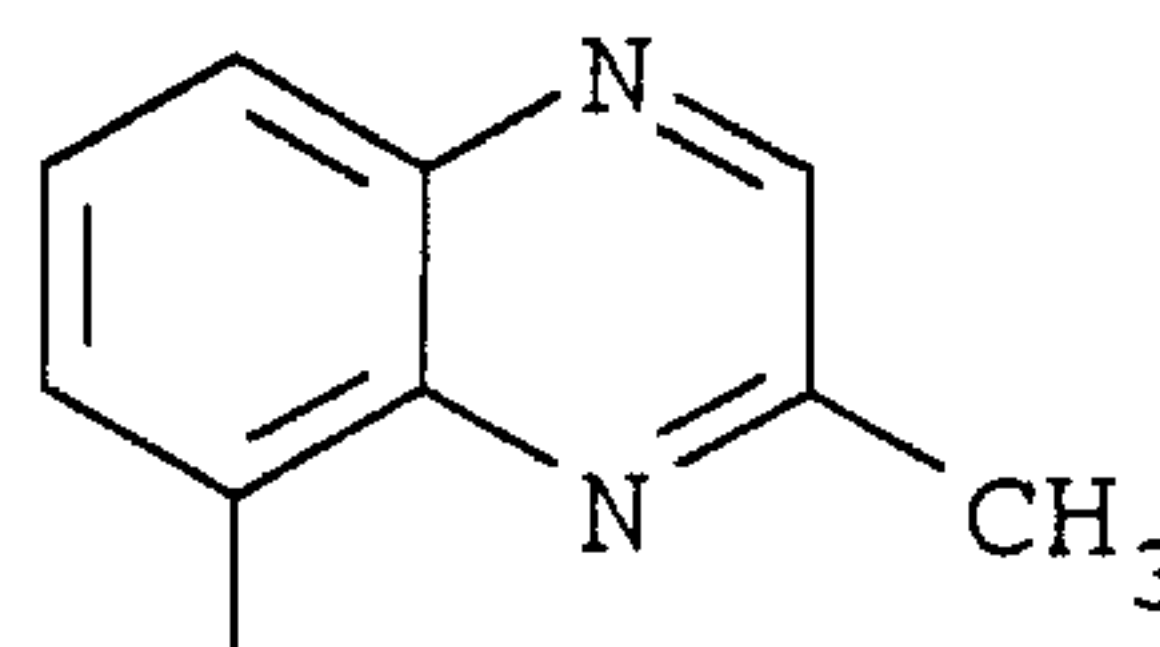
A is a divalent group



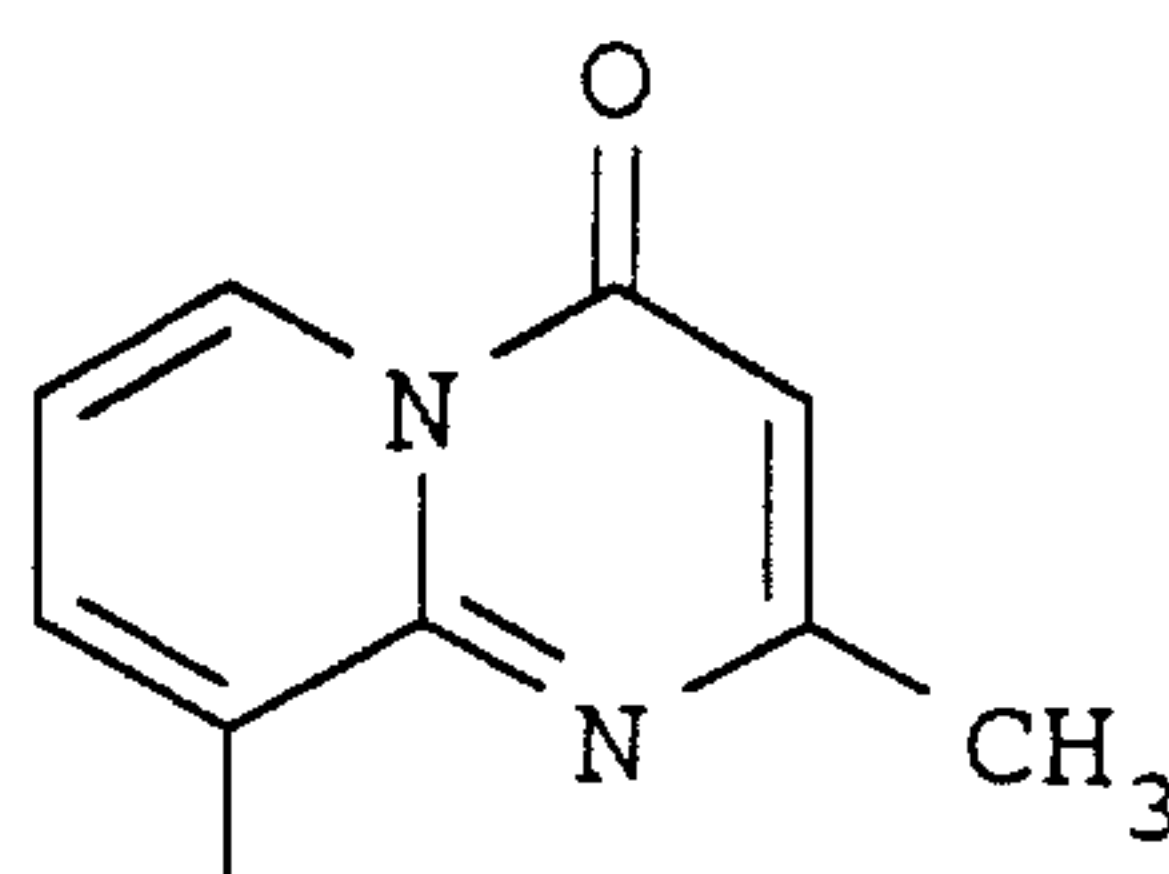
10 Q is a group



(Het 1)

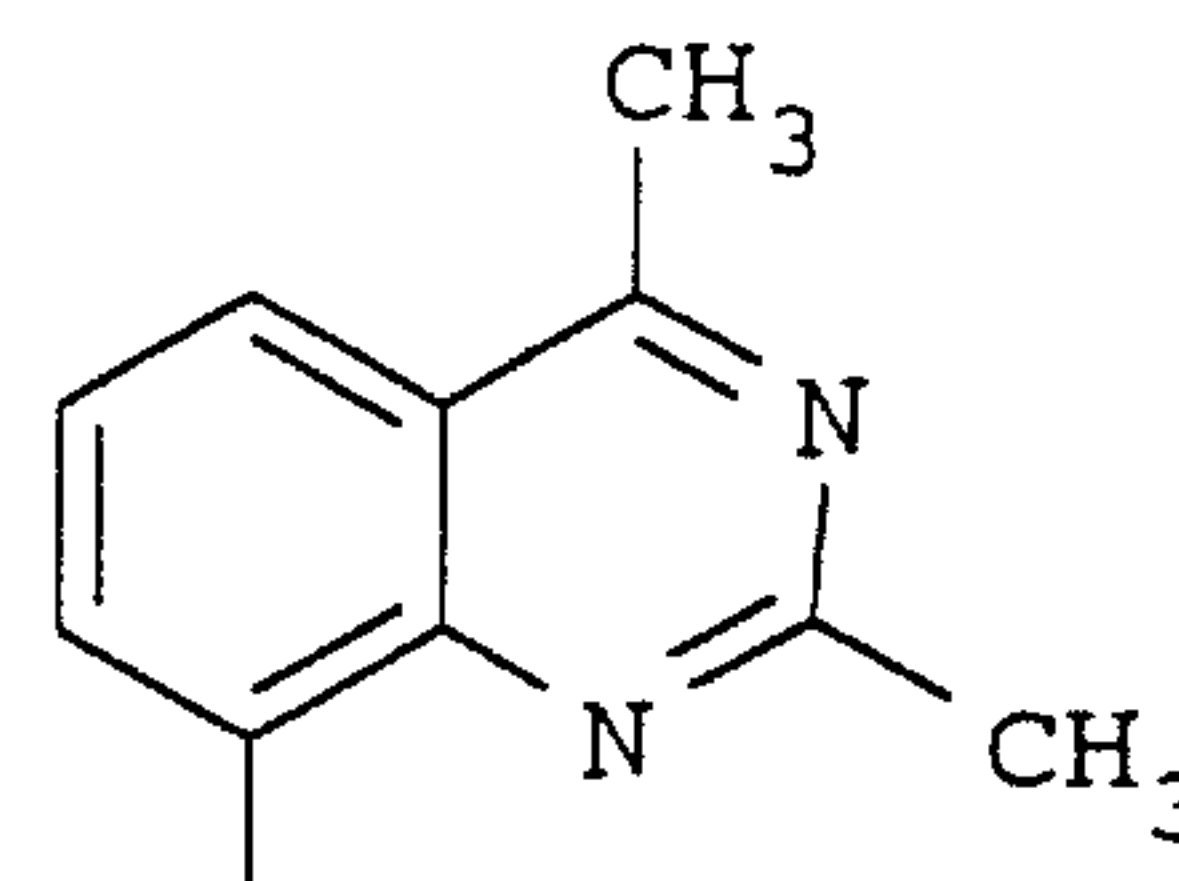


(Het 2)



(Het 3)

or



(Het 4)

15 R_1 is a hydrogen atom, a halogen atom, a C_1 - C_3 alkyl group with a linear or branched hydrocarbon chain, or a C_1 - C_5 1-oxoalkyl group,

R_2 is a hydrogen atom or an OH group, and

n is 2, 3 or 4; and

(ii) their addition salts.

According to the invention, a process for the preparation of the compounds of formula I and their addition salts is also recommended.

The use of a substance which antagonizes a receptor of bradykinin and analogous hormones is also recommended, wherein a bradykinin B₂ receptor antagonist selected from the compounds of formula I and their non-toxic addition salts is used for obtaining a drug intended for use in therapeutics to combat pathological conditions involving bradykinin or its analogs, in particular to combat pain, and especially in the treatment or prevention of pathological conditions associated with inflammatory or painful states.

10 Detailed description of the invention

In general formula I of the compounds of the invention, halogen atom is understood as meaning a fluorine, chlorine, bromine or iodine atom, the preferred halogen being the chlorine atom.

C₁-C₃ alkyl group with a linear or branched hydrocarbon chain is understood here as meaning a methyl, ethyl, propyl or 1-methylethyl group.

C₁-C₅ 1-oxoalkyl group is understood as meaning acetyl, 1-oxopropyl, 1-oxobutyl and 2-methyl-1-oxopropyl groups.

In the compound of formula I, the nitrogen heterocycle of pyrrolidine structure comprises 1 asymmetric carbon atom. According to the invention, this carbon has the S configuration, which corresponds to the configuration of L-proline.

"Addition salts" are understood as meaning the acid addition salts obtained by reacting a compound of formula I with a mineral acid or an organic acid. The preferred mineral acids for salifying a basic compound of formula I are hydrochloric, hydrobromic, phosphoric and sulfuric acids. The preferred organic acids for salifying a basic compound of formula I are methanesulfonic, benzenesulfonic, maleic, fumaric, oxalic, citric, lactic and trifluoroacetic acids.

"Room temperature" is understood here as meaning a temperature of 15 to 25°C and "temperature close to room temperature" is understood here as meaning a temperature of 0 to 40°C and preferably of 10 to 35°C.

The general process recommended according to the invention for the preparation of the compounds of formula I comprises, according to a first variant A, the steps which consist in:

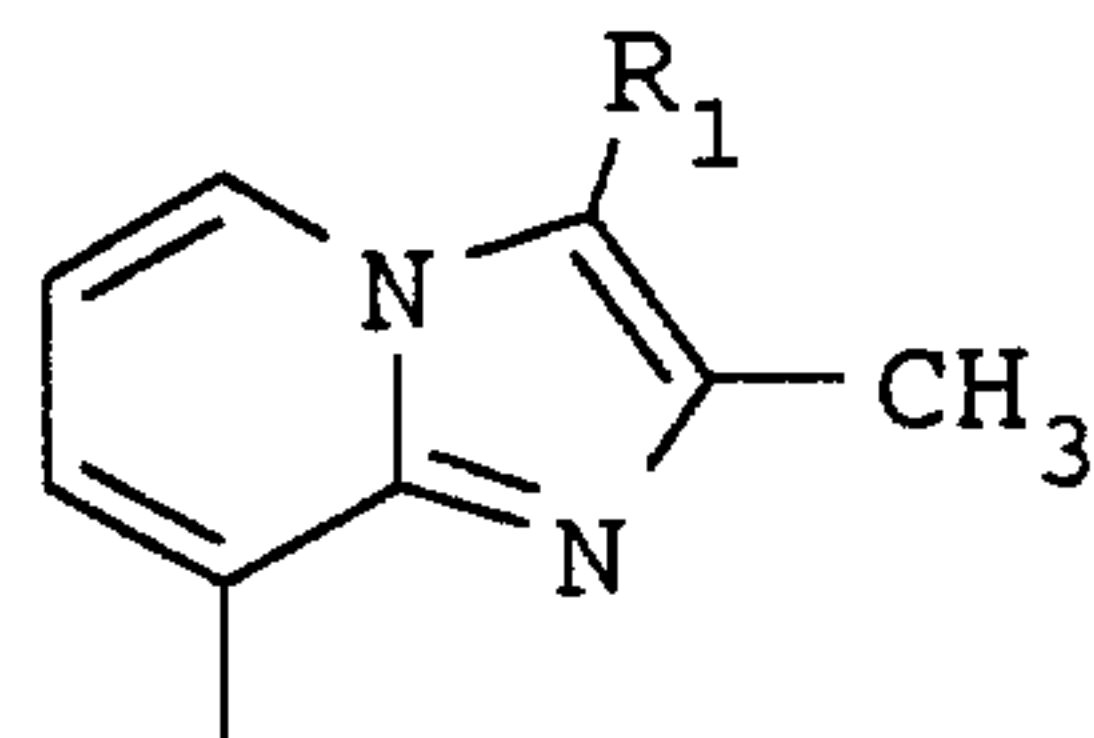
(1) reacting a hydroxylated heterocyclic compound of the formula

35 Q-O-Met

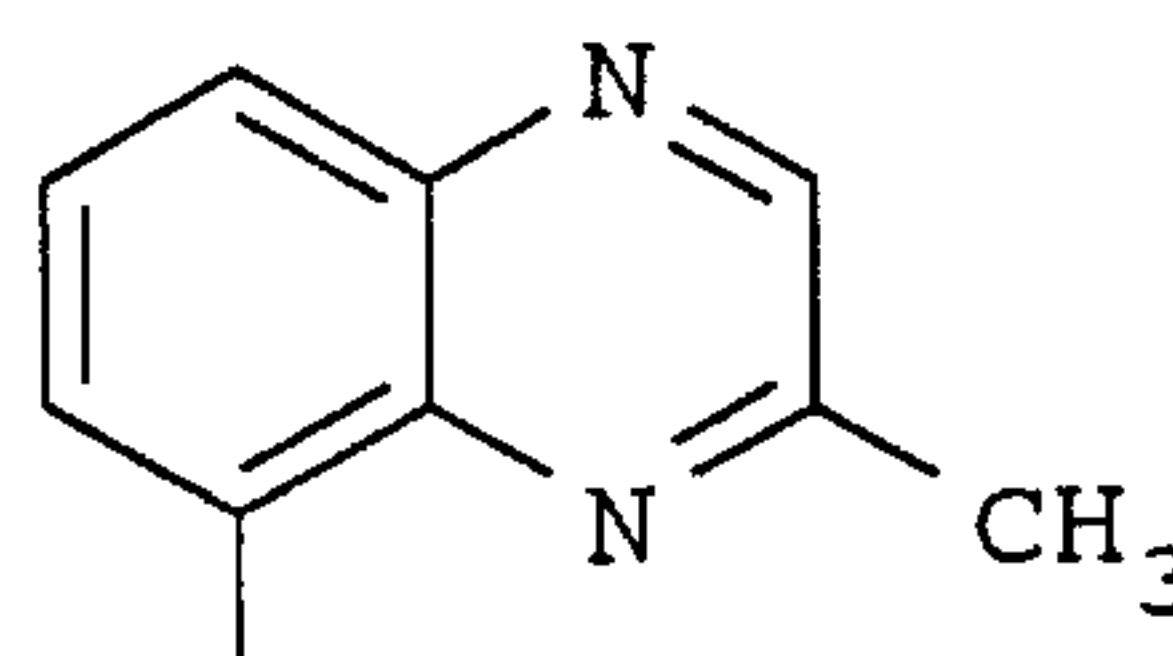
in which:

Met is an alkali metal, especially Na or K, and

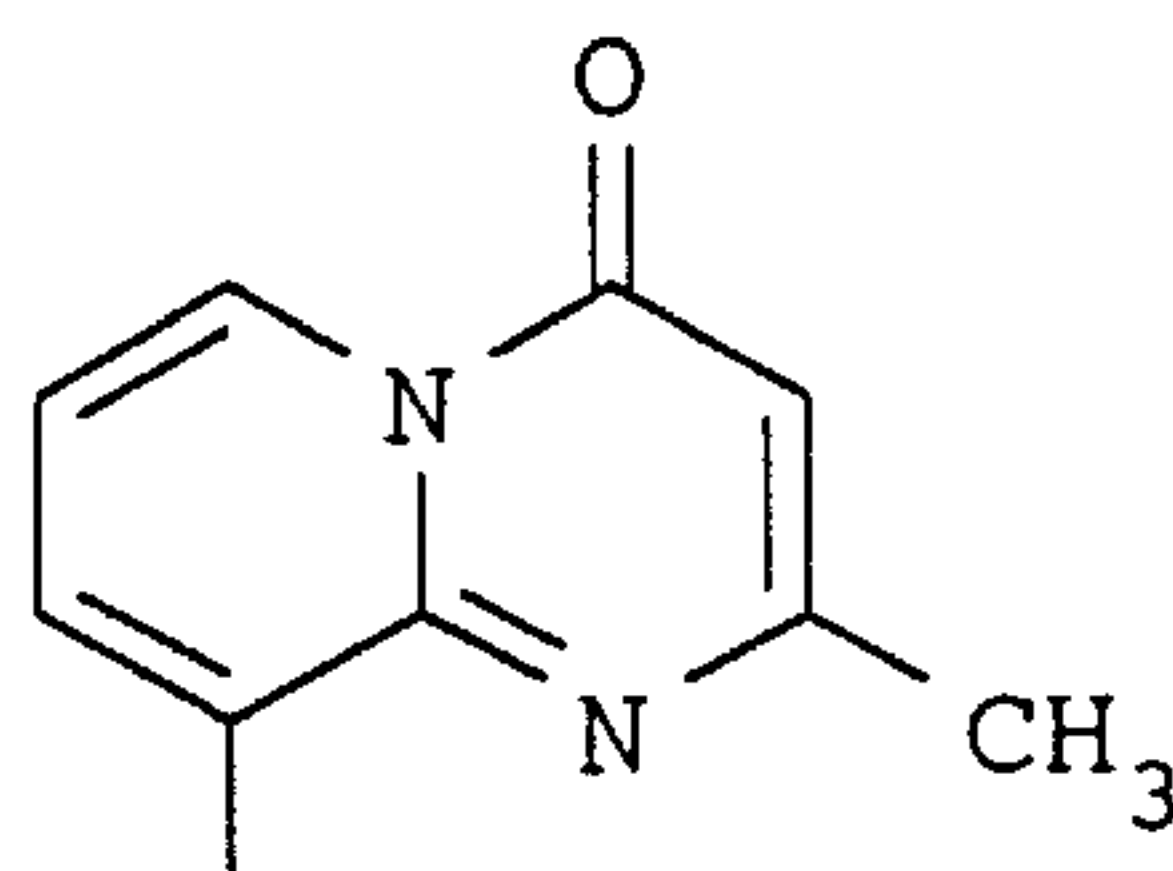
Q is a heterocyclic group selected from the structures Het 1, Het 2, Het 3 and Het 4:



(Het 1)

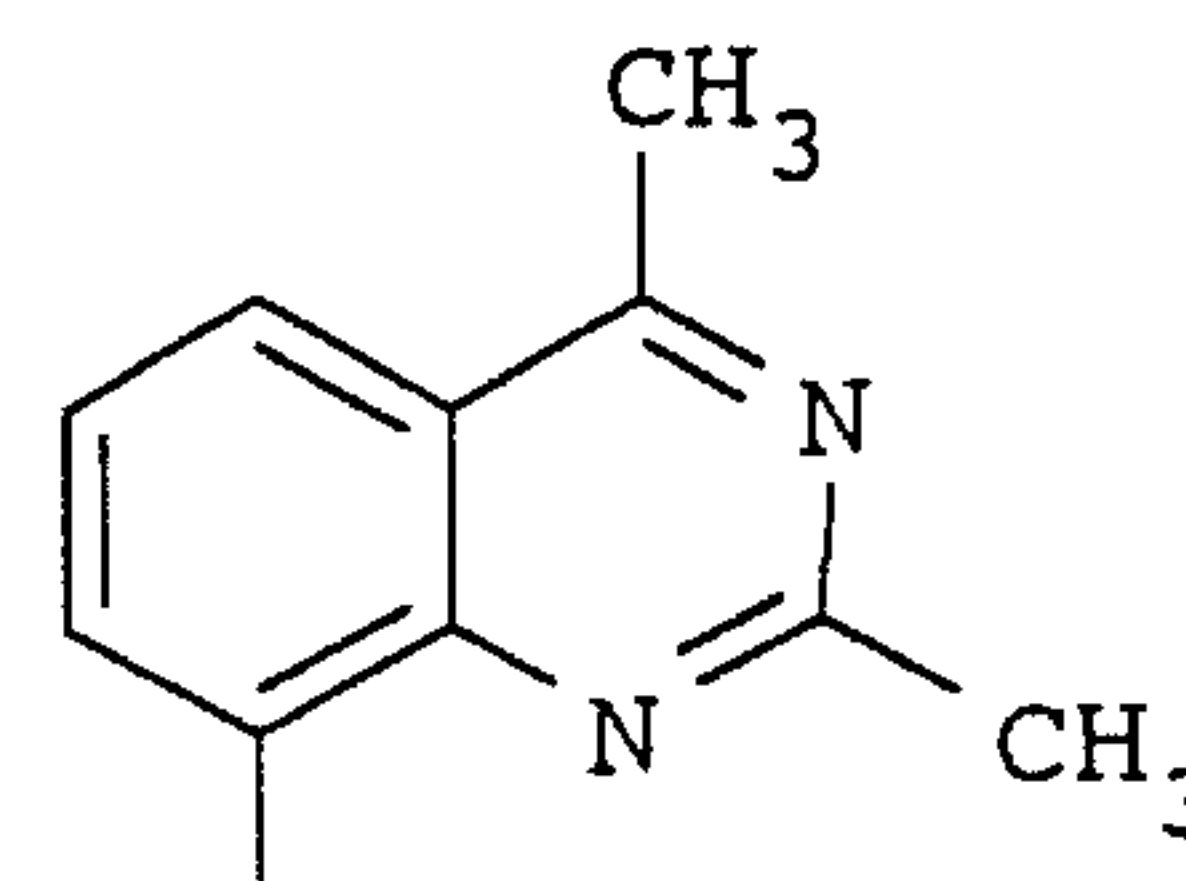


(Het 2)



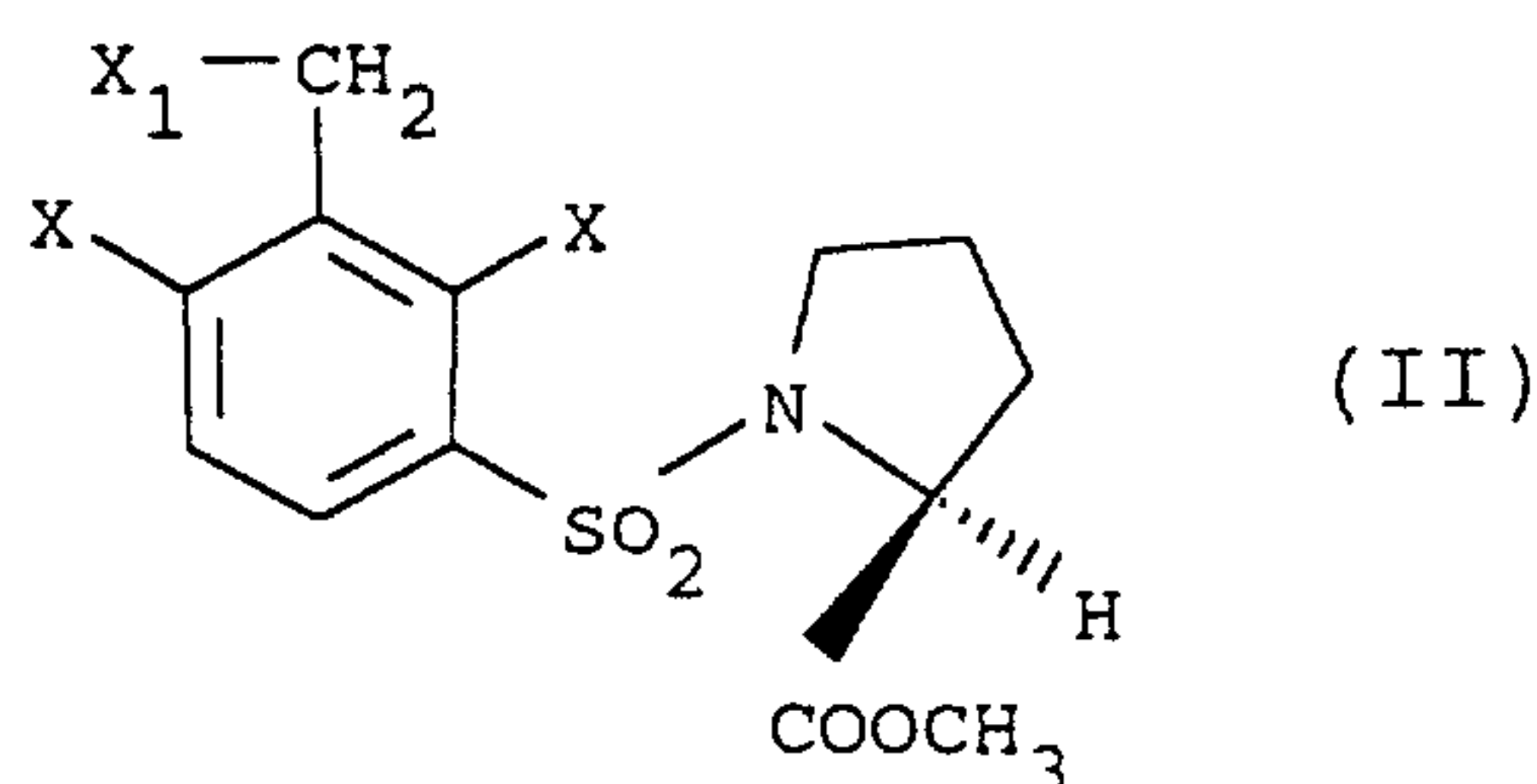
(Het 3)

and



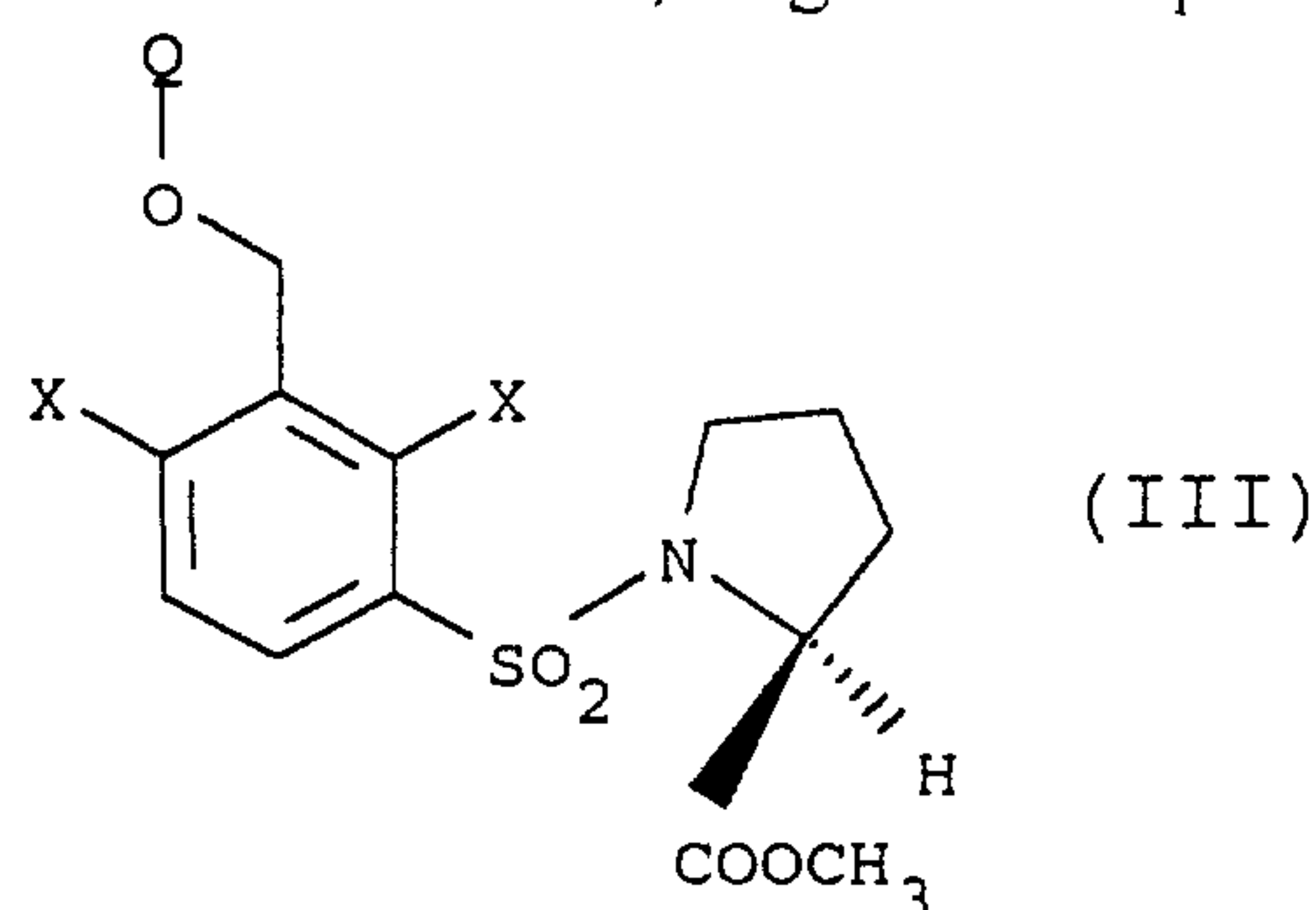
(Het 4)

- 5 R_1 being a hydrogen atom or a C_1 - C_3 alkyl group, with a compound of formula II:



(II)

- in which X is a halogen atom and X_1 is a halogen atom, preferably a bromine atom,
in an anhydrous solvent, for example dimethylformamide, at a temperature of
10 between 0 and 50°C, for 0.5 to 10 hours, to give a compound of formula III:

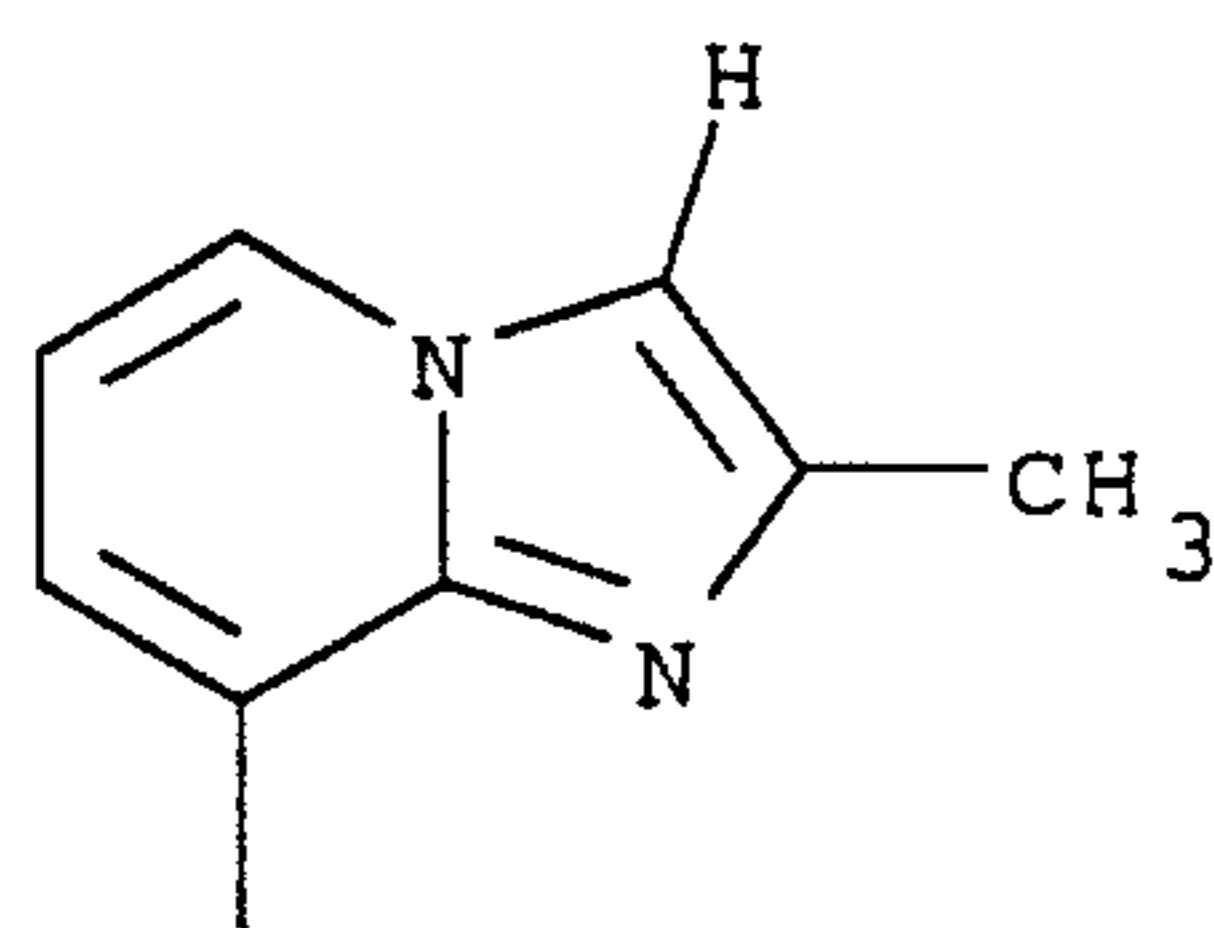


(III)

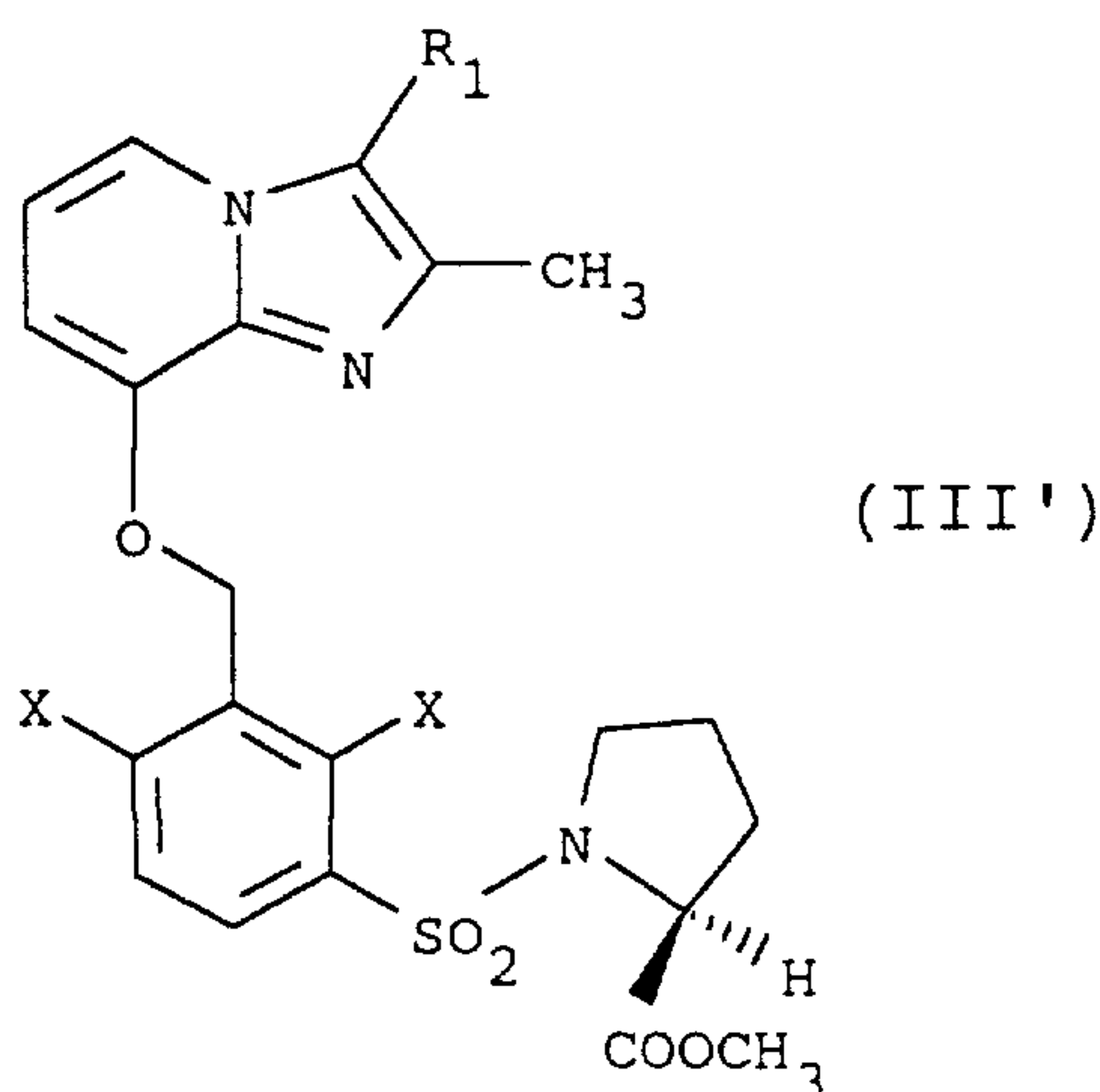
in which Q, X and R_1 are as defined above;

(2) if necessary, if Q in the compound of formula III is the group Het 1 in which R_1 is a hydrogen atom:

6



reacting said compound of formula III with a halogenating agent such as N-bromosuccinimide or N-chlorosuccinimide, in an appropriate solvent, especially a halogenated solvent, an ether or an alcohol, at a temperature of between about 0
5 and 50°C, for 0.5 to 20 hours, to give a compound of formula III':

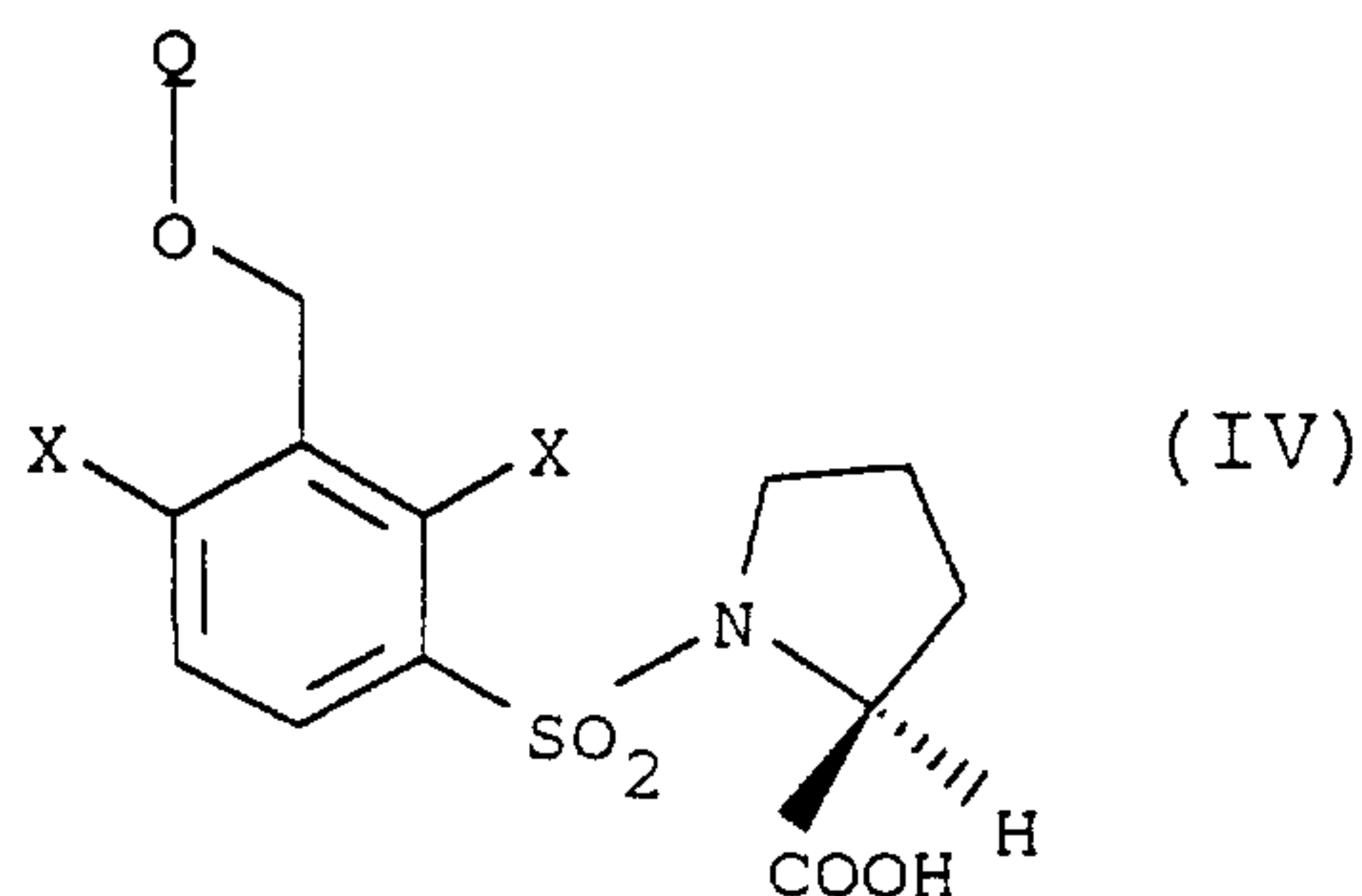


in which:

R₁ is a halogen atom, preferably bromine or chlorine;

10 (3) hydrolyzing the ester group of the compound of formula III or III' obtained according to one of steps (1) or (2) above, especially by reaction with aqueous sodium hydroxide solution in a miscible solvent such as methanol, at a temperature of the order of 20 to 60°C, for 1 to 5 hours, to give, after acidification, a compound of formula IV:

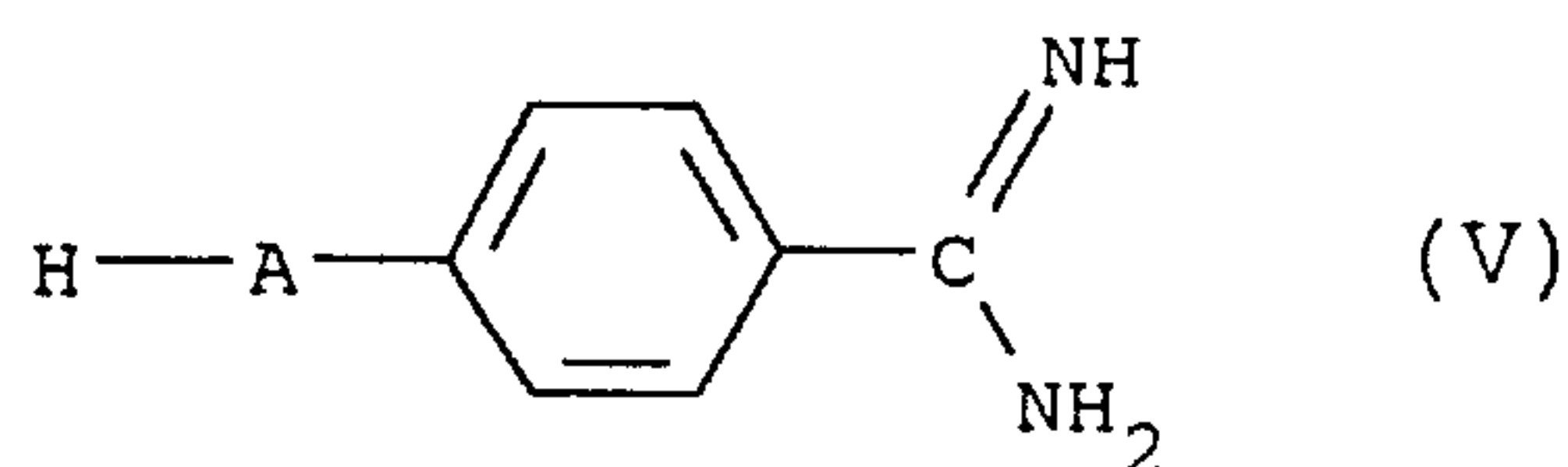
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in which Q and X are as defined above and R₁ is a hydrogen atom, a halogen atom

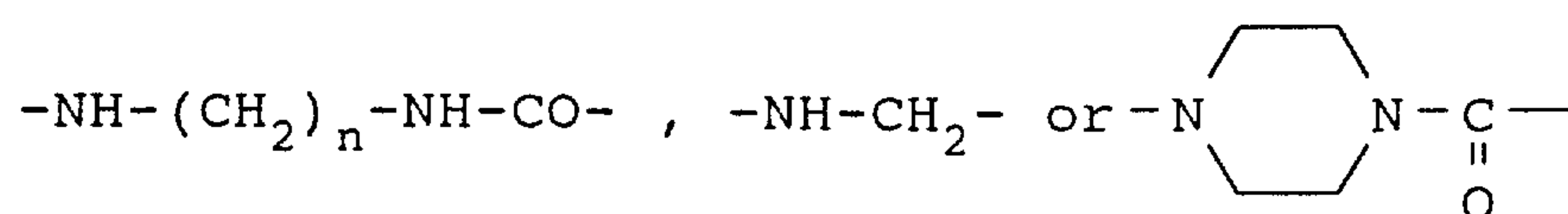
or a C₁-C₃ alkyl group;

(4) reacting the resulting compound of formula IV with the salt of an amine of the formula



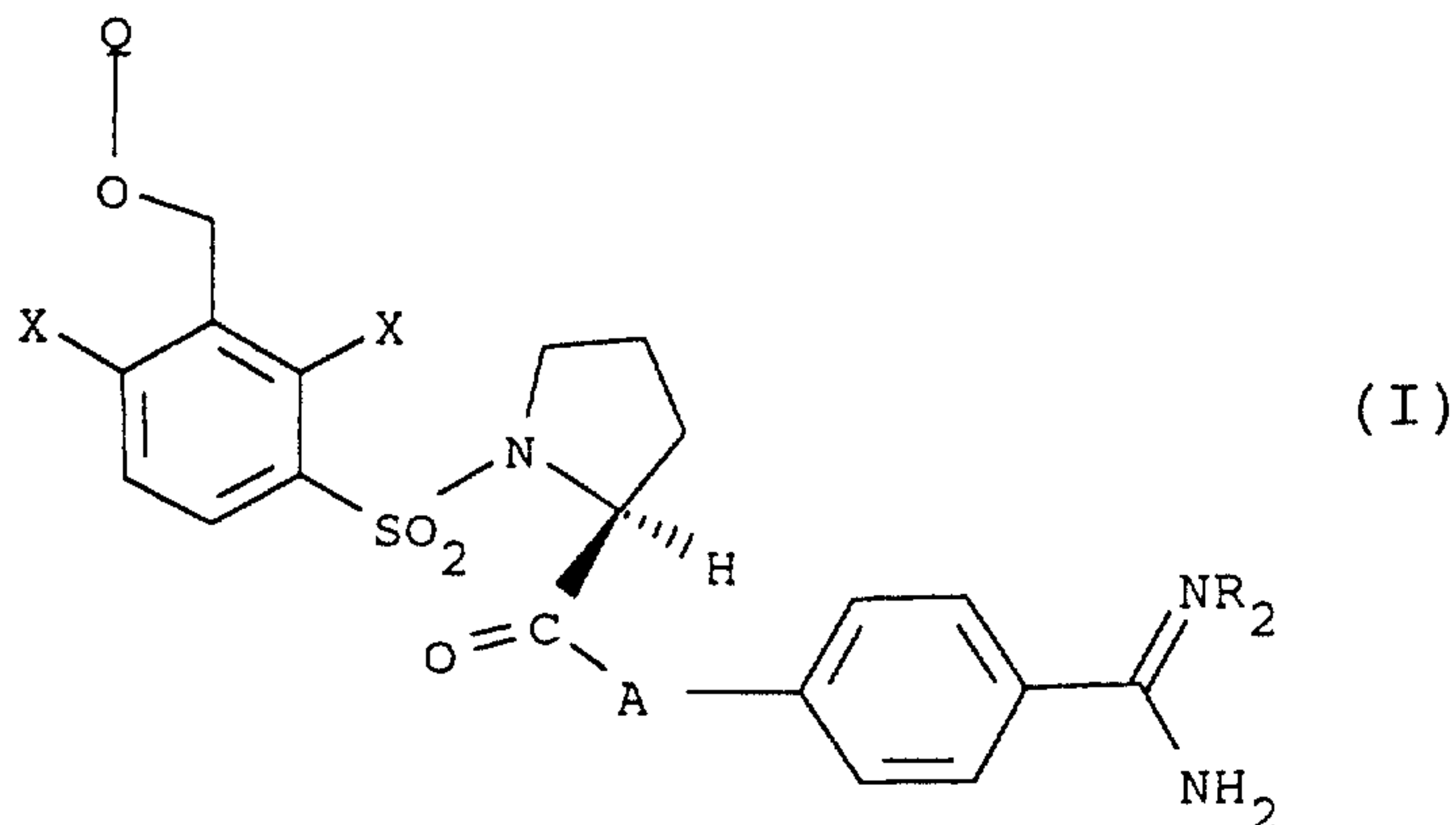
5

in which A is a group



in which n is 2, 3 or 4,

10 in an appropriate solvent, especially dichloromethane, in the presence of activators such as, in particular, 1-hydroxy-7-azabenzotriazole (HOAT) and 1-[3-(dimethylaminopropyl)-3-ethyl]carbodiimide (EDCI) hydrochloride, at a temperature close to room temperature (10 - 35°C), for 2 to 50 hours, to give a compound of formula I in which R₂ is H:



15

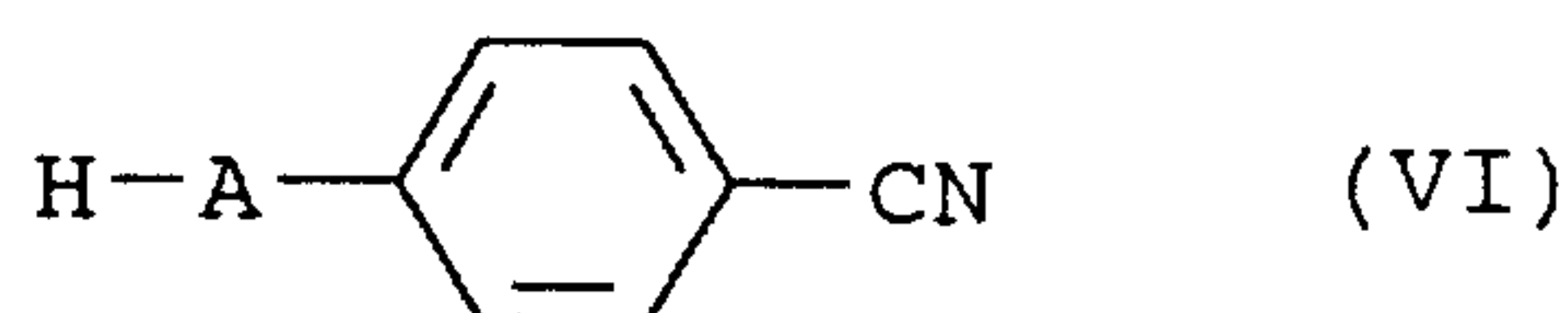
in which A, Q, X and R₁ are as defined above and R₂ is H; and

(5) if necessary, reacting the resulting compound of formula I with an acid to give the corresponding acid addition salt;

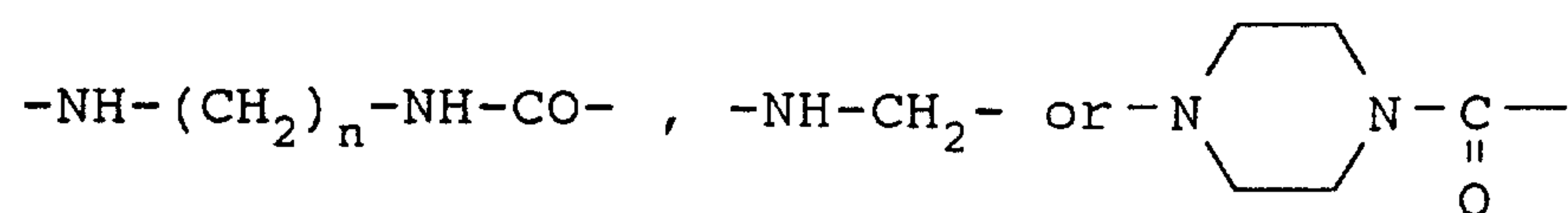
according to a second variant B, the steps which consist in:

20 (1) reacting the acid compound of formula IV, obtained for example in step (3) of variant A, in which R₁ is a hydrogen atom, a chlorine atom, a C₁-C₃ alkyl group with a linear or branched hydrocarbon chain, or a C₁-C₅ 1-oxoalkyl group, with a compound of formula VI:

8

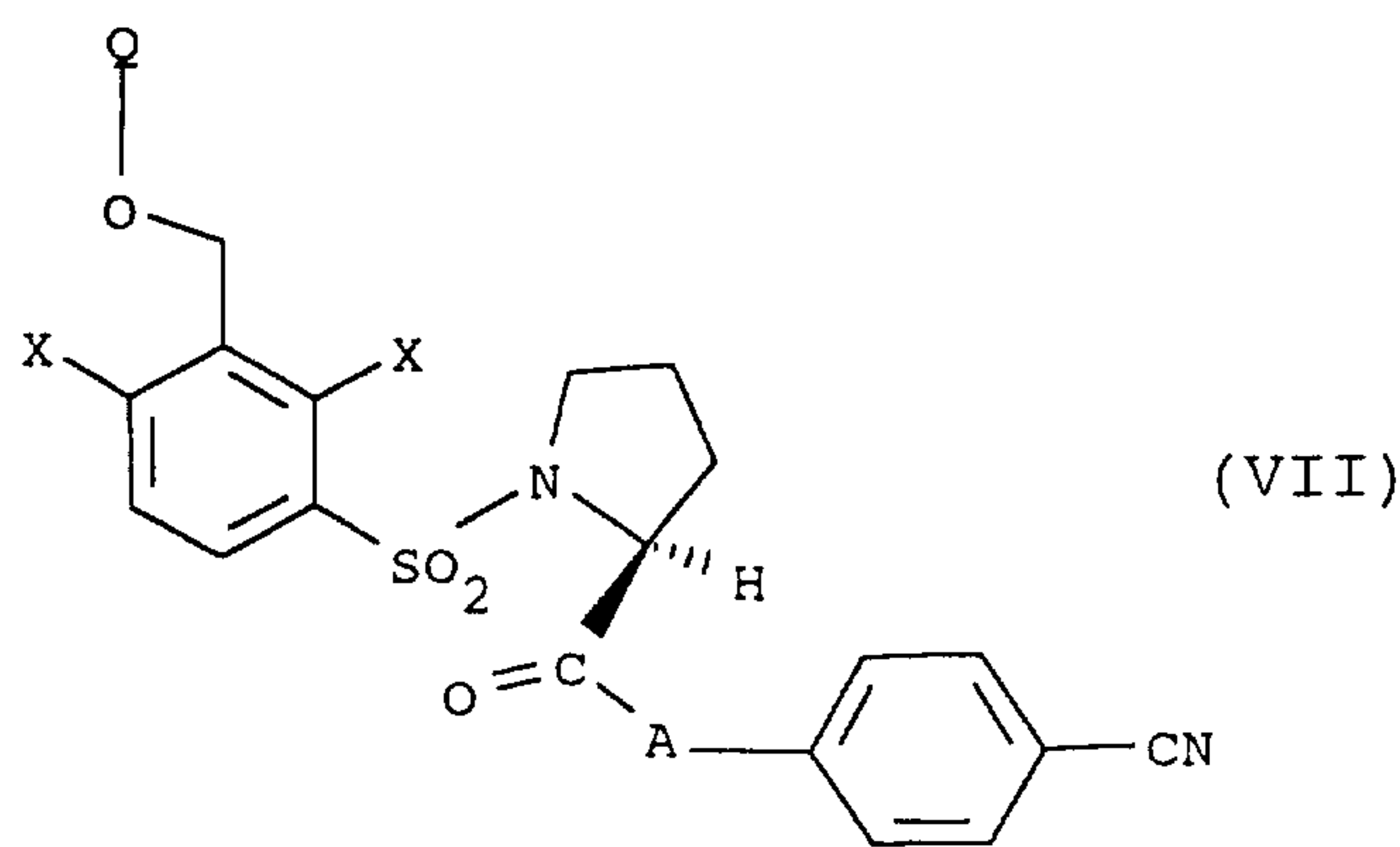


in which A is a group



in which n is 2, 3 or 4,

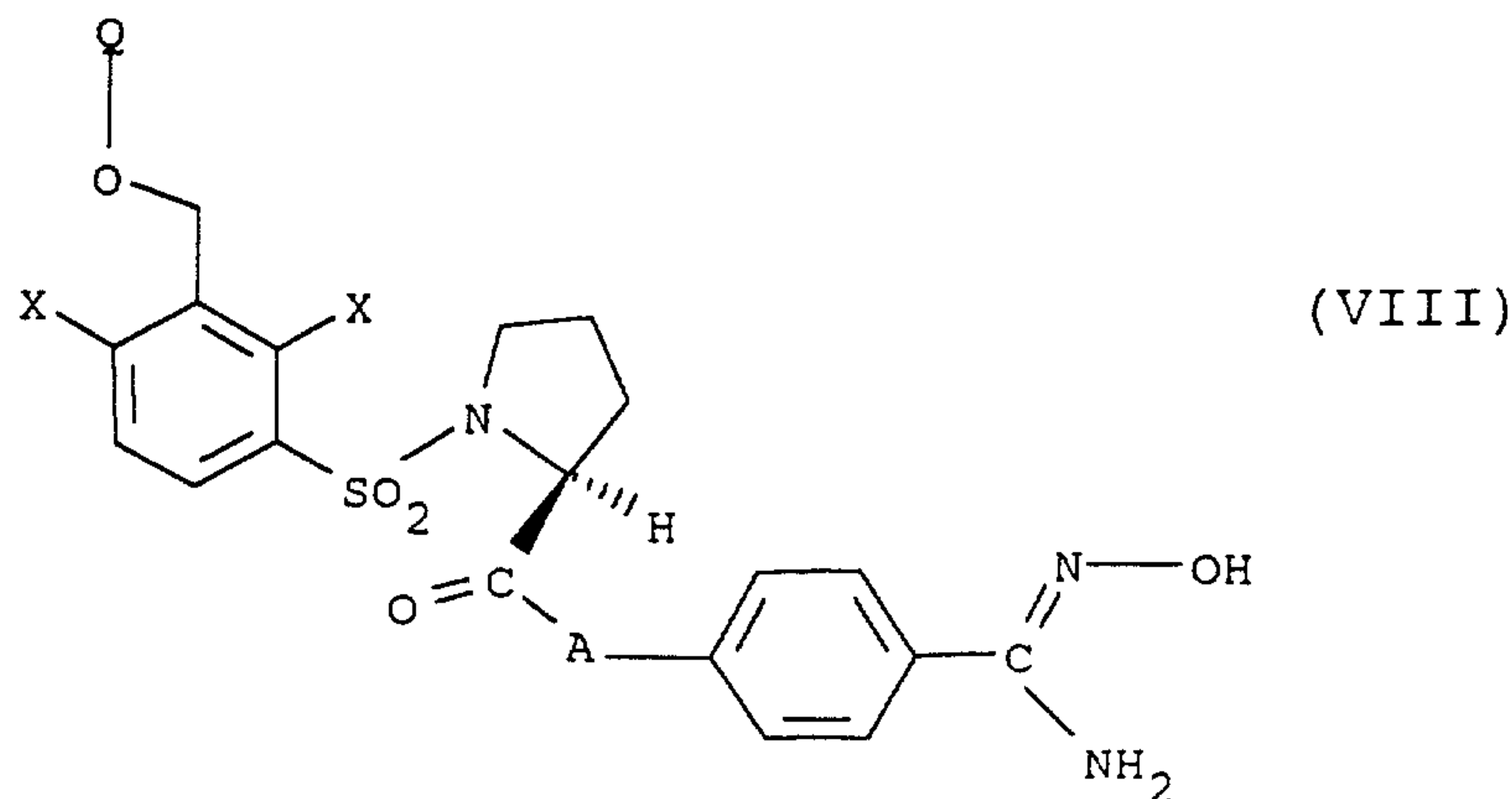
- 5 under conditions analogous to those recommended for carrying out step (4) of variant A above, to give a compound of formula VII:



in which Q, R₁, X and A are as defined in the starting materials;

- 10 (2) reacting the resulting compound of formula VII with hydroxylamine (freed from its hydrochloride by the action, in the reaction medium, of an aprotic strong base such as triethylamine) in an appropriate solvent, especially an aprotic solvent such as dimethyl sulfoxide (DMSO), at room temperature (15 - 25°C), for 1 to 12 hours, to give a compound of formula VIII:

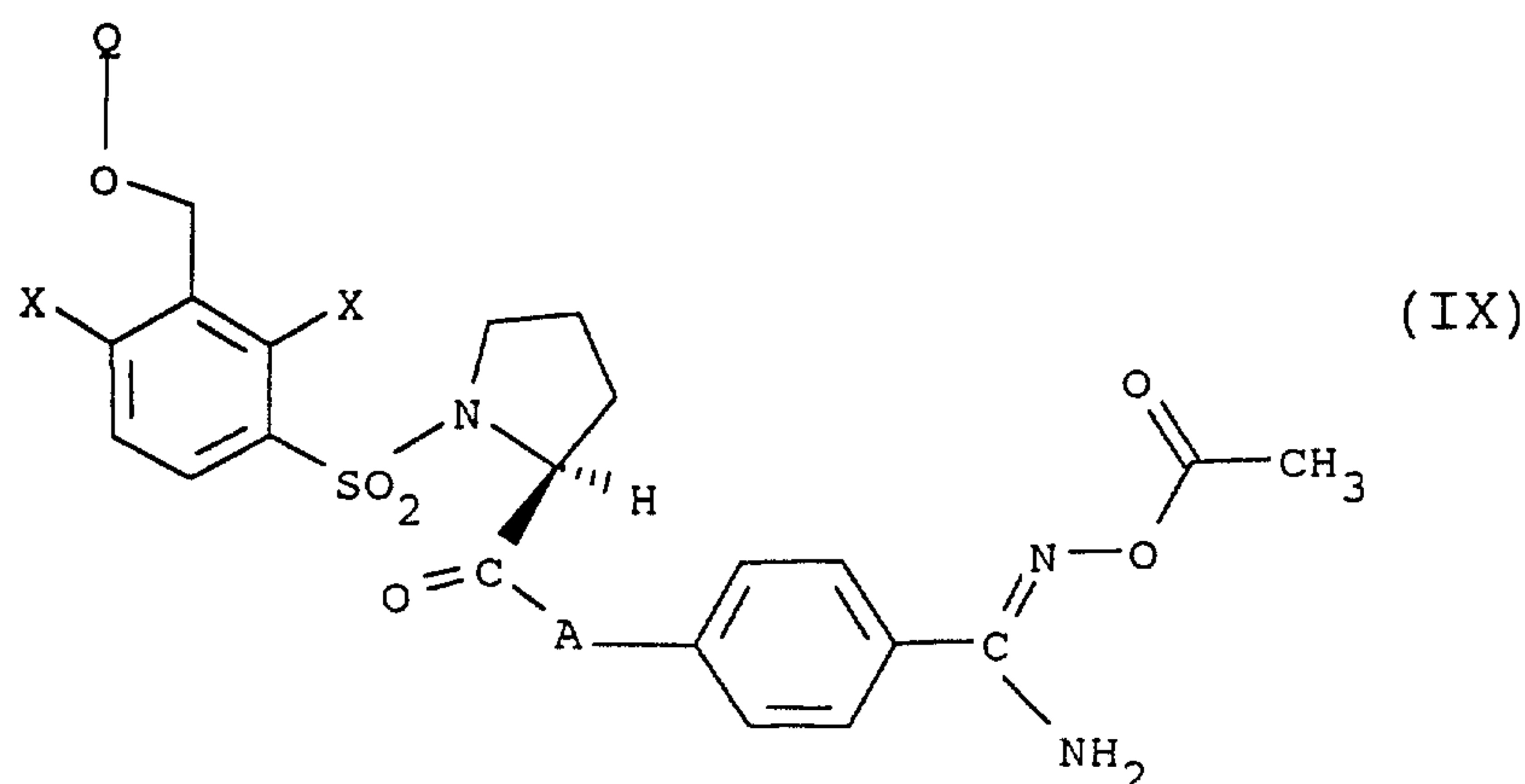
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in which Q, R₁, X and A are as defined above;

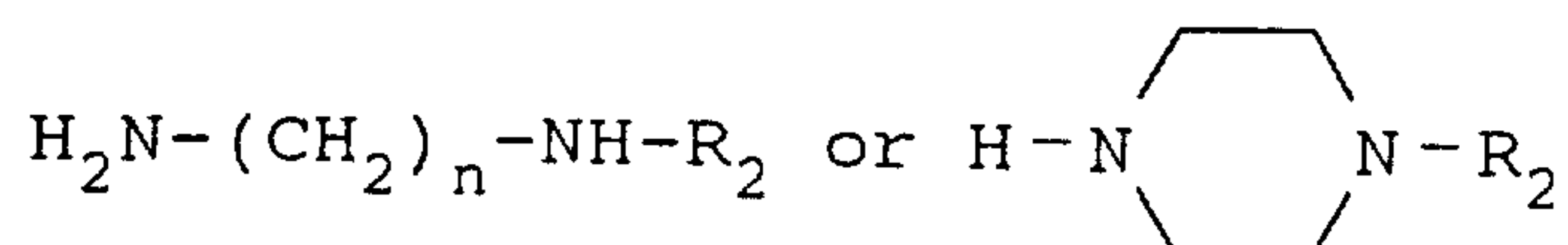
- (3) acetylating the resulting compound of formula VIII, at a temperature close to

room temperature, for 1 to 8 hours, to give the compound of formula IX:



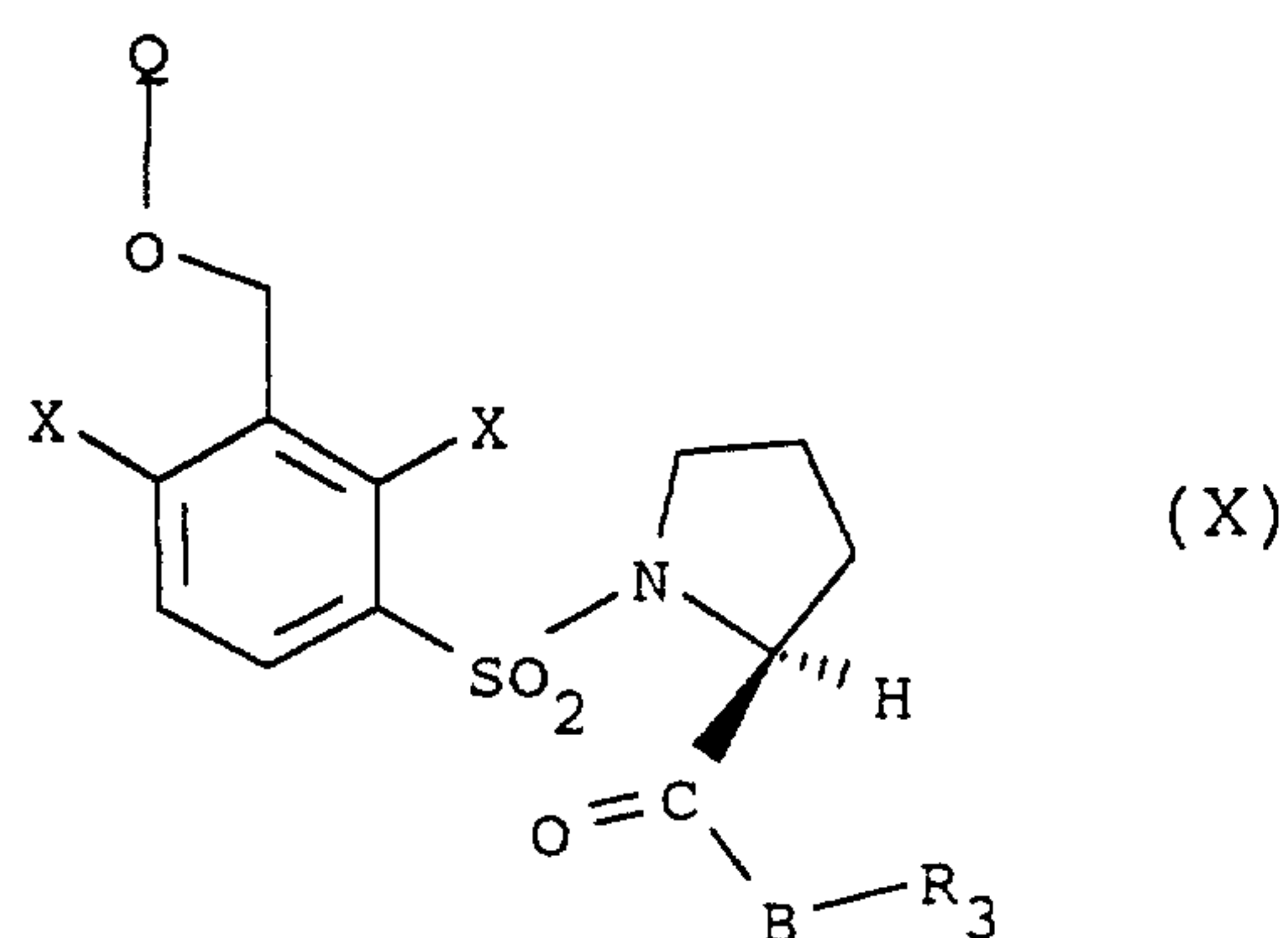
in which Q, R₁, X and A are as defined above; and

- 5 (4) reducing the resulting compound of formula IX by catalytic hydrogenation, especially in a solvent such as methanol, in the presence of a hydrogenation catalyst such as Lindlar's catalyst, at a temperature close to room temperature, under a hydrogen pressure of between 10⁵ and 10⁶ Pascals, to give the compound of formula I in which Q, R₁, X and A are as defined above and R₂ is H;
- 10 according to a third variant C, the steps which consist in:
 - (1) reacting the compound of formula V, obtained according to step (3) of variant A, with an amine of the formula

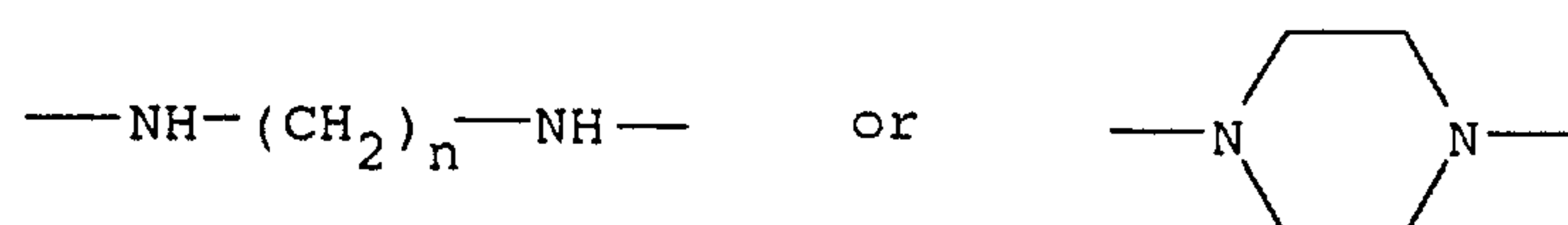


- 15 in which n is 2, 3 or 4, and
 R₂ is an amino-protecting group such as the "Boc" (1,1-dimethylethoxycarbonyl) group,
 under operating conditions analogous to those recommended for carrying out step
 (4) of variant A, to give a compound of formula X:

10



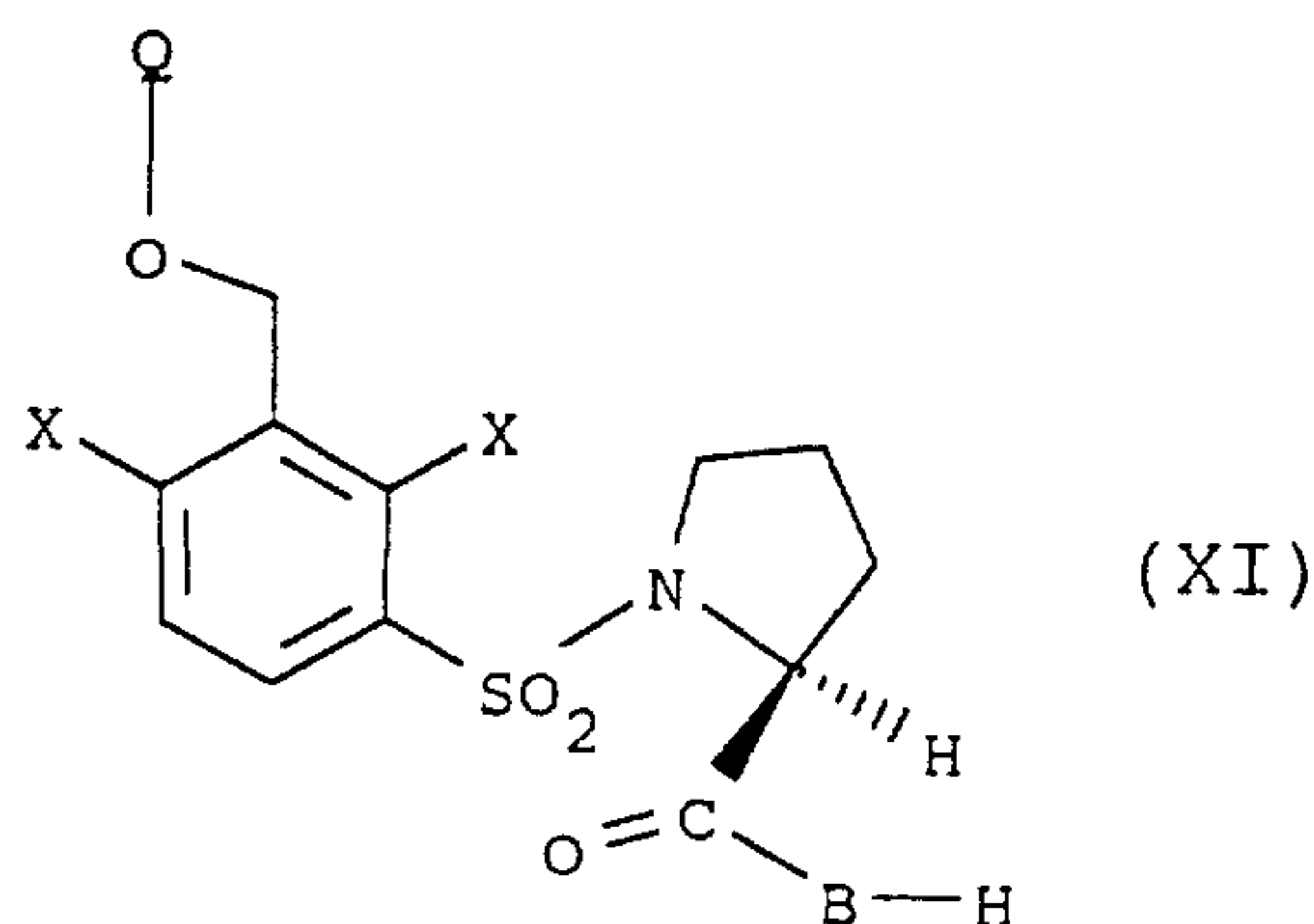
in which B is



5 and Q, R₁ and X are as defined above;

(2) deprotecting the amine group of the resulting compound of formula X so as to replace the group R₂ with a hydrogen atom, for example, if R₂ is the Boc group, by reaction with an acid in solution in a solvent such as ethyl acetate, at room temperature, for 4 to 30 hours, to give the compound of formula XI:

10

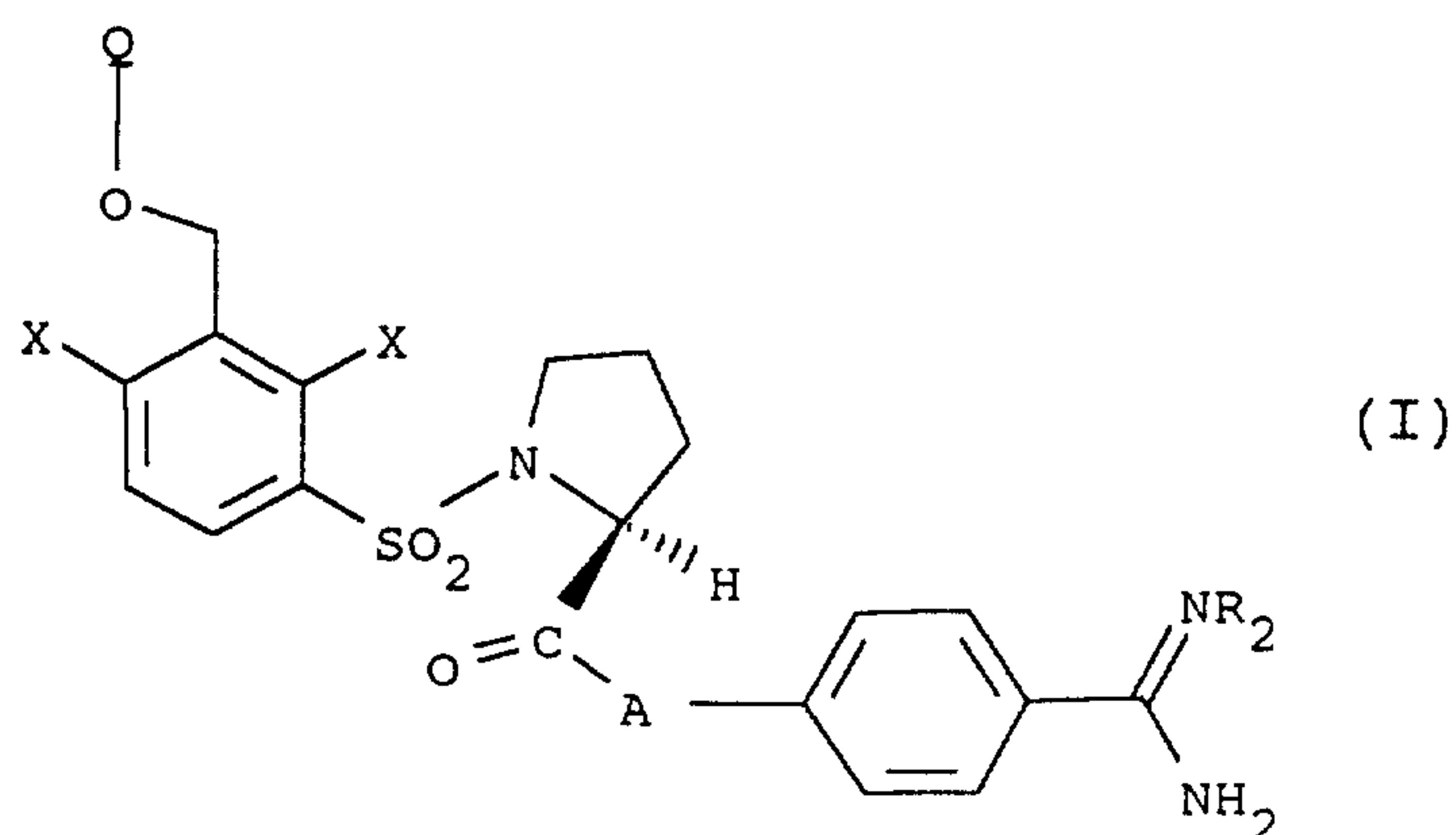


in which B, Q, R₁ and X are as defined above; and

(3) reacting the resulting compound of formula XI with 4-(aminoiminomethyl)-benzoic acid, under conditions analogous to those previously described in step (4) of variant A above, to give the compound of formula I in which R₂ is H:

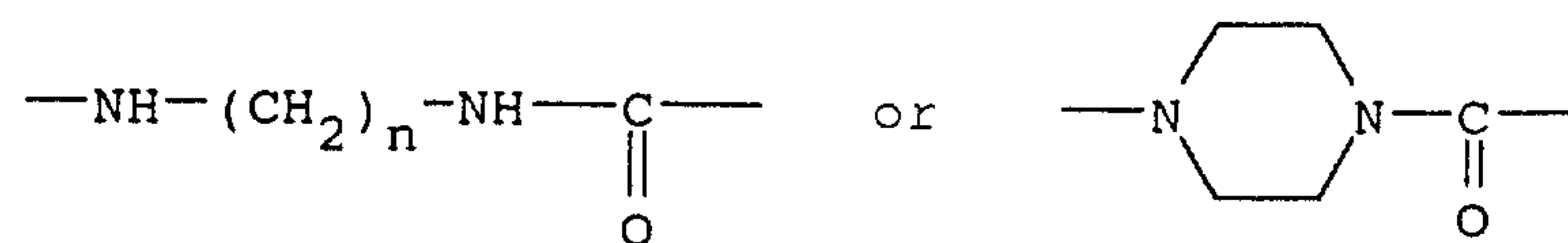
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in which:

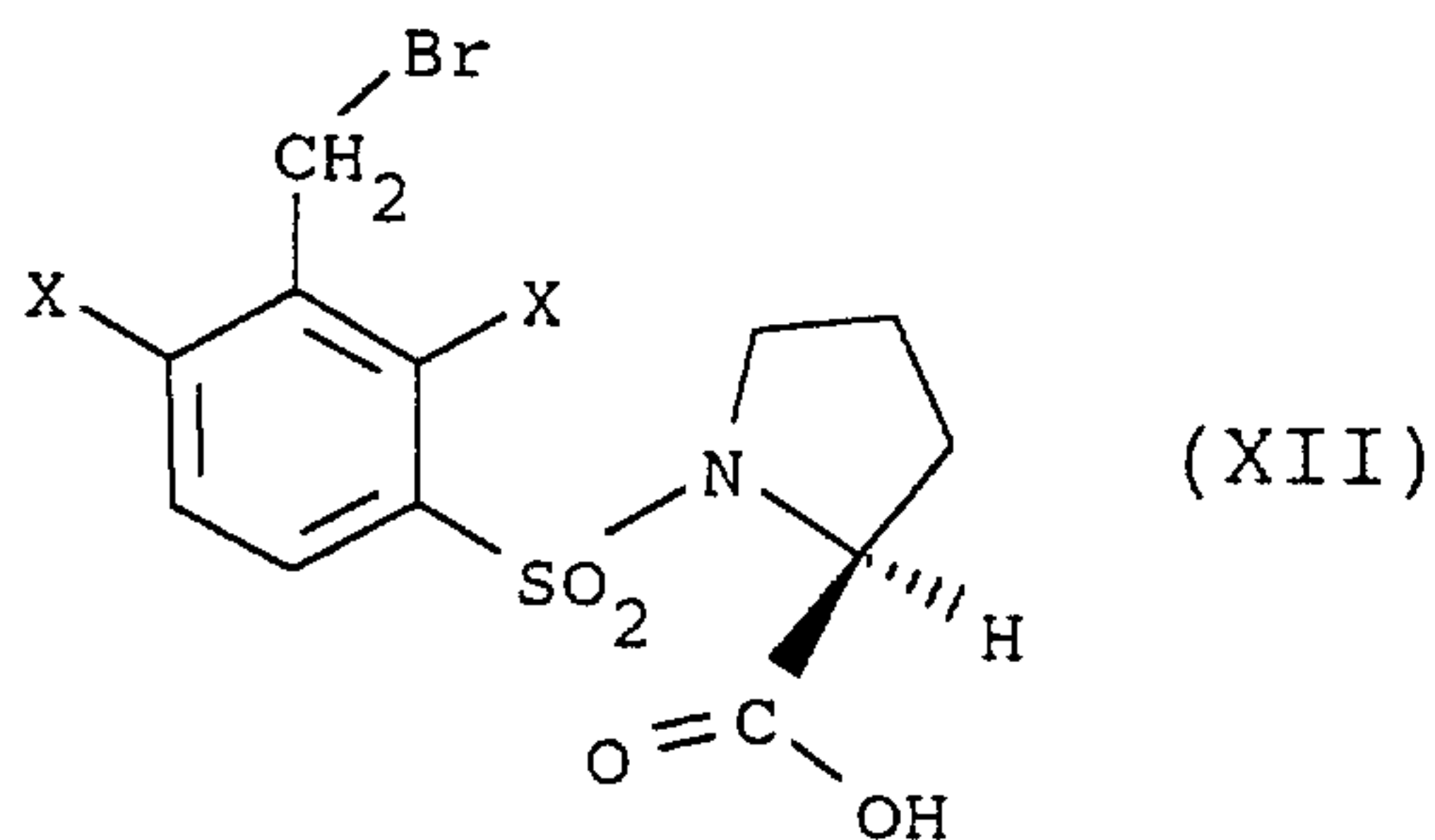
Q, R₁ and X are as defined above, R₂ is H and A is a group



5

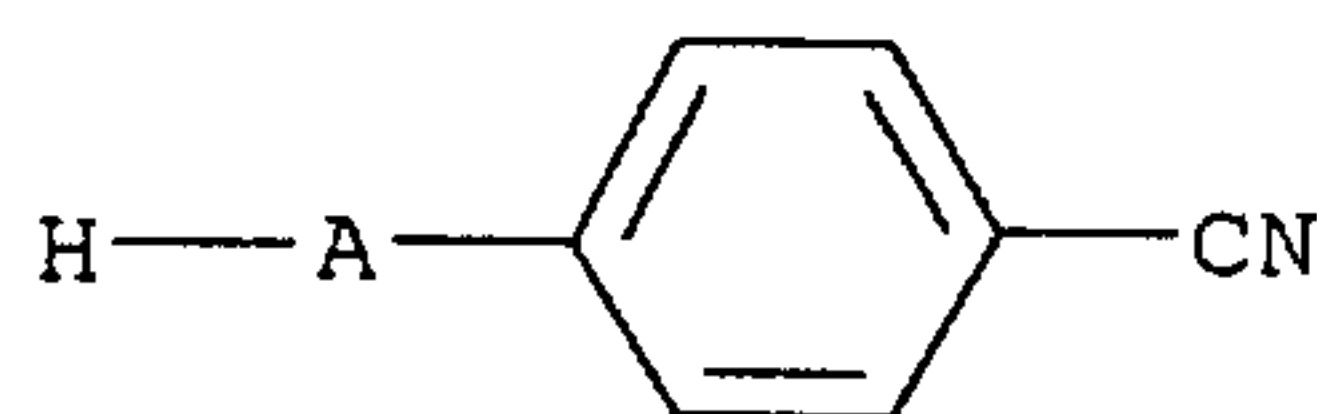
and according to a fourth variant D, the steps which consist in:

(1) reacting the acid of the formula

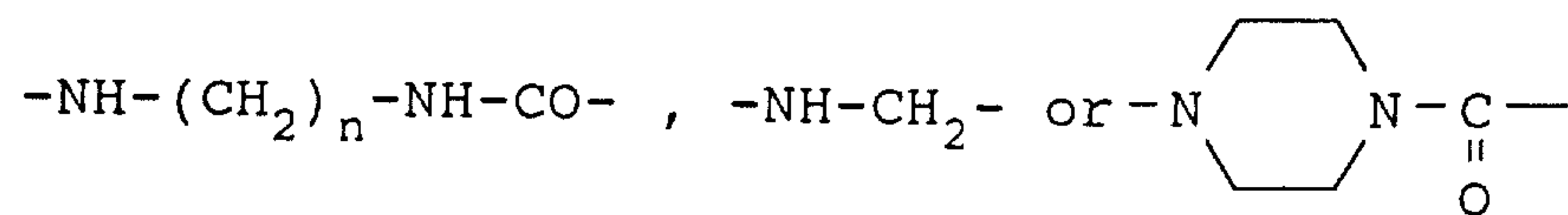


in which X is a halogen,

10 with a compound of the formula



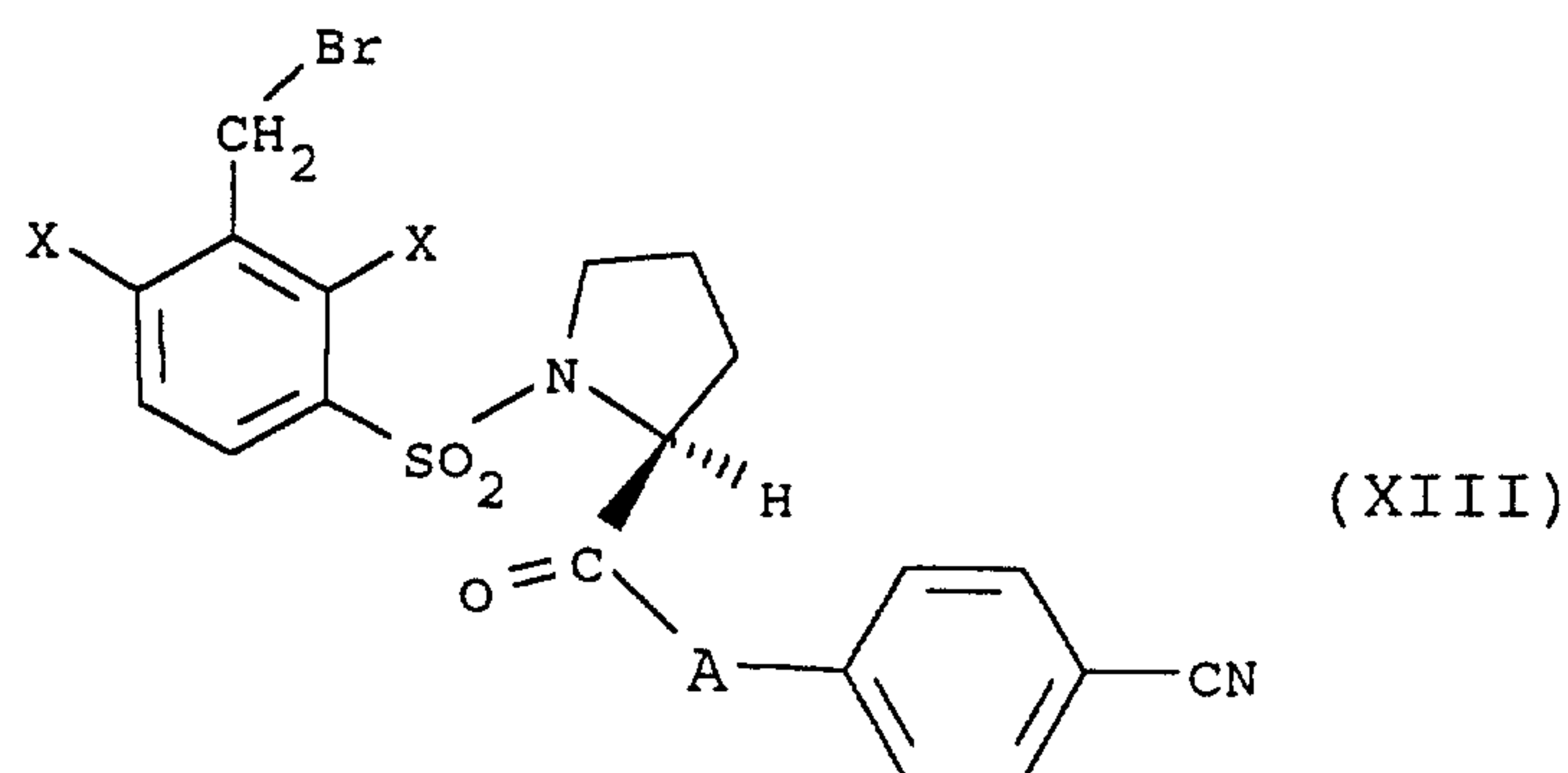
in which A is a group



15 in which n is 2, 3 or 4,

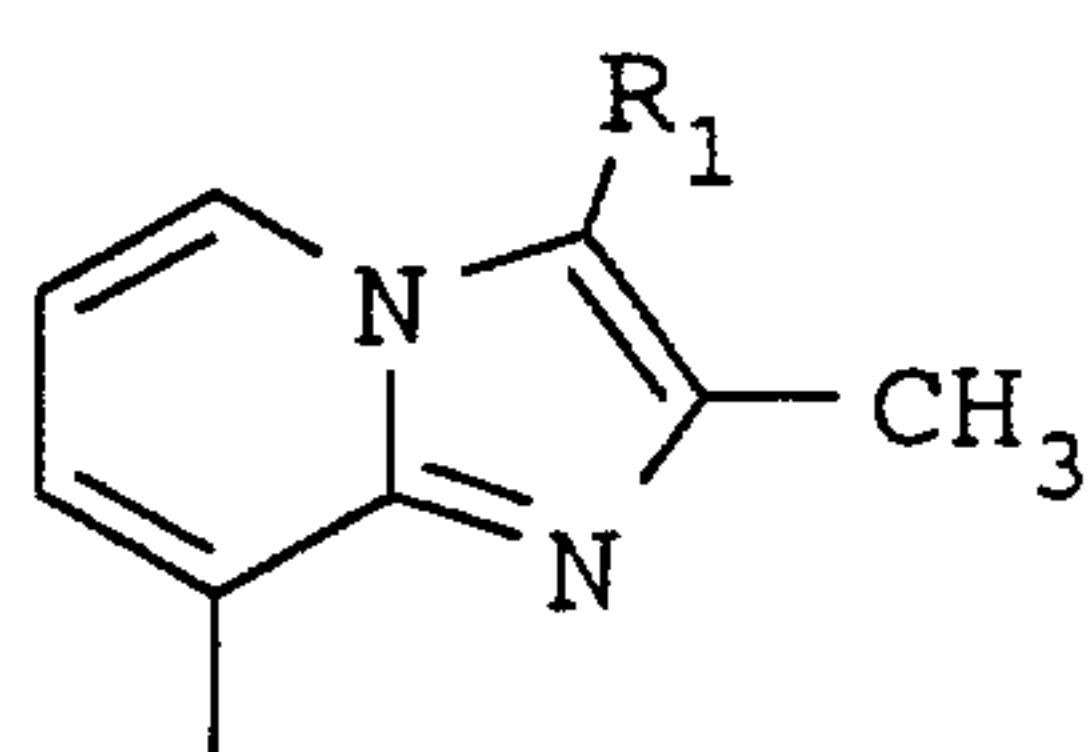
under reaction conditions analogous to those recommended for carrying out step (4) of variant A above, to give the compound of formula XIII:

12

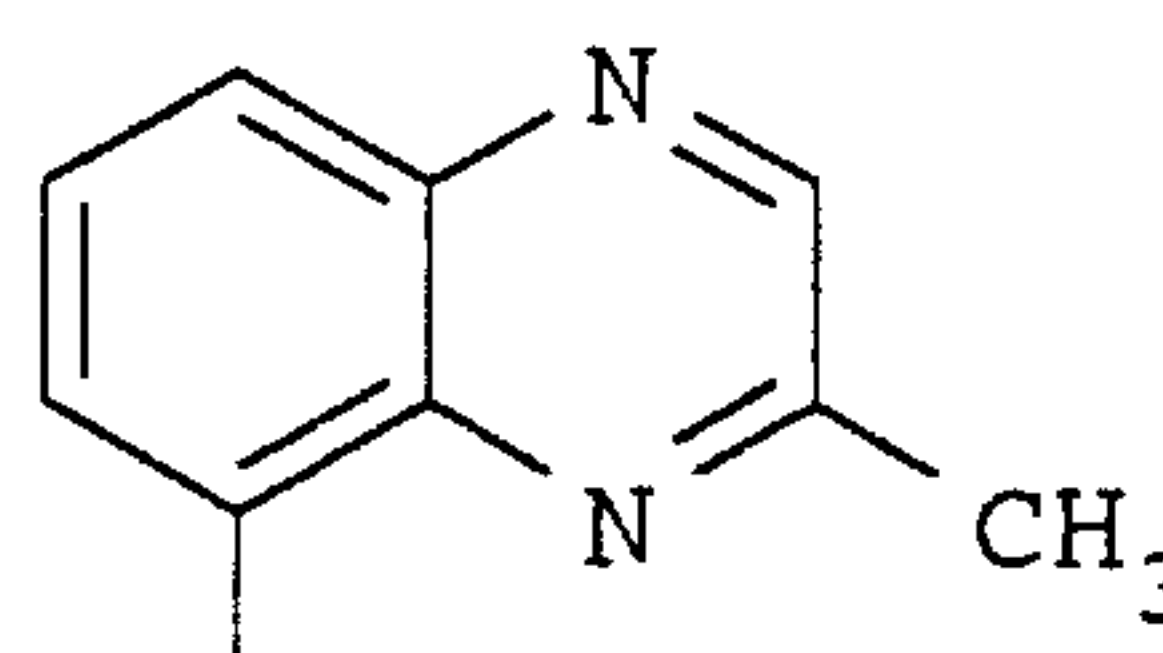


in which A and X are as defined above;

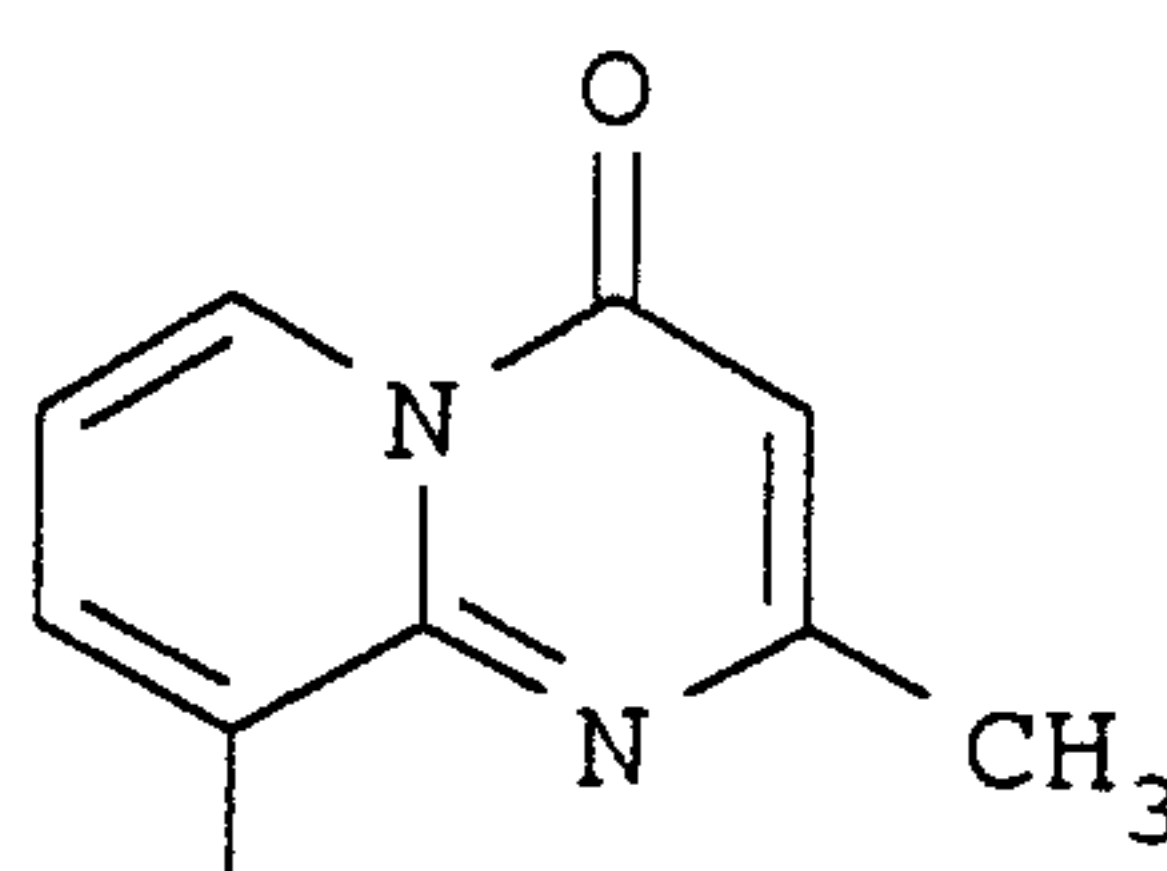
- (2) reacting the resulting compound of formula XIII with a hydroxylated heterocyclic derivative of the general structure Q-OH, Q being selected from the structures



(Het 1)

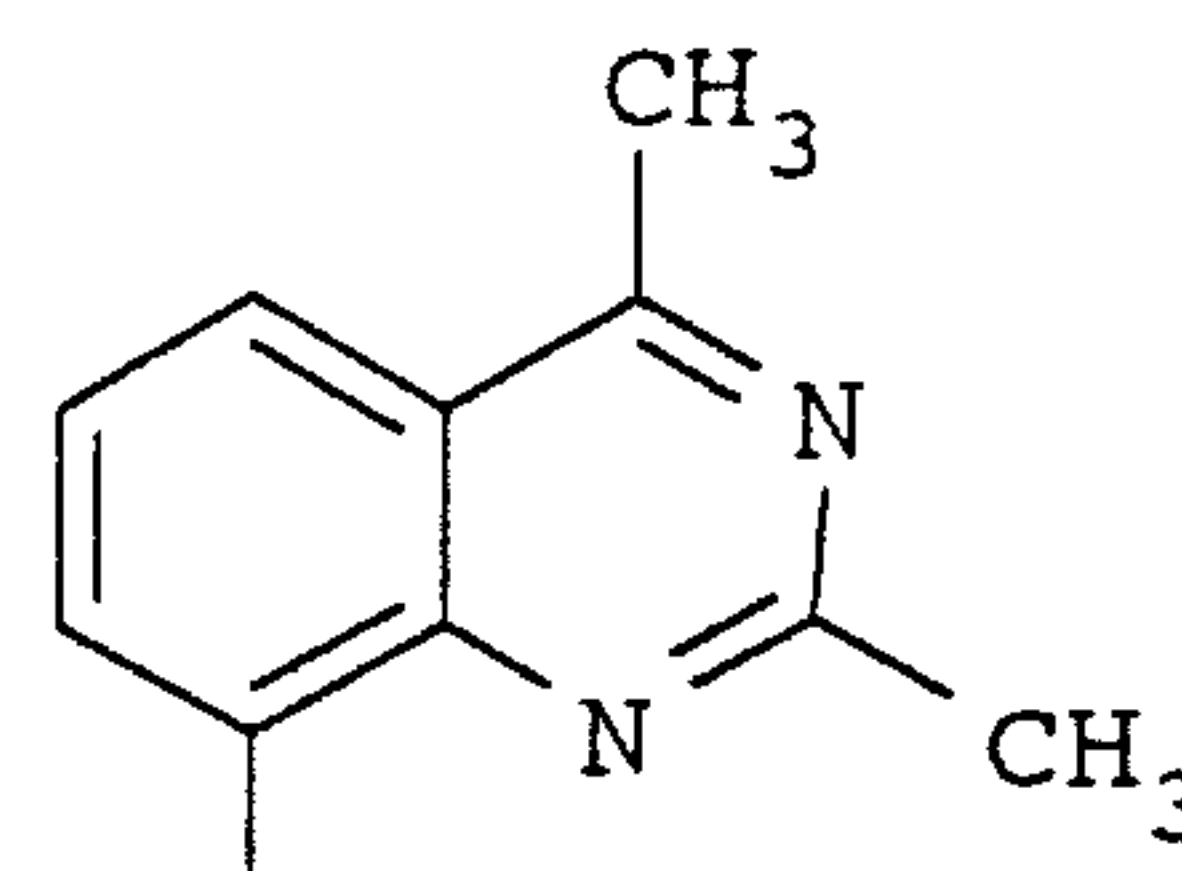


(Het 2)



(Het 3)

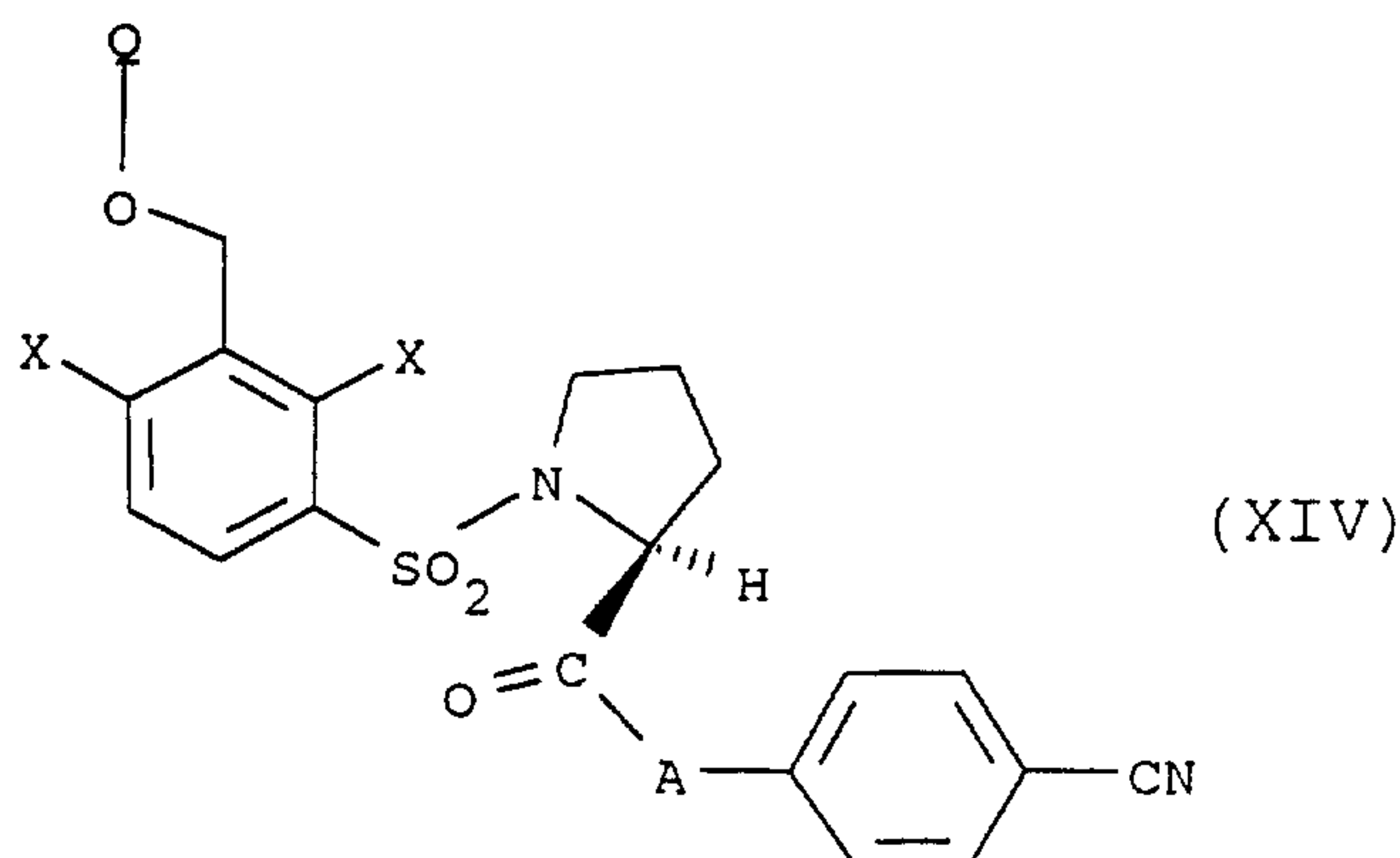
and



(Het 4)

in which R₁ is a hydrogen atom, a halogen atom, a C₁-C₃ alkyl group or a C₁-C₅ 1-oxoalkyl group,

- under operating conditions analogous to those described for carrying out step (1) of variant A above, to give the compound of formula XIV:



in which Q, R₁, X and A are as defined in the starting materials; and
(3) then performing, on the resulting compound of formula XIV, a series of
reactions analogous to those previously described in steps (2), (3) and (4) of variant
B above, to give the compound of formula I according to the invention in which Q,
5 X, R₁ and A are as defined in the starting compounds.

The invention will be understood more clearly from the following
description of (i) Preparatory Examples and (ii) results of pharmacological tests
performed with compounds according to the invention. Of course, these details as a
whole do not imply a limitation but are given by way of illustration.

10 In the case of compounds which have an asymmetric carbon in their
structure, the absence of a particular indication, or the notation (R,S), means that
the compounds are racemic; in the case of compounds which exhibit chirality, this is
indicated immediately after the numbering of the substituent carried by said
asymmetric carbon; the symbol (R) or (S) is then used in accordance with the Cahn-
15 Ingold-Prelog rules. The nomenclature used in the Examples is that recommended
by Chemical Abstracts; thus, after reaction of the acid group with an amine, certain
L-proline derivatives may become 2(S)-pyrrolidinecarboxamide derivatives.

In the experimental section, the "Preparations" relate to the intermediates
and the "Examples" relate the products according to the invention.

20 The melting points (m.p.) indicated below are generally measured using a
Koffler bench and are not corrected, so they represent instantaneous melting points.

The spectral characteristics of the nuclear magnetic resonance (NMR)
signals are given for the proton (¹H) or for the 13 isotope of carbon (¹³C); the
chemical shift is indicated relative to the tetramethylsilane signal and is followed, in
25 brackets, by the shape of the signal (s for singlet, d for doublet, t for triplet, q for
quadruplet, m for multiplet, bs for broad signal) and the number of protons
corresponding to the signal. By way of indication, the ¹H NMR spectra were run at
300 MHz.

PREPARATION I

30 **N-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-
sulfonyl]-L-proline methyl ester**

A solution of 10 g (67.10⁻³ mol) of 2-methyl-8-hydroxyimidazo[1,2-a]-
pyridine in 300 ml of dimethylformamide (DMF) is prepared and 2.02 g (67.10⁻³
mol) of an 80% suspension of sodium hydride in oil are added. The mixture is
35 stirred at room temperature for 30 min and a solution of 2.91 g (67.10⁻³ mol) of N-
[[3-(bromomethyl)-2,4-dichlorophenyl]sulfonyl]-L-proline methyl ester in 100 ml of

DMF is then added. After stirring at room temperature for 15 hours, the reaction mixture is poured into 500 ml of water and extracted 3 times with ethyl acetate. The combined organic phases are washed with water, dried over sodium sulfate and concentrated under reduced pressure. The resulting crude product is purified by chromatography on silica gel (silica gel 60 of particle size 15 to 40 μm) using a toluene/2-propanol mixture (96/4; v/v) as the eluent to give 22.5 g of the expected product in the form of a pinkish solid (yield = 67%).

M.p. = 149°C

$[\alpha]_{\text{D}}^{23} = -19.0^\circ$ (c = 1.5; CHCl_3)

10 **PREPARATION II**

N-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-sulfonyl]-L-proline

A solution of 12.2 g ($24 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation I in 180 ml of methanol and 120 ml of water is prepared and 48 ml of 1 N sodium hydroxide solution are then added. The reaction mixture is heated to 40°C and stirred for 1.5 hours. The methanol is evaporated off under reduced pressure, the residue is cooled, 200 ml of water are added and the mixture is acidified to pH 2 by the slow addition of 1 N hydrochloric acid solution, with stirring. The medium is extracted with dichloromethane and the organic phase obtained is dried over sodium sulfate and concentrated under reduced pressure to give 11.6 g of the expected product in the form of pinkish white crystals.

M.p. = 135°C

$[\alpha]_{\text{D}}^{22} = -50.7^\circ$ (c = 1.02; CH_2Cl_2)

PREPARATION III

25 **[3-[(4-Cyanobenzoyl)amino]propyl]carbamic acid 1,1-dimethylethyl ester**

A solution of 10 g ($57 \cdot 10^{-3}$ mol) of (3-aminopropyl)carbamic acid 1,1-dimethylethyl ester (or N-Boc-1,3-propanediamine) in 75 ml of dichloromethane is prepared and 15.9 ml ($114 \cdot 10^{-3}$ mol) of triethylamine are added. The mixture is cooled with an ice bath and 10.38 g ($60 \cdot 10^{-3}$ mol) of 4-cyanobenzoyl chloride are added gradually. The reaction medium is allowed to warm up to room temperature, stirred for 10 hours and then poured into 150 ml of water. It is extracted with dichloromethane and the organic phase obtained is washed with 1 N hydrochloric acid solution and then with water and is finally dried over sodium sulfate and concentrated under reduced pressure to give 16.4 g of the expected product in the form of ochre crystals (yield = 94%).

^1H NMR (DMSO): 1.37 (s, 9H); 1.63 (m, 2H); 2.97 (m, 2H); 3.26 (m, 2H); 6.84 (t,

1H); 7.97 (s, 4H); 8.70 (t, 1H)

PREPARATION IV

N-(3-Aminopropyl)-4-cyanobenzamide hydrochloride

16.4 g ($54 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation III are dissolved in 150 ml of ethyl acetate, and 104 ml of a solution of hydrogen chloride containing 2.6 mol/l in ethyl acetate are then added. The mixture is stirred at room temperature for 24 hours and then concentrated under reduced pressure. The resulting crude product is washed with ethyl ether and dried under vacuum at 40°C to give 12.15 g of the expected product in the form of an off-white solid (yield = 94%).

M.p. = 176 - 180°C

PREPARATION V

1-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-sulfonyl]-N-[3-[(4-cyanobenzoyl)amino]propyl]-2(S)-pyrrolidinecarboxamide

A solution of 5.8 g ($12 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation II in 200 ml of dichloromethane is prepared and 2.53 g ($13 \cdot 10^{-3}$ mol) of EDCI [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide] and 1.79 g ($13 \cdot 10^{-3}$ mol) of HOAT (1-hydroxy-7-azabenzotriazole) are then added. The resulting mixture is stirred for 30 min at room temperature and a solution of 2.69 g ($12 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation IV in a mixture of 150 ml of dichloromethane and 2.6 ml ($24 \cdot 10^{-3}$ mol) of N-methylmorpholine is then added. The reaction medium is stirred for 16 hours at room temperature and then washed successively with water, with 0.5 N hydrochloric acid solution, with sodium bicarbonate solution and finally with water again. After drying over sodium sulfate, the organic phase is concentrated under reduced pressure and the crude product obtained is purified by chromatography on silica gel using a dichloromethane/methanol mixture (97/3; v/v) as the eluent to give 6.66 g of the expected product in the form of white crystals (yield = 83%).

M.p. = 100 - 102°C

$[\alpha]_D^{23} = -15^\circ$ (c = 0.99; CH₂Cl₂)

Example 1

1-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-sulfonyl]-N-[3-[[4-[(amino)(hydroxyimino)methyl]benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide

A solution of 6.53 g ($9.7 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation V in 100 ml of dimethyl sulfoxide (DMSO) is prepared and 1.36 g

($19 \cdot 10^{-3}$ mol) of hydroxylamine hydrochloride and then 2.7 ml ($19 \cdot 10^{-3}$ mol) of triethylamine are added. The reaction mixture is stirred for 3 hours at room temperature, the same amounts of hydroxylamine hydrochloride and triethylamine are then added again and the reaction medium is stirred for 8 hours. It is poured
 5 into 400 ml of water, with stirring, and the precipitate obtained is filtered off and redissolved in dichloromethane. The organic phase obtained is washed with water and then dried over sodium sulfate. After removal of the solvent under reduced pressure, 5.37 g of the expected product are obtained in the form of white crystals (yield = 78%).

10 M.p. = 135°C
 $[\alpha]_{\text{D}}^{22} = -6.9^{\circ}$ (c = 1.04; DMSO)

PREPARATION VI

1-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-sulfonyl]-N-[3-[[4-[(acetoxylimino)(amino)methyl]benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide
 15

A solution of 5.28 g ($7.5 \cdot 10^{-3}$ mol) of the compound obtained according to Example 1 in 150 ml of dichloromethane is prepared and 0.96 ml ($10 \cdot 10^{-3}$ mol) of acetic anhydride is added. After stirring at room temperature for 15 hours, the reaction medium is concentrated under reduced pressure to give 5.48 g of the
 20 expected product in the form of beige crystals.

M.p. = $105 - 107^{\circ}\text{C}$
 $[\alpha]_{\text{D}}^{20} = -19^{\circ}$ (c = 1.0; CH_3OH)

Example 2

1-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-sulfonyl]-N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide
 25

A solution of 5.4 g ($7.2 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation VI in 150 ml of methanol is prepared and 1.08 g of Lindlar's catalyst (containing 5% of palladium) are added. The mixture is stirred under a hydrogen
 30 atmosphere, under a pressure of $3 \cdot 10^5$ Pascals, for 5 hours, at room temperature. After the catalyst has been filtered off, the solvent is removed by evaporation under reduced pressure and the crude product is purified by chromatography on NH_2 grafted silica gel ("Lichroprep NH_2 ") using a dichloromethane/methanol mixture (95/5; v/v) as the eluent to give 2.02 g of the expected product in the form of white
 35 crystals (yield = 41%).

M.p. = $120 - 125^{\circ}\text{C}$

$[\alpha]_D^{25} = -36^\circ$ ($c = 1.03$; CH_3OH)

Example 3

1-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-sulfonyl]-N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide methanesulfonate

A solution of 1.95 g ($2.8 \cdot 10^{-3}$ mol) of the compound obtained according to Example 2 in 14 ml of methanol is prepared. 184 μl ($2.8 \cdot 10^{-3}$ mol) of methanesulfonic acid are added, with stirring. After stirring for 30 min at room temperature, the reaction medium is poured into 500 ml of ethyl ether. The precipitate obtained is filtered off, washed with ether and dissolved in 60 ml of distilled water. The solution obtained is lyophilized to give 2.07 g of the expected product in the form of white crystals (yield = 94%).

M.p. = 170 - 172°C

$[\alpha]_D^{25} = -38.2^\circ$ ($c = 1.03$; CH_3OH)

PREPARATION VII

4-(4-Cyanobenzoyl)-1-piperazinecarboxylic acid 1,1-dimethylethyl ester

The expected product is obtained in the form of white crystals (yield = 90%) by following a procedure analogous to Preparation III, starting from 1-piperazinecarboxylic acid 1,1-dimethylethyl ester.

^1H NMR: 1.46 (s, 9H); 3.38 (m, 4H); 3.51 (m, 2H); 3.73 (m, 2H); 7.50 (d, 2H); 7.73 (d, 2H)

PREPARATION VIII

1-(4-Cyanobenzoyl)piperazine hydrochloride

The expected product is obtained in the form of white crystals (yield = 99%) by following a procedure analogous to Preparation IV, starting from the compound obtained according to Preparation VII.

M.p. = 262 - 264°C

PREPARATION IX

1-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-sulfonyl]-2(S)-[[4-(4-cyanobenzoyl)piperazin-1-yl]carbonyl]pyrrolidine

The expected product is obtained in the form of white crystals (yield = 93%) by following a procedure analogous to Preparation V, starting from the compound obtained according to Preparation VIII.

M.p. = 112 - 115°C

$[\alpha]_D^{21} = +2.8^\circ$ ($c = 1.03$; CH_2Cl_2)

Example 4

1-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-sulfonyl]-2(S)-[[4-[4-[(amino)(hydroxyimino)methyl]benzoyl]piperazin-1-yl]-carbonyl]pyrrolidine

5 The expected product is obtained in the form of white crystals (yield = 84%) by following a procedure analogous to Example 1, starting from the compound obtained according to Preparation IX.

M.p. = 165 - 167°C

$[\alpha]_D^{23} = +9.6^\circ$ (c = 1.04; DMSO)

10 **PREPARATION X**

1-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-sulfonyl]-2(S)-[[4-[4-[(acetoxyimino)(amino)methyl]benzoyl]piperazin-1-yl]-carbonyl]pyrrolidine

15 The expected product is obtained in the form of white crystals (yield = 98%) by following a procedure analogous to Preparation VI, starting from the compound obtained according to Example 4.

M.p. = 115 - 118°C

$[\alpha]_D^{23} = +10.2^\circ$ (c = 1; DMSO)

Example 5

20 **1-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-sulfonyl]-2(S)-[[4-[4-(aminoiminomethyl)benzoyl]piperazin-1-yl]carbonyl]-pyrrolidine**

25 The expected product is obtained in the form of pale yellow crystals (yield = 60%) by following a procedure analogous to Example 2, starting from the compound obtained according to Preparation X.

M.p. = 159 - 161°C

$[\alpha]_D^{24} = -30^\circ$ (c = 1.02; CH₃OH)

Example 6

30 **1-[[3-[[2-Methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]-sulfonyl]-2(S)-[[4-[4-(aminoiminomethyl)benzoyl]piperazin-1-yl]carbonyl]-pyrrolidine methanesulfonate**

 The expected product is obtained in the form of white crystals (yield = 93%) by following a procedure analogous to Example 3, starting from the compound obtained according to Example 5.

35 M.p. = 172 - 174°C

$[\alpha]_D^{26} = -19.3^\circ$ (c = 1.01; CH₃OH)

PREPARATION XI

N-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-L-proline methyl ester

- 5 The expected product is obtained in the form of beige crystals (yield = 50%) by following a procedure analogous to Preparation I, starting from 2,3-dimethyl-8-hydroxyimidazo[1,2-a]pyridine.

M.p. = 128 - 130°C

$[\alpha]_D^{29} = -8.4^\circ$ (c = 0.97; C₂H₅OH)

PREPARATION XII

- 10 **N-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-L-proline**

The expected product is obtained in the form of off-white crystals (yield = 60%) by following a procedure analogous to Preparation II, starting from the compound obtained according to Preparation XI.

- 15 M.p. = 140 - 145°C

$[\alpha]_D^{22} = +15.8^\circ$ (c = 0.99; C₂H₅OH)

PREPARATION XIII

- 20 **1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[(4-cyanobenzoyl)amino]propyl]-2(S)-pyrrolidine-carboxamide**

The expected product is obtained in the form of beige crystals (yield = 62%) by following a procedure analogous to Preparation V, starting from the compound obtained according to Preparation XII.

M.p. = 128 - 130°C

- 25 $[\alpha]_D^{26} = -7^\circ$ (c = 0.95; CH₂Cl₂)

Example 7

1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-[(amino)(hydroxyimino)methyl]benzoyl]amino]-propyl]-2(S)-pyrrolidinecarboxamide

- 30 The expected product is obtained in the form of off-white crystals (yield = 74%) by following a procedure analogous to Example 1, starting from the compound obtained according to Preparation XIII.

M.p. = 131 - 133°C

$[\alpha]_D^{24} = -9.5^\circ$ (c = 1.01; DMSO)

PREPARATION XIV

1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-[(acetoxymino)(amino)methyl]benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide

- 5 The expected product is obtained in the form of white crystals (yield = 98%) by following a procedure analogous to Preparation VI, starting from the compound obtained according to Example 7.

M.p. = 140 - 142°C

$[\alpha]_D^{22} = -7.5^\circ$ (c = 1.00; DMSO)

10 **Example 8**

1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-(iminoaminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide

- 15 The expected product is obtained in the form of pale yellow crystals (yield = 53%) by following a procedure analogous to Example 2, starting from the compound obtained according to Preparation XIV.

M.p. = 150 - 152°C

$[\alpha]_D^{25} = -15.5^\circ$ (c = 1.1; CH₂Cl₂)

Example 9

- 20 **1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide methanesulfonate**

- 25 The expected product is obtained in the form of white crystals (yield = 82%) by following a procedure analogous to Example 3, starting from the compound obtained according to Example 8.

M.p. = 179 - 181°C

$[\alpha]_D^{23} = -39^\circ$ (c = 1.02; CH₃OH)

PREPARATION XV

- 30 **1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-(4-cyanobenzoyl)piperazin-1-yl]carbonyl]pyrrolidine**

The expected product is obtained in the form of yellow crystals (yield = 41%) by following a procedure analogous to Preparation IX, starting from the compound obtained according to Preparation XII.

M.p. = 125 - 128°C

- 35 $[\alpha]_D^{26} = +0.9^\circ$ (c = 0.85; CH₂Cl₂)

Example 10

1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-[4-[(amino)(hydroxyimino)methyl]benzoyl]-piperazin-1-yl]carbonyl]pyrrolidine

- 5 The expected product is obtained in the form of cream-colored crystals (yield = 76%) by following a procedure analogous to Example 4, starting from the compound obtained according to Preparation XV.

M.p. = 179 - 181°C

$[\alpha]_D^{26} = -0.7^\circ$ (c = 1.01; CH₂Cl₂)

10 **PREPARATION XVI**

1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-[4-[(acetoxyimino)(amino)methyl]benzoyl]-piperazin-1-yl]carbonyl]pyrrolidine

- 15 The expected product is obtained in the form of white crystals (yield = 98%) by following a procedure analogous to Preparation X, starting from the compound obtained according to Example 10.

M.p. = 142 - 145°C

$[\alpha]_D^{26} = -13.5^\circ$ (c = 1.05; CH₂Cl₂)

Example 11

- 20 **1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-[4-(aminoiminomethyl)benzoyl]piperazin-1-yl]-carbonyl]pyrrolidine**

- 25 The expected product is obtained in the form of white crystals (yield = 47%) by following a procedure analogous to Example 5, starting from the compound obtained according to Preparation XVI.

M.p. = 170 - 172°C

$[\alpha]_D^{21} = -2.9^\circ$ (c = 1.00; CH₂Cl₂)

Example 12

- 30 **1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-[4-(aminoiminomethyl)benzoyl]piperazin-1-yl]-carbonyl]pyrrolidine dihydrochloride**

- 35 A solution of 736 mg ($1.03 \cdot 10^{-3}$ mol) of the compound obtained according to Example 11 in 25 ml of dichloromethane is prepared and 650 μ l ($2.6 \cdot 10^{-3}$ mol) of a 4 N solution of hydrogen chloride in dioxane are added. After stirring for 3 hours, the precipitate formed is separated off and taken up with diethyl ether to give a pale yellow solid, which is filtered off. After drying under vacuum, the product is

redissolved in water and the solution is filtered and lyophilized to give 710 mg of the expected product in the form of a cream-colored flaky solid (yield = 87%).

M.p. = 225 - 229°C

$[\alpha]_D^{26} = +19.5^\circ$ (c = 1.07; CH₃OH)

5 **Example 13**

1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[4-(aminoiminomethyl)phenylmethyl]-2(S)-pyrrolidine-carboxamide

10 A solution of 5 g ($10.1 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation XII in 100 ml of dimethylformamide is prepared and 2.12 g ($11 \cdot 10^{-3}$ mol) of EDCI and 1.52 g ($11 \cdot 10^{-3}$ mol) of HOAT are added. After stirring for one hour at room temperature, this solution is added to a solution of 2.5 g ($11 \cdot 10^{-3}$ mol) of 4-(aminomethyl)benzenecarboximidamide [or 4-(aminoiminomethyl)benzylamine] dihydrochloride in 100 ml of DMF and 1.2 ml ($11 \cdot 10^{-3}$ mol) of N-methyl-
15 morpholine. The reaction medium is stirred for 15 hours at room temperature. It is filtered and the filtrate is poured into ethyl ether, with stirring. The precipitate formed in this way is separated off and redissolved in water. Dichloromethane is added and 2 N sodium hydroxide solution is added in order to bring the medium to pH 13. The aqueous and organic phases are separated and the organic phase is
20 washed with water. After drying over magnesium sulfate, the organic phase is concentrated under reduced pressure. The crude product obtained is purified by chromatography on NH₂ grafted silica gel using a dichloromethane/ethanol mixture (95/5; v/v) as the eluent to give 3.6 g of the expected product in the form of a white solid (yield = 57%).

25 M.p. = 144 - 146°C

$[\alpha]_D^{21} = -34.5^\circ$ (c = 1.03; CHCl₃)

Example 14

**1-[[3-[[2,3-Dimethylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[4-(aminoiminomethyl)phenylmethyl]-2(S)-pyrrolidine-
30 carboxamide hydrochloride**

A solution of 0.42 g ($0.66 \cdot 10^{-3}$ mol) of the compound obtained according to Example 13 in 100 ml of diethyl ether is prepared and 0.75 ml of a 1 N solution of hydrogen chloride in diethyl ether is added, with stirring. The crystals formed are filtered off, washed with ether and dried under vacuum to give the expected product
35 in the form of white crystals (yield = 81%).

M.p. = 210 - 214°C

$[\alpha]_D^{22} = -12^\circ$ ($c = 1.00$; C_2H_5OH)

PREPARATION XVII

N-[[3-[[3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-L-proline methyl ester

- 5 A solution of 7 g ($14 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation I in a mixture of 100 ml of dioxane and 100 ml of ethanol is prepared and 2.5 g ($14 \cdot 10^{-3}$ mol) of N-bromosuccinimide are added in portions at room temperature, with stirring. After stirring for 1 hour, the solvents are driven off under reduced pressure. The evaporation residue is taken up with dichloromethane and the solution is washed with water and then dried over magnesium sulfate and concentrated under reduced pressure. After purification by chromatography on silica gel using a toluene/2-propanol mixture (97/3; v/v) as the eluent, and recrystallization from 2-propanol, 7.3 g of the expected product (yield = 90%) are obtained.

- 15 M.p. = $146^\circ C$

$[\alpha]_D^{23} = -17^\circ$ ($c = 1.5$; CH_2Cl_2)

PREPARATION XVIII

N-[[3-[[3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-L-proline

- 20 The expected product is obtained in the form of a cream-colored powdery solid (yield = 98%) by following a procedure analogous to Preparation II, starting from the compound obtained according to Preparation XVII.

M.p. = $145^\circ C$

$[\alpha]_D^{20} = -30.5^\circ$ ($c = 1.05$; CH_2Cl_2)

- 25 **PREPARATION XIX**

1-[[3-[[3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[1,1-dimethylethoxycarbonylamino]propyl]-2(S)-pyrrolidinecarboxamide

- 30 The expected product is obtained in the form of a white solid (yield = 95%) by following a procedure analogous to Preparation V, starting from the compound obtained according to Preparation XVIII and (3-aminopropyl)carbamic acid 1,1-dimethylethyl ester [or N-Boc-propanediamine].

M.p. = $65^\circ C$

$[\alpha]_D^{22} = -43^\circ$ ($c = 0.44$; CH_3OH)

PREPARATION XX**1-[[3-[[3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-aminopropyl]-2(S)-pyrrolidinecarboxamide**

A solution of 0.6 g ($0.83 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation XIX in 10 ml of dichloromethane is prepared and 89 mg ($0.83 \cdot 10^{-3}$ mol) of anisole and 3 ml of trifluoroacetic acid are added at 0°C. The reaction mixture is then stirred for 4 hours at room temperature, after which the solvent is driven off under reduced pressure. The residue is taken up with 50 ml of water and the aqueous phase obtained is brought to pH 10 with 1 N sodium hydroxide solution and then extracted with dichloromethane. The organic phase is washed with water, dried over sodium sulfate and then concentrated under reduced pressure to give 0.45 g of the expected product in the form of a white powdery solid.

M.p. = 75°C

$[\alpha]_D^{22} = -72^\circ$ (c = 0.40; CH₃OH)

15 Example 15**1-[[3-[[3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[4-(aminoiminomethyl)benzoylamino]propyl]-2(S)-pyrrolidinecarboxamide**

A suspension of 80 mg ($0.4 \cdot 10^{-3}$ mol) of 4-(aminoiminomethyl)benzoic acid hydrochloride in 6 ml of DMF is prepared and 84 mg ($0.44 \cdot 10^{-3}$ mol) of EDCI and 60 mg ($0.44 \cdot 10^{-3}$ mol) of HOAT are added. The mixture is stirred at room temperature for 10 min and 250 mg ($0.40 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation XX are then added. The reaction mixture is stirred for 20 hours at room temperature and then poured into water. It is extracted with dichloromethane and the resulting organic phase is subsequently washed with saturated sodium bicarbonate solution and then with water. It is dried over sodium sulfate and concentrated under reduced pressure. The crude product is purified by chromatography on NH₂ grafted silica gel using a dichloromethane/methanol mixture (98/2; v/v) as the eluent to give 170 mg of the expected product in the form of a white solid (yield = 55%).

M.p. = 170°C

$[\alpha]_D^{22} = -2.6^\circ$ (c = 0.16; CH₃OH)

Example 16**35 1-[[3-[[3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[4-(aminoiminomethyl)benzoylamino]propyl]-2(S)-pyrrolidinecarboxamide hydrochloride**

A solution of 153 mg ($0.2 \cdot 10^{-3}$ mol) of the compound obtained according to Example 15 in 8 ml of ethyl acetate and 2 ml of ethanol is prepared and 0.5 ml of a saturated solution of hydrogen chloride in diethyl ether is added. The mixture is stirred for 10 min and the solvents are then removed under reduced pressure. The residue is then redissolved in water, the solution is filtered and the filtrate is lyophilized to give 120 mg of the expected product in the form of a white powder (yield = 75%).

M.p. = 200°C

$[\alpha]_D^{22} = -13^\circ$ (c = 0.39; CH₃OH)

10 **PREPARATION XXI**

1-[[3-[[3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-[[4-(1,1-dimethylethoxycarbonyl)piperazin-1-yl]-carbonyl]pyrrolidine

The expected product is obtained in the form of white crystals (yield = 90%) by following a procedure analogous to Preparation XIX, starting from 1-piperazine-carboxylic acid 1,1-dimethylethyl ester.

M.p. = 85°C

$[\alpha]_D^{22} = +9.6^\circ$ (c = 1.00; DMSO)

PREPARATION XXII

20 **1-[[3-[[3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-[[piperazin-1-yl]carbonyl]pyrrolidine**

The expected product is obtained in the form of white crystals (yield = 90%) by following a procedure analogous to Preparation XX, starting from the compound obtained according to Preparation XXI.

25 M.p. = 178 - 180°C

$[\alpha]_D^{21} = +16.5^\circ$ (c = 1.01; CH₃OH)

Example 17

30 **1-[[3-[[3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-[[4-[4-(aminoiminomethyl)benzoyl]piperazin-1-yl]-carbonyl]pyrrolidine hydrochloride**

The expected product is obtained in the form of pale yellow crystals (yield = 40%) by following a procedure analogous to Example 15, starting from the compound obtained according to Preparation XXII, and after purification by reversed phase chromatography on silica gel (grafted silica gel marketed under the name RP18) using an acetonitrile/water/hydrochloric acid mixture (75/25/1; v/v/v) as the eluent.

M.p. = 200 - 204°C

$[\alpha]_D^{19} = +21^\circ$ (c = 1.02; CH₃OH)

Example 18

1-[[3-[[3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-
5 phenyl]sulfonyl]-N-[4-(aminoiminomethyl)phenylmethyl]-2(S)-pyrrolidine-
carboxamide

A solution of 1.13 g ($2 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation XVIII in 10 ml of DMF is prepared and 382 mg ($2 \cdot 10^{-3}$ mol) of EDCI and 272 mg ($2 \cdot 10^{-3}$ mol) of HOAT are added. The solution is stirred for 20 min at
10 room temperature and then added slowly to a mixture of 453 mg ($2 \cdot 10^{-3}$ mol) of 4-(aminomethyl)benzenecarboximidamide dihydrochloride and 202 mg ($2 \cdot 10^{-3}$ mol) of N-methylmorpholine in 10 ml of DMF. The reaction mixture is stirred for 20 hours at room temperature and then poured into 150 ml of water. 1 N sodium hydroxide solution is added, with stirring, in order to bring the medium to pH 13, and the
15 medium is then extracted with dichloromethane. The organic phase is washed and then dried over magnesium sulfate and concentrated under reduced pressure. The product obtained is purified by chromatography on silica gel (NH₂ grafted silica gel) using a dichloromethane/methanol mixture (95/5; v/v) as the eluent to give 280 mg of the expected product in the form of a white solid (yield = 24%).

20 M.p. = 124°C

$[\alpha]_D^{25} = -30^\circ$ (c = 0.57; CH₃OH)

Example 19

1-[[3-[[3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-
phenyl]sulfonyl]-N-[4-(aminoiminomethyl)phenylmethyl]-2(S)-pyrrolidine-
25 carboxamide hydrochloride

The expected product is obtained in the form of a white solid (yield = 92%) by following a procedure analogous to Example 16, starting from the compound obtained according to Example 18 (yield = 92%).

M.p. = 214°C

30 $[\alpha]_D^{25} = -27^\circ$ (c = 0.68; CH₃OH)

PREPARATION XXIII

N-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-L-proline methyl ester

The expected product is obtained in the form of white crystals (yield = 92%)
35 by following a procedure analogous to Preparation I, starting from 8-hydroxy-2-methylquinoxaline.

M.p. = 158 - 159°C

$[\alpha]_D^{24} = -24.5^\circ$ (c = 1.00; CHCl₃)

PREPARATION XXIV

5 **N-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-L-proline**

The expected product is obtained in the form of off-white crystals (yield = 90%) by following a procedure analogous to Preparation II, starting from the product obtained according to Preparation XXIII.

M.p. = 238 - 240°C

10 $[\alpha]_D^{26} = -111^\circ$ (c = 0.97; CHCl₃)

PREPARATION XXV

1-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[(4-cyanobenzoyl)amino]propyl]-2(S)-pyrrolidinecarboxamide

15 The expected product is obtained in the form of white crystals (yield = 79%) by following a procedure analogous to Preparation V, starting from the product obtained according to Preparation XXIV.

M.p. = 104 - 106°C

$[\alpha]_D^{26} = -32^\circ$ (c = 0.96; CHCl₃)

Example 20

20 **1-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[[4-[(amino)(hydroxyimino)methyl]benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide**

25 The expected product is obtained in the form of white crystals (yield = 88%) by following a procedure analogous to Example 1, starting from the product obtained according to Preparation XXV.

M.p. = 172 - 176°C

$[\alpha]_D^{23} = -7.5^\circ$ (c = 0.98; DMSO)

PREPARATION XXVI

30 **1-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[[4-[(acetoxymimino)(amino)methyl]benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide**

The expected product is obtained in the form of pinkish crystals (yield = 95%) by following a procedure analogous to Preparation VI, starting from the compound obtained according to Example 20.

35 M.p. = 151 - 154°C

$[\alpha]_D^{24} = -10^\circ$ (c = 0.95; DMSO)

Example 21

1-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidine-carboxamide

5 The expected product is obtained in the form of pinkish crystals (yield = 55%) by following a procedure analogous to Example 2, starting from the compound obtained according to Preparation XXVI.

M.p. = 136 - 140°C

$[\alpha]_D^{24} = -10^\circ$ (c = 1.00; DMSO)

10 **Example 22**

1-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidine-carboxamide methanesulfonate

15 The expected product is obtained in the form of light yellow crystals (yield = 84%) by following a procedure analogous to Example 3, starting from the compound obtained according to Example 21.

M.p. = 165 - 167°C

$[\alpha]_D^{25} = -38.2^\circ$ (c = 1.03; CH₃OH)

PREPARATION XXVII

20 1-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-[[4-(4-cyanobenzoyl)piperazin-1-yl]carbonyl]pyrrolidine

The expected product is obtained in the form of white crystals (yield = 96%) by following a procedure analogous to Preparation IX, starting from the compound obtained according to Preparation XXIV.

25 M.p. = 126 - 130°C

$[\alpha]_D^{26} = -0.4^\circ$ (c = 1.13; CHCl₃)

Example 23

30 1-[[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-[[4-[4-[(amino)(hydroxyimino)methyl]benzoyl]piperazin-1-yl]carbonyl]-pyrrolidine

The expected product is obtained in the form of white crystals (yield = 86%) by following a procedure analogous to Example 4, starting from the compound obtained according to Preparation XXVII.

M.p. = 210 - 212°C

35 $[\alpha]_D^{24} = +19.5^\circ$ (c = 0.47; DMSO)

PREPARATION XXVIII

1-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-[[4-[4-[(acetoxymino)(amino)methyl]benzoyl]piperazin-1-yl]carbonyl]-pyrrolidine

- 5 The expected product is obtained in the form of yellow crystals (yield = 98%) by following a procedure analogous to Preparation X, starting from the compound obtained according to Example 23.

M.p. = 161 - 165°C

$[\alpha]_D^{23} = +9^\circ$ (c = 1.02; DMSO)

10 **Example 24**

1-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-[[4-[4-(aminoiminomethyl)benzoyl]piperazin-1-yl]carbonyl]pyrrolidine

- The expected product is obtained in the form of beige crystals (yield = 45%) by following a procedure analogous to Example 5, starting from the compound
15 obtained according to Preparation XXVIII.

M.p. = 155 - 158°C

$[\alpha]_D^{24} = +9.7^\circ$ (c = 0.95; DMSO)

Example 25

- 1-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-
20 [[4-[4-(aminoiminomethyl)benzoyl]piperazin-1-yl]carbonyl]pyrrolidine
hydrochloride**

 The expected product is obtained in the form of a white solid (yield = 95%) by following a procedure analogous to Example 16, starting from the compound obtained according to Example 24.

- 25 M.p. = 192 - 195°C

$[\alpha]_D^{24} = +6.7^\circ$ (c = 1.03; DMSO)

Example 26

1-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[4-(aminoiminomethyl)phenylmethyl]-2(S)-pyrrolidinecarboxamide

- 30 The expected product is obtained in the form of a beige solid (yield = 27%) by following a procedure analogous to Example 13, starting from the compound obtained according to Preparation XXIV.

M.p. = 120 - 125°C

$[\alpha]_D^{23} = -42^\circ$ (c = 1.00; CHCl₃)

Example 27

1-[[3-[(2-Methylquinoxalin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[4-(aminoiminomethyl)phenylmethyl]-2(S)-pyrrolidinecarboxamide hydrochloride

- 5 A solution of 387 mg ($0.62 \cdot 10^{-3}$ mol) of the compound obtained according to Example 26 in 100 ml of ethyl ether is prepared and 0.7 ml of a 1 N solution of hydrogen chloride in ethyl ether is added. The crystals formed are filtered off, washed with ether, dried under vacuum and redissolved in 10 ml of water. After filtration and lyophilization of the filtrate, 376 mg of the expected product are
10 obtained in the form of a white powder (yield = 92%).

M.p. = 180 - 184°C

$[\alpha]_D^{23} = -43^\circ$ (c = 0.99; ethanol)

PREPARATION XXIX

- N-[[3-[[2-Methyl-4H-pyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-(L)-proline methyl ester**
15

The expected product is obtained in the form of off-white crystals (yield = 56%) by following a procedure analogous to Preparation I, starting from 9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

M.p. = 166°C

- 20 $[\alpha]_D^{22} = -24^\circ$ (c = 0.37; CHCl₃)

PREPARATION XXX

N-[[3-[[2-Methyl-4H-pyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-(L)-proline

- The expected product is obtained in the form of a beige solid (yield = 92%)
25 by following a procedure analogous to Preparation II, starting from the compound obtained according to Preparation XXIX.

M.p. = 150°C

$[\alpha]_D^{22} = -86^\circ$ (c = 0.4; CHCl₃)

PREPARATION XXXI

- 1-[[3-[[2-Methyl-4H-pyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[(4-cyanobenzoyl)amino]propyl]-2(S)-pyrrolidinecarboxamide**
30

- The expected product is obtained in the form of a white solid (yield = 83%)
by following a procedure analogous to Preparation V, starting from the compound
35 obtained according to Preparation XXX.

M.p. = 112°C

$[\alpha]_D^{22} = -50^\circ$ ($c = 0.31$; CHCl_3)

Example 28

1-[[3-[[2-Methyl-4H-pyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[4-[(amino)(hydroxyimino)methyl]benzoyl-amino]propyl]-2(S)-pyrrolidinecarboxamide

The expected product is obtained in the form of a white solid (yield = 87%) by following a procedure analogous to Example 1, starting from the compound obtained according to Preparation XXXI.

M.p. = 251°C

10 $[\alpha]_D^{22} = -11^\circ$ ($c = 0.36$; DMSO)

PREPARATION XXXII

1-[[3-[[2-Methyl-4H-pyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[4-[(acetoxyimino)(amino)methyl]benzoyl-amino]propyl]-2(S)-pyrrolidinecarboxamide

15 The expected product is obtained in the form of a creamy white powder (yield = 95%) by following a procedure analogous to Preparation VI, starting from the compound obtained according to Example 28.

M.p. = 150°C

$[\alpha]_D^{22} = -24.5^\circ$ ($c = 0.33$; CHCl_3)

Example 29

1-[[3-[[2-Methyl-4H-pyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide

25 The expected product is obtained in the form of a white powdery solid (yield = 62%) by following a procedure analogous to Example 2, starting from the compound obtained according to Preparation XXXII.

M.p. = 153°C

$[\alpha]_D^{22} = -19^\circ$ ($c = 0.32$; DMSO)

Example 30

30 1-[[3-[[2-Methyl-4H-pyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide bis(methanesulfonate)

35 A solution of 160 mg ($0.224 \cdot 10^{-3}$ mol) of the compound obtained according to Example 29 in 3 ml of dichloromethane and 3 ml of ethanol is prepared. 43 mg ($0.45 \cdot 10^{-3}$ mol) of methanesulfonic acid are added and the mixture is stirred for 10 min. 20 ml of diethyl ether are then added and, after 5 min, the crystals formed are

filtered off and washed on the filter with ether. After drying under vacuum, the crystals are redissolved in 20 ml of water and the solution is lyophilized to give 170 mg of the expected product in the form of fine white crystals (yield = 85%).

M.p. = 183°C

5 $[\alpha]_D^{24} = -32^\circ$ (c = 0.46; CH₃OH)

PREPARATION XXXIII

1-[4-Cyanobenzoyl]piperazine trifluoroacetate

A solution of 40.7 g ($129 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation VII in 500 ml of dichloromethane is prepared and 150 ml of trifluoro-
10 acetic acid are added gradually. The mixture is subsequently stirred at room temperature for 30 min and then concentrated under reduced pressure. The residue is taken up with 400 ml of diethyl ether, with stirring; the crystals formed are filtered off and then dried under vacuum to give 30.8 g of the expected product in the form of white crystals (yield = 87%).

15 M.p. = 180°C

PREPARATION XXXIV

1-(1,1-Dimethylethoxycarbonyl)-2(S)-[[4-(4-cyanobenzoyl)piperazin-1-yl]-carbonyl]pyrrolidine

A solution of 10.78 g ($50 \cdot 10^{-3}$ mol) of N-(1,1-dimethylethoxycarbonyl)-L-proline (or N-Boc-L-proline) in 90 ml of DMF is prepared and 11.47 g ($60 \cdot 10^{-3}$ mol) of EDCI and 8.18 g ($60 \cdot 10^{-3}$ mol) of HOAT are added. The mixture is stirred for 30 min at room temperature and a solution of 15 g ($55 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation XXXIII in 90 ml of DMF and 6.08 g ($60 \cdot 10^{-3}$ mol) of triethylamine is then added. After stirring for 3 hours at room
25 temperature, the reaction medium is poured into iced water and extracted with dichloromethane. The organic phase is washed and then dried over magnesium sulfate and concentrated under reduced pressure. The crude product is purified by chromatography on silica gel using a dichloromethane/methanol mixture (98/2; v/v) as the eluent to give 20 g of the expected product in the form of a white solid
30 (yield = 97%).

M.p. = 50°C

$[\alpha]_D^{23} = +3^\circ$ (c = 0.50; CHCl₃)

PREPARATION XXXV

2(S)-[4-(4-Cyanobenzoyl)piperazin-1-ylcarbonyl]pyrrolidine trifluoroacetate

35 The expected product is obtained in the form of a white solid (yield = 81%) by following a procedure analogous to Preparation XX, starting from the

compound obtained according to Preparation XXXIV.

M.p. = 50°C

$[\alpha]_D^{22} = -35^\circ$ (c = 0.58; CHCl₃)

PREPARATION XXXVI

5 1-[(3-Bromomethyl-2,4-dichlorophenyl)sulfonyl]-2(S)-[[4-(4-cyanobenzoyl)-piperazin-1-yl]carbonyl]pyrrolidine

A solution of 13.4 g ($39.5 \cdot 10^{-3}$ mol) of 3-bromomethyl-2,4-dichlorobenzenesulfonyl chloride in 35 ml of acetonitrile is prepared and 16.9 g ($39.5 \cdot 10^{-3}$ mol) of the compound obtained according to Preparation XXXV are added at room temperature. A solution of 10 g (0.1 mol) of potassium bicarbonate in 40 ml of water is then added dropwise. The reaction mixture is stirred for 20 hours, water is then added and the mixture is extracted with ethyl acetate. The organic phase obtained is washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The crude product is purified by chromatography on silica gel using a dichloromethane/ethyl acetate mixture (9/1; v/v) as the eluent to give 18.8 g of the expected product (partly containing its chlorinated analog) in the form of a beige solid.

M.p. = 115°C

PREPARATION XXXVII

20 1-[[3-[[2-Methylpyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-[[4-(4-cyanobenzoyl)piperazin-1-yl]carbonyl]pyrrolidine

The expected product is obtained in the form of white crystals (yield = 62%) by following a procedure analogous to Preparation I, starting from 9-hydroxy-2-methylpyrido[1,2-a]pyrimidin-4-one and the compound obtained according to Preparation XXXVI, and after recrystallization from an ethyl acetate/diisopropyl ether mixture.

M.p. = 160°C

$[\alpha]_D^{22} = +9^\circ$ (c = 0.39; CHCl₃)

Example 31

30 1-[[3-[[2-Methylpyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-2(S)-[[4-[4-[(amino)(hydroxyimino)methyl]benzoyl]-piperazin-1-yl]carbonyl]pyrrolidine

The expected product is obtained in the form of a white solid (yield = 77%) by following a procedure analogous to Example I, starting from the compound obtained according to Preparation XXXVII.

M.p. = 180°C

$[\alpha]_D^{22} = +26^\circ$ ($c = 0.36$; CHCl_3)

PREPARATION XXXVIII

1-[[3-[[2-Methylpyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-[4-[(acetoxymino)(amino)methyl]benzoyl]-piperazin-1-yl]carbonyl]pyrrolidine

The expected product is obtained in the form of a white solid (yield = 93%) by following a procedure analogous to Preparation VI, starting from the compound obtained according to Example 31.

M.p. = 160°C

10 $[\alpha]_D^{22} = +6^\circ$ ($c = 0.37$; DMSO)

Example 32

1-[[3-[[2-Methylpyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-[4-(aminoiminomethyl)benzoyl]piperazin-1-yl]-carbonyl]pyrrolidine

15 The expected product is obtained in the form of a yellow solid (yield = 44%) by following a procedure analogous to Example 2, starting from the compound obtained according to Preparation XXXVIII.

M.p. = 168°C

$[\alpha]_D^{22} = +32^\circ$ ($c = 0.38$; CHCl_3)

Example 33

1-[[3-[[2-Methylpyrido[1,2-a]pyrimidin-9-yl-4-one]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-[4-(aminoiminomethyl)benzoyl]piperazin-1-yl]-carbonyl]pyrrolidine bis(methanesulfonate)

25 The expected product is obtained in the form of a white solid (yield = 80%) by following a procedure analogous to Example 30, starting from the compound obtained according to Example 32.

M.p. = 181°C

$[\alpha]_D^{24} = +13^\circ$ ($c = 0.35$; CH_3OH)

PREPARATION XXXIX

30 N-[[3-[(2,4-Dimethylquinazolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-L-proline methyl ester

The expected product is obtained in the form of a white solid (yield = 70%) by following a procedure analogous to Preparation I, starting from 2,4-dimethyl-8-hydroxyquinazoline.

35 M.p. = $140 - 142^\circ\text{C}$

$[\alpha]_D^{24} = -29^\circ$ ($c = 1$; CHCl_3)

PREPARATION XL

N-[[3-[(2,4-Dimethylquinazolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-L-proline

5 The expected product is obtained in the form of a beige solid (yield = 98%) by following a procedure analogous to Preparation II, starting from the compound obtained in Preparation XXXIX.

M.p. = 94 - 96°C

Example 34

10 **1-[[3-[(2,4-Dimethylquinazolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[4-(aminoiminomethyl)phenylmethyl]-2(S)-pyrrolidinecarboxamide**

The expected product is obtained in the form of a white powder (yield = 25%) by following a procedure analogous to Example 13, starting from the compound obtained in Preparation XL.

M.p. = 139 - 142°C

15 **Example 35**

1-[[3-[(2,4-Dimethylquinazolin-8-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-N-[4-(aminoiminomethyl)phenylmethyl]-2(S)-pyrrolidinecarboxamide hydrochloride

20 The expected product is obtained in the form of a white powder (yield = 95%) by following a procedure analogous to Example 16, starting from the compound obtained according to Example 34.

M.p. = 177 - 179°C

$[\alpha]_D^{21} = -43^\circ$ (c = 0.80; CH₃OH)

PREPARATION XLI

25 **N-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-L-proline methyl ester**

The expected product is obtained in the form of a beige solid (yield = 95%) by following a procedure analogous to Preparation XVII, the N-bromosuccinimide being replaced with N-chlorosuccinimide.

30 M.p. = 60°C

$[\alpha]_D^{22} = +13^\circ$ (c = 0.35; DMSO)

PREPARATION XLII

N-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichlorophenyl]sulfonyl]-L-proline

35 The expected product is obtained in the form of a white solid (yield = 88%) by following a procedure analogous to Preparation XVIII, starting from the

compound obtained according to Preparation XLI.

M.p. = 144°C

$[\alpha]_D^{22} = -60.5^\circ$ (c = 0.35; CHCl₃)

PREPARATION XLIII

- 5 **1-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[(4-cyanobenzoyl)amino]propyl]-2(S)-pyrrolidine-carboxamide**

The expected product is obtained in the form of an off-white solid (yield = 51%) by following a procedure analogous to Preparation V, starting from the
10 compound obtained in Preparation XLII.

M.p. = 115°C

$[\alpha]_D^{22} = -32^\circ$ (c = 0.60; CHCl₃)

Example 36

- 15 **1-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-[(amino)(hydroxyimino)methyl]benzoyl]amino]-propyl]-2(S)-pyrrolidinecarboxamide**

The expected product is obtained in the form of a white solid (yield = 96%) by following a procedure analogous to Example 1, starting from the compound obtained in Preparation XLIII.

20 M.p. = 155°C

$[\alpha]_D^{22} = -41^\circ$ (c = 0.40; CHCl₃)

PREPARATION XLIV

- 25 **1-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-[(acetoxylimino)(amino)methyl]benzoyl]amino]-propyl]-2(S)-pyrrolidinecarboxamide**

The expected product is obtained in the form of a crude solid (yield = 82%) by following a procedure analogous to Preparation VI, starting from the compound obtained according to Example 36.

M.p. = 170°C

30 $[\alpha]_D^{21} = -32^\circ$ (c = 0.35; CHCl₃)

Example 37

- 35 **1-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide**

The expected product is obtained in the form of a beige solid (yield = 47%) by following a procedure analogous to Example 2, starting from the compound

obtained in Preparation XLIV.

M.p. = 115°C

$[\alpha]_D^{22} = -9.5^\circ$ (c = 0.55; DMSO)

Example 38

- 5 **1-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide bis(methanesulfonate)**

The expected product is obtained in the form of a white solid (yield = 90%) by following a procedure analogous to Example 30, starting from the compound
10 obtained according to Example 37.

M.p. = 154°C

$[\alpha]_D^{27} = -19^\circ$ (c = 0.32; CH₃OH)

PREPARATION XLV

- 15 **1-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-(4-cyanobenzoyl)piperazin-1-yl]carbonyl]pyrrolidine**

The expected product is obtained in the form of a creamy white solid (yield = 49%) by following a procedure analogous to Preparation V, starting from the compounds obtained according to Preparations XLII and VIII.

M.p. = 100°C

- 20 $[\alpha]_D^{28} = -11^\circ$ (c = 0.35; CH₃OH)

Example 39

- 1-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-[4-[(amino)(hydroxyimino)methyl]benzoyl]-piperazin-1-yl]carbonyl]pyrrolidine**

25 The expected product is obtained in the form of a white solid (yield = 96%) by following a procedure analogous to Example 1, starting from the compound obtained according to Preparation XLV.

M.p. = 168°C

$[\alpha]_D^{28} = -25^\circ$ (c = 0.59; CH₃OH)

- 30 **PREPARATION XLVI**

- 1-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-2(S)-[[4-[4-[(acetoxyimino)(amino)methyl]benzoyl]-piperazin-1-yl]carbonyl]pyrrolidine**

35 The expected product is obtained in the form of an off-white solid (yield = 88%) by following a procedure analogous to Preparation VI, starting from the compound obtained according to Example 39.

M.p. = 150°C

$[\alpha]_D^{26} = -16.5^\circ$ (c = 0.40; CH₃OH)

Example 40

1-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-
5 phenyl]sulfonyl]-2(S)-[[4-[4-[(aminoiminomethyl)benzoyl]piperazin-1-yl]-
carbonyl]pyrrolidine

The expected product is obtained in the form of a pale yellow solid (yield = 96%) by following a procedure analogous to Example 2, starting from the compound obtained according to Preparation XLVI.

10 M.p. = 164°C

$[\alpha]_D^{26} = -14^\circ$ (c = 0.33; CH₃OH)

Example 41

1-[[3-[[3-Chloro-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-
15 phenyl]sulfonyl]-2(S)-[[4-[4-[(aminoiminomethyl)benzoyl]piperazin-1-yl]-
carbonyl]pyrrolidine bis(methanesulfonate)

The expected product is obtained in the form of a fine white solid (yield = 83%) by following a procedure analogous to Example 3 (in this case dichloromethane is used to dissolve the starting compound), starting from the compound obtained according to Example 40.

20 M.p. = 192°C

$[\alpha]_D^{27} = +21^\circ$ (c = 0.42; CH₃OH)

PREPARATION XLVII

N-[[3-[(2-Aminopyridin-3-yl)oxymethyl]-2,4-dichlorophenyl]sulfonyl]-(L)-
proline methyl ester

25 A solution of 4 g ($36.4 \cdot 10^{-3}$ mol) of 2-amino-3-hydroxypyridine in 200 ml of dimethylformamide is prepared and 1.09 g ($36.4 \cdot 10^{-3}$ mol) of sodium hydride are added at room temperature. After stirring for 30 min, 15.7 g ($36.4 \cdot 10^{-3}$ mol) of N-
30 [(3-bromomethyl-2,4-dichlorophenyl)sulfonyl]-(L)-proline methyl ester are added and the mixture is stirred for 2 hours at room temperature. The reaction medium is then poured into 250 ml of iced water. The product is filtered off and redissolved in ethyl acetate. The solution is washed with water and then dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained is purified by chromatography on silica gel using a dichloromethane/methanol mixture (97/3; v/v) as the eluent to give 12.4 g of the expected compound in the form of orange-
35 yellow crystals (yield = 74.5%).

M.p. = 68°C

$[\alpha]_D^{25} = -12.8^\circ$ ($c = 1.05$; CH_3OH)

PREPARATION XLVIII

N-[[3-[[3-Acetyl-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]proline methyl ester

- 5 A solution of 10.1 g (22.10^{-3} mol) of the compound obtained according to Preparation XLVII in 160 ml of ethanol is prepared. 6 ml (50.10^{-3} mol) of 3-chloro-2,4-pentanedione are added, with stirring, and the reaction mixture is stirred at the reflux point of the solvent for 15 hours. It is then concentrated under reduced pressure and the crude product obtained is purified by chromatography on
10 silica gel using a methylcyclohexane/ethyl acetate mixture (1/1; v/v) as the eluent to give 2.67 g of the expected product in the form of beige crystals (yield = 22.5%).

M.p. = 178°C

$[\alpha]_D^{25} = -8.6^\circ$ ($c = 1.05$; DMSO)

PREPARATION IL

- 15 **N-[[3-[[3-Acetyl-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]proline**

The expected product is obtained in the form of creamy white crystals (yield = 91%) by following a procedure analogous to Preparation II, starting from the compound obtained according to Preparation XLVIII.

- 20 M.p. = $162 - 164^\circ\text{C}$

$[\alpha]_D^{25} = -8.3^\circ$ ($c = 1.01$; CH_3OH)

PREPARATION L

- 25 **1-[[3-[[3-Acetyl-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[(4-cyanobenzoyl)amino]propyl]-2(S)-pyrrolidine-carboxamide**

The expected product is obtained in the form of off-white crystals (yield = 94%) by following a procedure analogous to Preparation V, starting from the compound obtained in Preparation IL.

M.p. = $100 - 102^\circ\text{C}$

- 30 $[\alpha]_D^{20} = -30.6^\circ$ ($c = 1.02$; CHCl_3)

Example 42

1-[[3-[[3-Acetyl-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-[(amino)(hydroxyimino)methyl]benzoyl]amino]-propyl]-2(S)-pyrrolidinecarboxamide

- 35 The expected product is obtained in the form of white crystals (yield = 88%) by following a procedure analogous to Example 1, starting from the compound

obtained in Preparation L.

M.p. = 164 - 166°C

$[\alpha]_D^{25} = -22^\circ$ (c = 1.00; CH₃OH)

PREPARATION LI

- 5 **1-[[3-[[3-Acetyl-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-[(acetoxymino)(amino)methyl]benzoyl]amino]-propyl]-2(S)-pyrrolidinecarboxamide**

The expected product is obtained in the form of white crystals (yield = 97%) by following a procedure analogous to Preparation VI, starting from the compound
10 obtained according to Example 42.

M.p. = 115 - 117°C

$[\alpha]_D^{24} = -6.4^\circ$ (c = 1.06; DMSO)

Example 43

- 15 **1-[[3-[[3-Acetyl-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide**

The expected product is obtained in the form of white crystals (yield = 69%) by following a procedure analogous to Example 2, starting from the compound obtained in Preparation LI.

20 M.p. = 158 - 160°C

$[\alpha]_D^{21} = -9.5^\circ$ (c = 1.01; DMSO)

Example 44

- 25 **1-[[3-[[3-Acetyl-2-methylimidazo[1,2-a]pyridin-8-yl]oxymethyl]-2,4-dichloro-phenyl]sulfonyl]-N-[3-[[4-(aminoiminomethyl)benzoyl]amino]propyl]-2(S)-pyrrolidinecarboxamide bis(methanesulfonate)**

The expected product is obtained in the form of white crystals (yield = 84%) by following a procedure analogous to Example 3, starting from the compound obtained according to Example 43.

M.p. = 170 - 172°C

30 $[\alpha]_D^{22} = -7.5^\circ$ (c = 1.02; DMSO)

The activity of the products according to the invention was evaluated in respect of their ability to bind to the bradykinin receptors. Kinins, of which bradykinin is the main representative, actually form a group of small peptides which make an important contribution to the inflammatory response and therefore appear
35 to be involved in the pathophysiology of inflammatory diseases. Furthermore, bradykinin is one of the most potent analgesics known. Kinins activate two types of

receptor, called B₁ and B₂. The B₂ receptor belongs to the large family of receptors with seven transmembrane domains coupled to the G proteins. In the present invention we describe compounds which bind to the B₂ receptor and thereby block the binding of bradykinin.

5 The following pharmacological test is used: Ileum segments are isolated from male guinea-pigs [of the Dunkin-Hartley strain (Iffa Credo, l'Arbresle, France)] and ground in the following TES buffer: TES 25 mM, 1,10-phenanthroline 1 mM (pH 6.8), bacitracin 140 µg/ml, BSA 1 g/l. The membranes are then isolated by centrifugation (18,000 rpm; 20 min; 4°C). The binding studies are carried out in
10 this TES buffer using [³H]-bradykinin (120 pM) and 50 µg of membrane protein per test (final volume 500 µl) with an equilibrium time of 90 min at 20°C. The percentage inhibition of the binding of [³H]-bradykinin is then determined in the presence of one of the test compounds according to the invention at a concentration of 10⁻⁶ M.

15 The results obtained from these tests (shown as "activity") are collated in Table I below with reference to the Examples given in the description. In this Table, the meaning of the heterocyclic radicals Q is given in the notes and the nature of the salts is indicated by the abbreviations Chl in the case of a hydrochloric acid salt and Ms in the case of a methanesulfonic acid salt.

20 The compounds according to the invention have an antagonistic effect towards the bradykinin B₂ receptor (they inhibit the activation of the B₂ receptors which is induced by bradykinin). This property has been demonstrated experimentally by means of pharmacological tests described in the publication by D. PRUNEAU et al. (British Journal of Pharmacology, Oct. 1995, vol. 116 (no. 3), pp.
25 2106 - 2112) and performed on guinea-pig ileum. The experimental results, evaluated by the pK_B described in the above publication, are reported in the summary Table.

 The compounds of the present invention which inhibit the binding of [³H]-bradykinin to the guinea-pig B₂ receptor (see Table I) also bind to the human B₂
30 receptor cloned and transfected in a stable manner into CHO cells (Chinese Hamster Ovary cells). Thus, in this test, some compounds inhibit the binding of [³H]-bradykinin to the B₂ receptor by at least 95% at a concentration of 10 µM.

 The compounds of the present invention can be useful in the treatment of pain and particularly in the treatment of numerous pathological conditions involving
35 bradykinin or its homologs. These pathological conditions include septic and hemorrhagic shock, anaphylactic reactions, arthrosis, rheumatoid polyarthrititis,

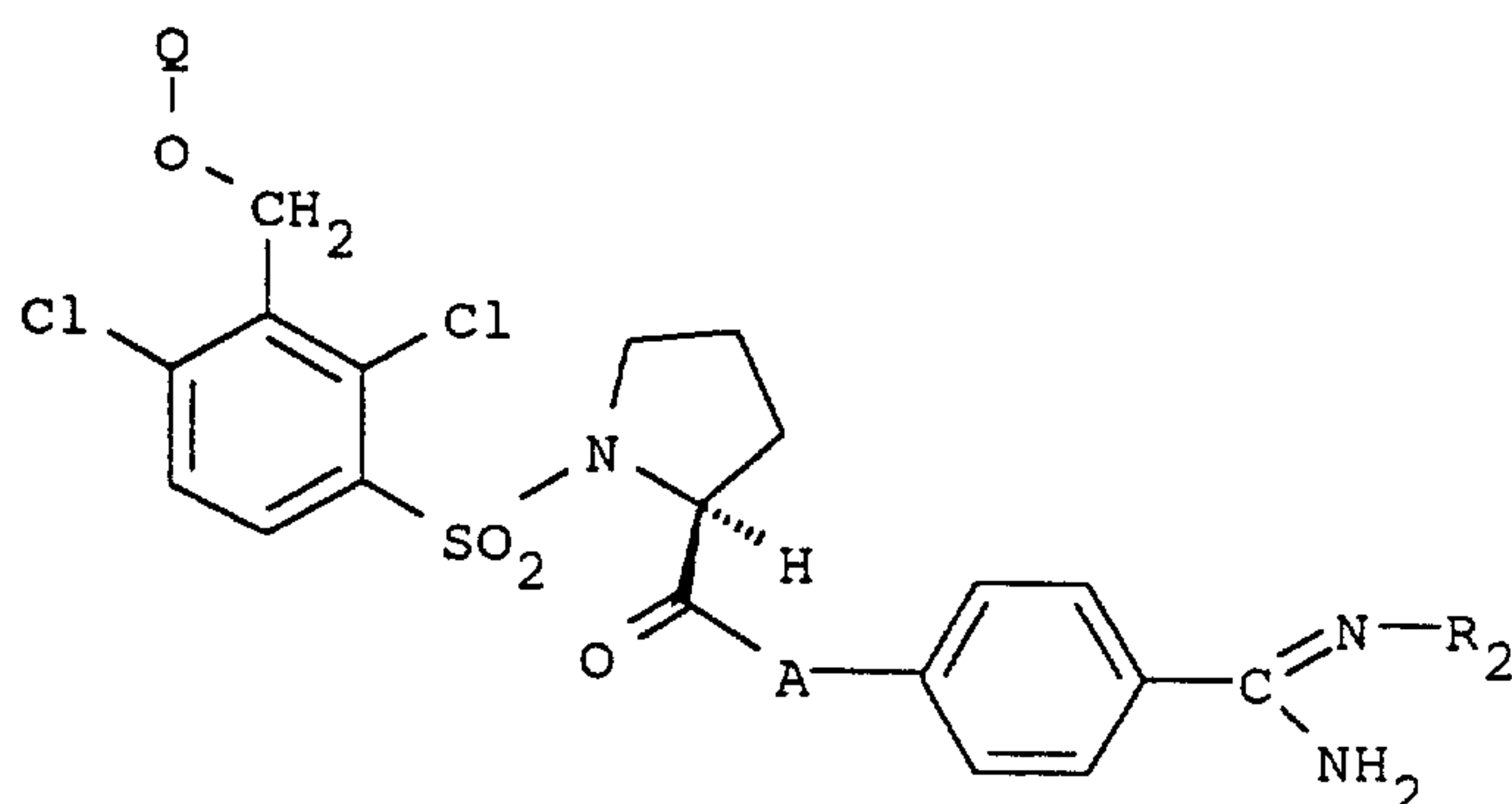
rhinitis, asthma, inflammatory diseases of the gastrointestinal tract (for example colitis, rectitis, Crohn's disease), pancreatitis, certain carcinomas, hereditary angioedema, migraine, encephalomyelitis, meningitis, cerebrovascular complications (especially those caused by cerebral traumatic shock), certain neurological disorders, vascular inflammatory states (for example atherosclerosis and arteritis of the lower limbs), painful states (for example headache, toothache, menstrual pain), premature uterine contractions, cystitis and burns. The compounds according to the invention can also be useful for the potentiation of antiviral agents.

The compounds of the present invention, which can be used in the form of the free base or in the form of their non-toxic addition salts in association with a physiologically acceptable excipient, are generally prescribed in human therapeutics at doses of about 1 to 1000 mg/day in a form which can be administered orally, by intravenous, intramuscular or subcutaneous injection, transdermally, by means of aerosols or by means of suppositories.

These compounds can also be administered topically, for example in the form of a gel or ointment.

The compounds of the present invention are also useful as pharmacological reagents, especially for the study of hormone-receptor interactions. Use as a pharmacological reagent may require a radiolabeled derivative of one of the compounds according to the invention (for example with tritium [^3H] or sulfur [^{35}S]) in order to obtain a radioligand intended for conformational studies of the bradykinin B_2 receptor or for binding tests involving this type of receptor, for example for the evaluation of novel compounds which are capable of exhibiting an affinity for the bradykinin B_2 receptor.

TABLE I



Ex.	Q	R ₁	A	R ₂	Salt	Activity %	pK _B
1	Het 1	H	-NH-(CH ₂) ₃ -NH-CO-	OH	-		
2	Het 1	H	-NH-(CH ₂) ₃ -NH-CO-	H	-		
3	Het 1	H	-NH-(CH ₂) ₃ -NH-CO-	H	Ms		
4	Het 1	H		OH	-		
5	Het 1	H		H	-		
6	Het 1	H		H	Ms		
7	Het 1	CH ₃	-NH-(CH ₂) ₃ -NH-CO-	OH	-		
8	Het 1	CH ₃	-NH-(CH ₂) ₃ -NH-CO-	H	-		
9	Het 1	CH ₃	-NH-(CH ₂) ₃ -NH-CO-	H	Ms	97.4	8.6

TABLE I (continuation 1)

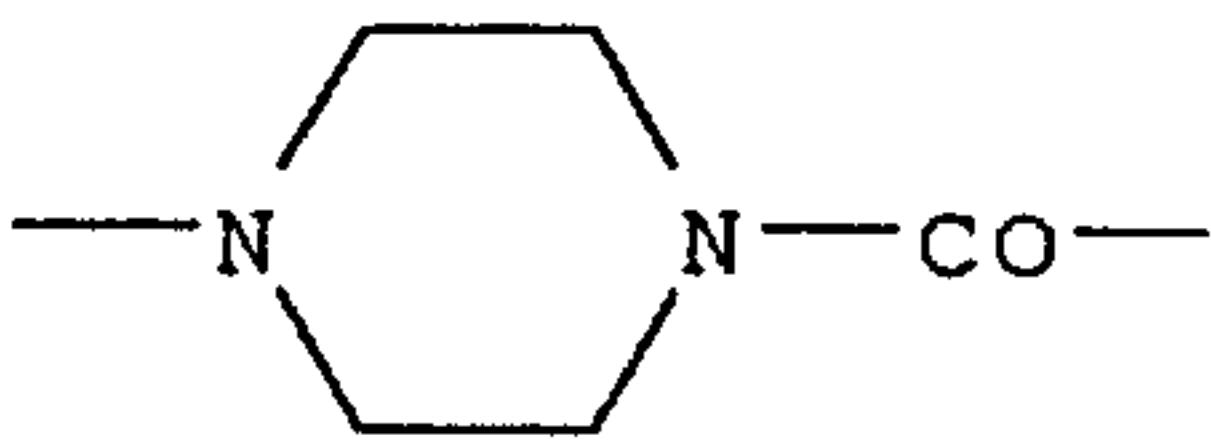
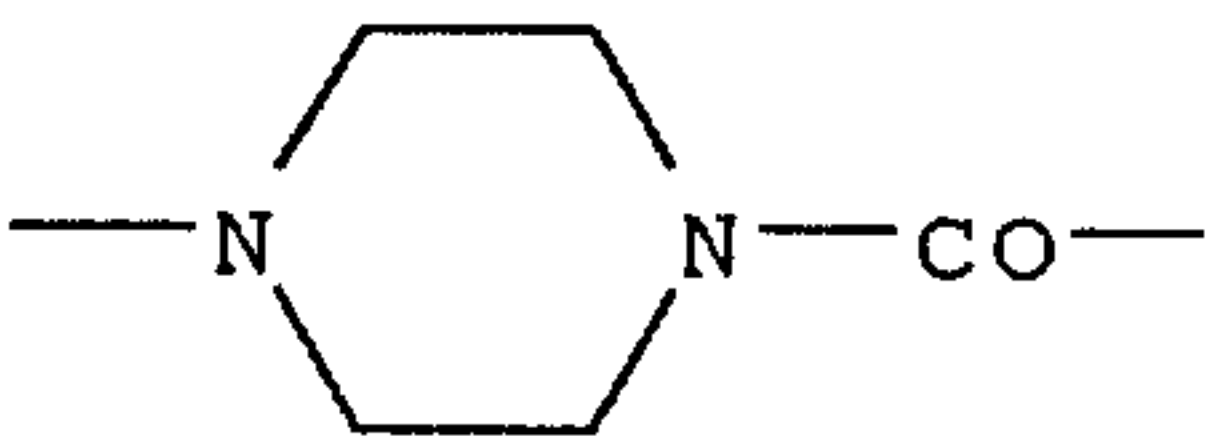
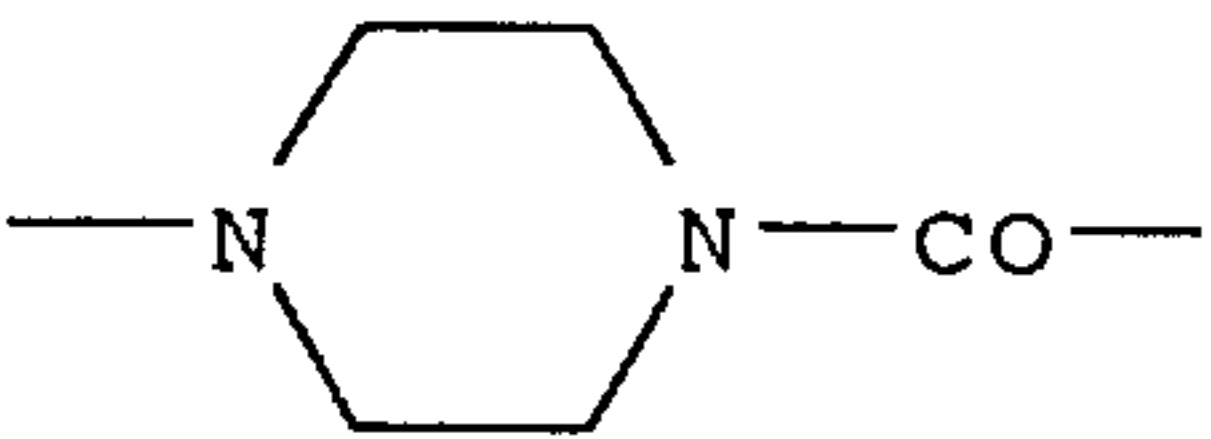
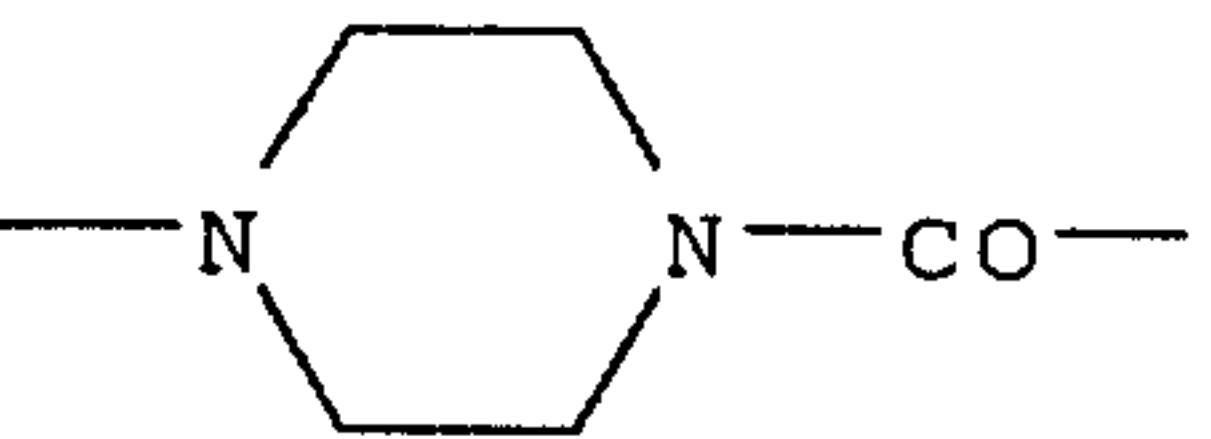
Ex.	Q	R ₁	A	R ₂	Salt	Activity %	pK _B
10	Het 1	CH ₃		OH	-		
11	Het 1	CH ₃		H	-		
12	Het 1	CH ₃		H	Chl		
13	Het 1	CH ₃	-NH-CH ₂ -	H	-		
14	Het 1	CH ₃	-NH-CH ₂ -	H	Chl		
15	Het 1	Br	-NH-(CH ₂) ₃ -NH-CO-	H	-		
16	Het 1	Br	-NH-(CH ₂) ₃ -NH-CO-	H	Chl	100	9.1
17	Het 1	Br		H	Chl	100	8.4
18	Het 1	Br	-NH-CH ₂ -	H	-		
19	Het 1	Br	-NH-CH ₂ -	H	Chl		
20	Het 2	-	-NH-(CH ₂) ₃ -NH-CO-	OH	-		

TABLE I (continuation 2)

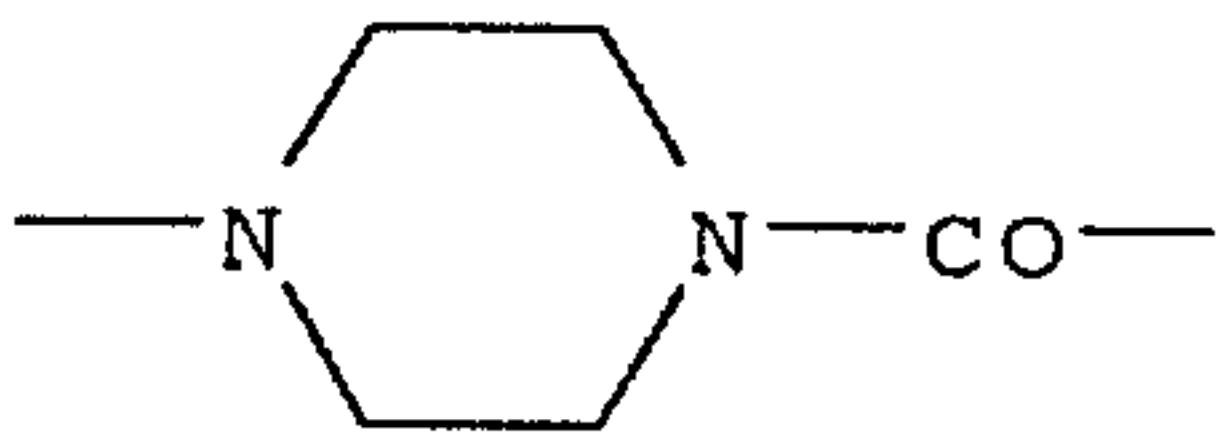
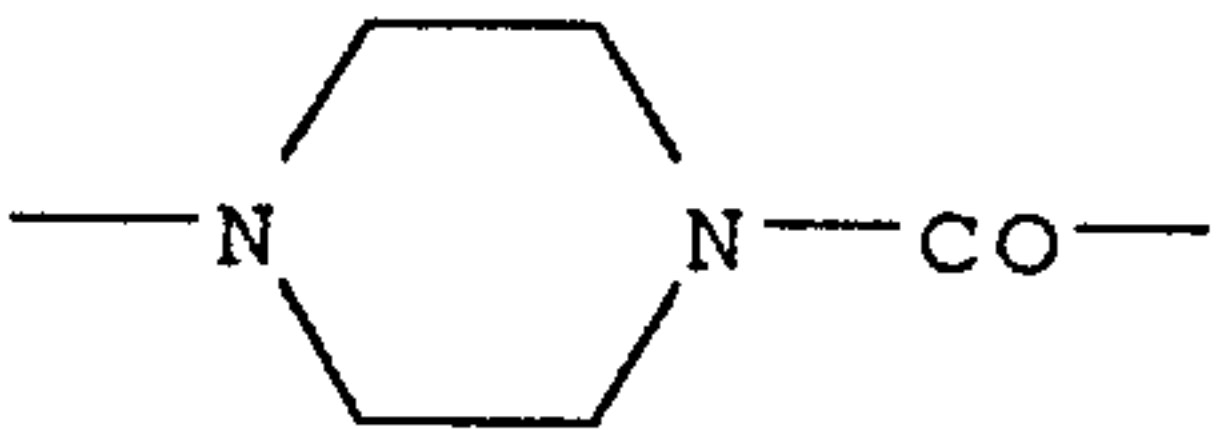
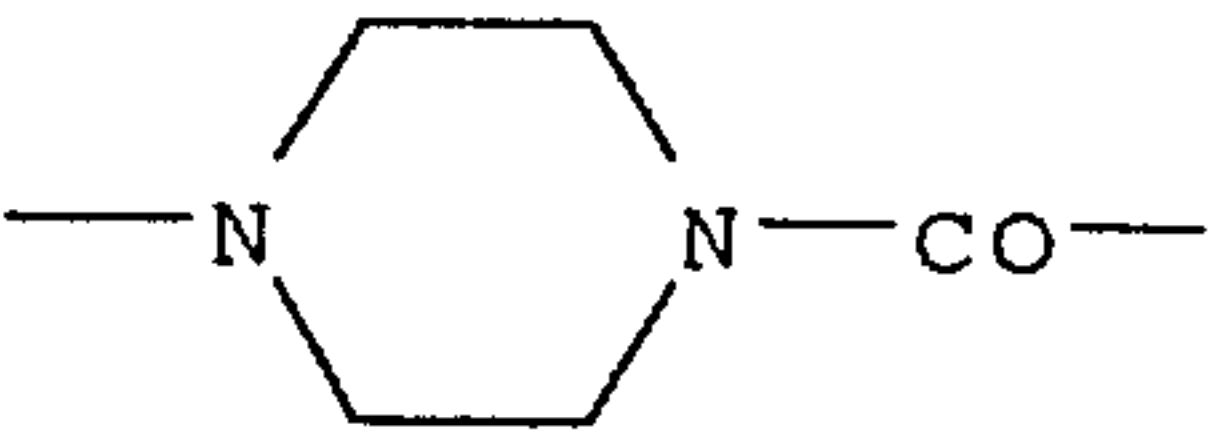
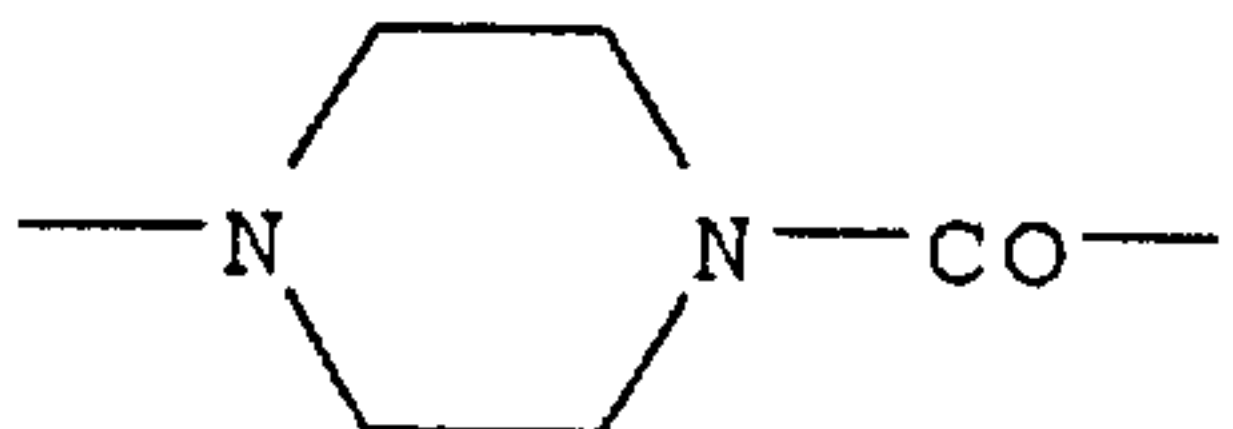
Ex.	Q	R ₁	A	R ₂	Salt	Activity %	pK _B
21	Het 2	-	-NH-(CH ₂) ₃ -NH-CO-	H			
22	Het 2	-	-NH-(CH ₂) ₃ -NH-CO-	H	Ms	97.5	8.4
23	Het 2	-		OH			
24	Het 2	-		H			
25	Het 2	-		H	Chl		
26	Het 2	-	-NH-CH ₂ -	H	-		
27	Het 2	-	-NH-CH ₂ -	H	Chl		
28	Het 3	-	-NH-(CH ₂) ₃ -NH-CO-	OH	-		
29	Het 3	-	-NH-(CH ₂) ₃ -NH-CO-	H	-		
30	Het 3	-	-NH-(CH ₂) ₃ -NH-CO-	H	Ms	99.3	7.9
31	Het 3	-		OH	-		

TABLE I (continuation 3)

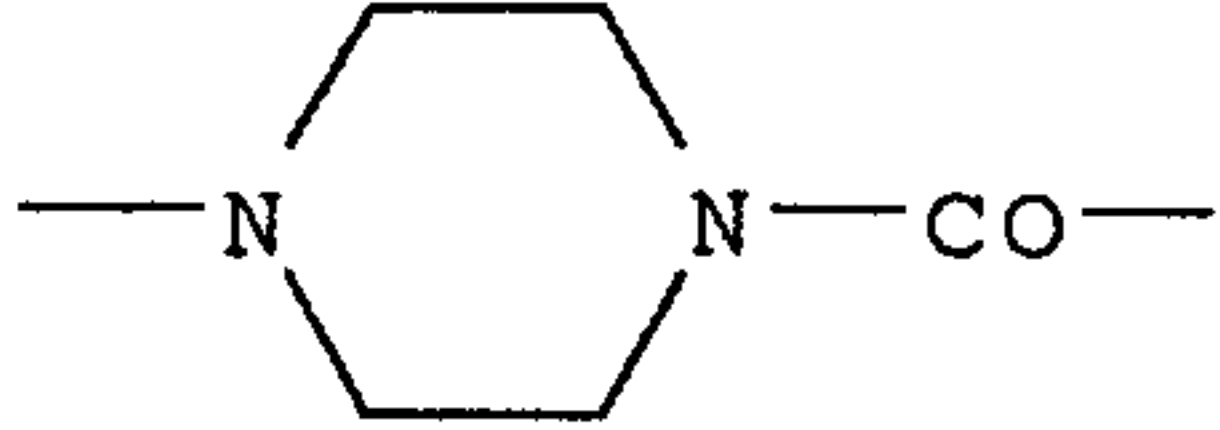
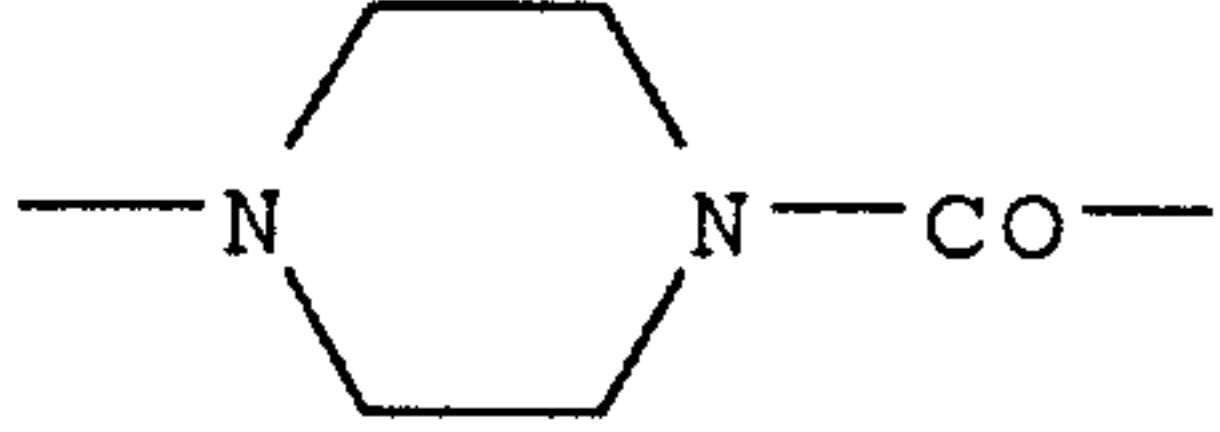
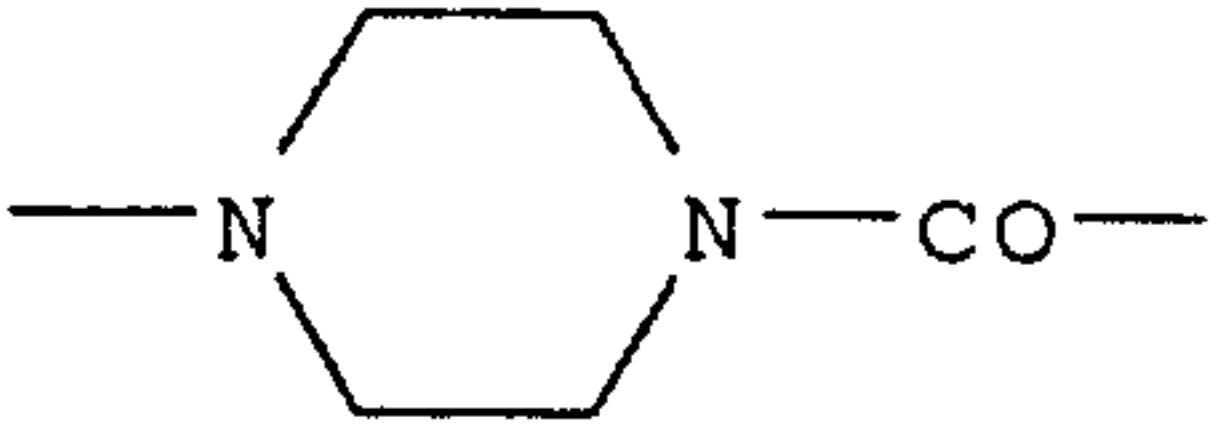
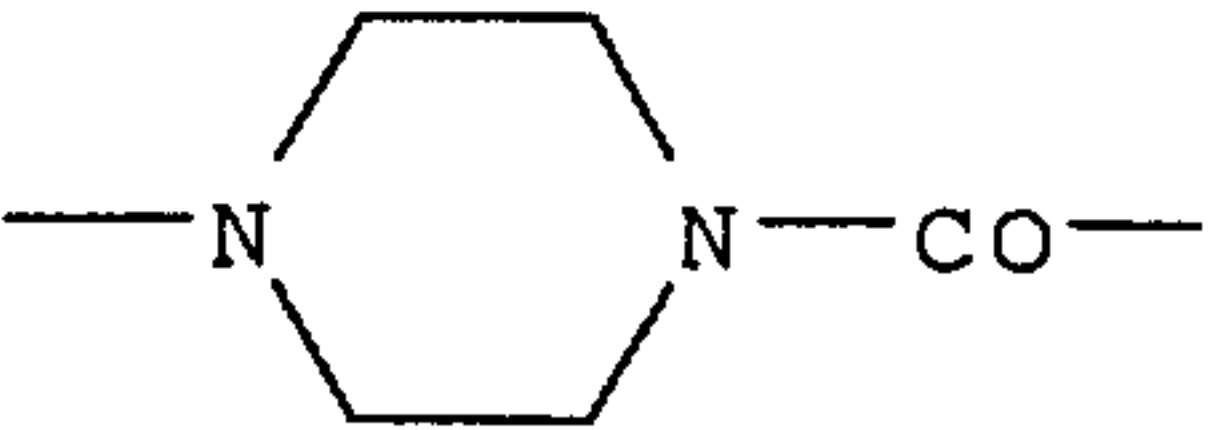
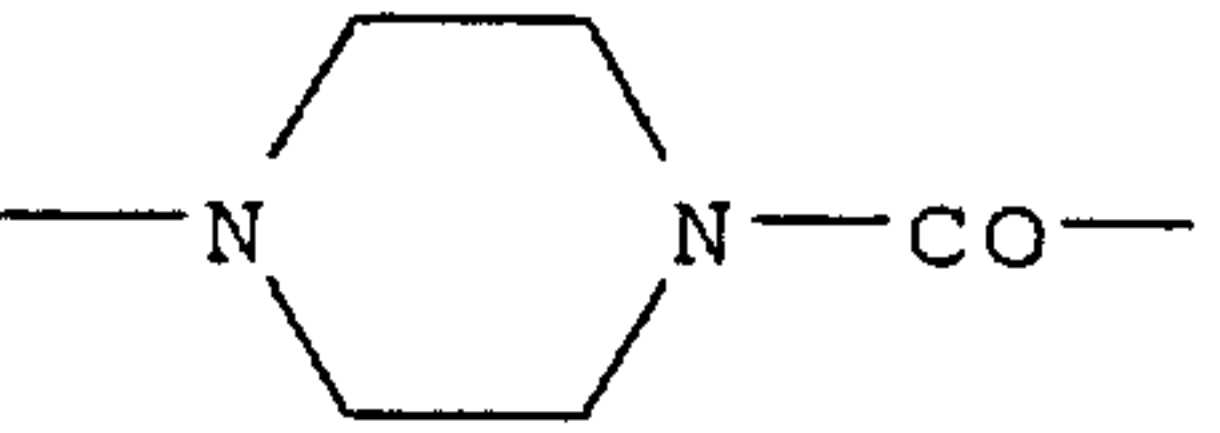
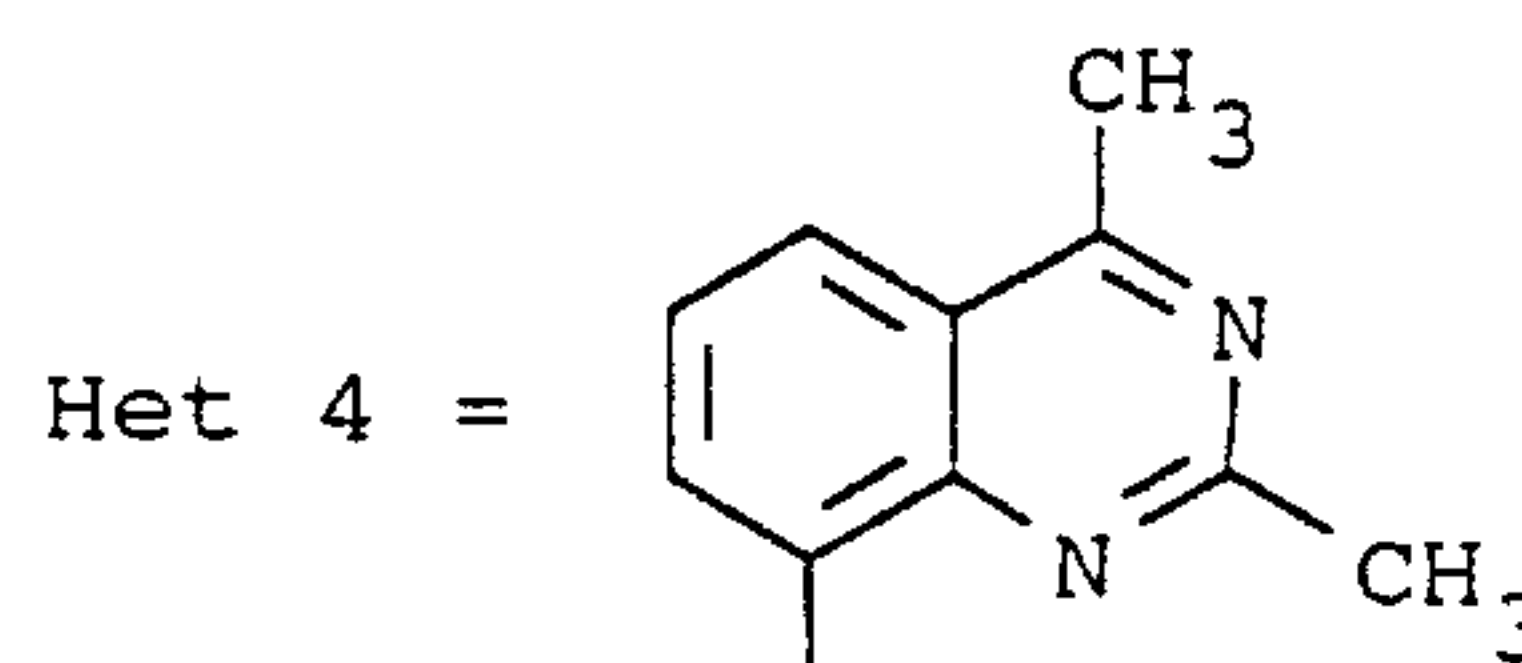
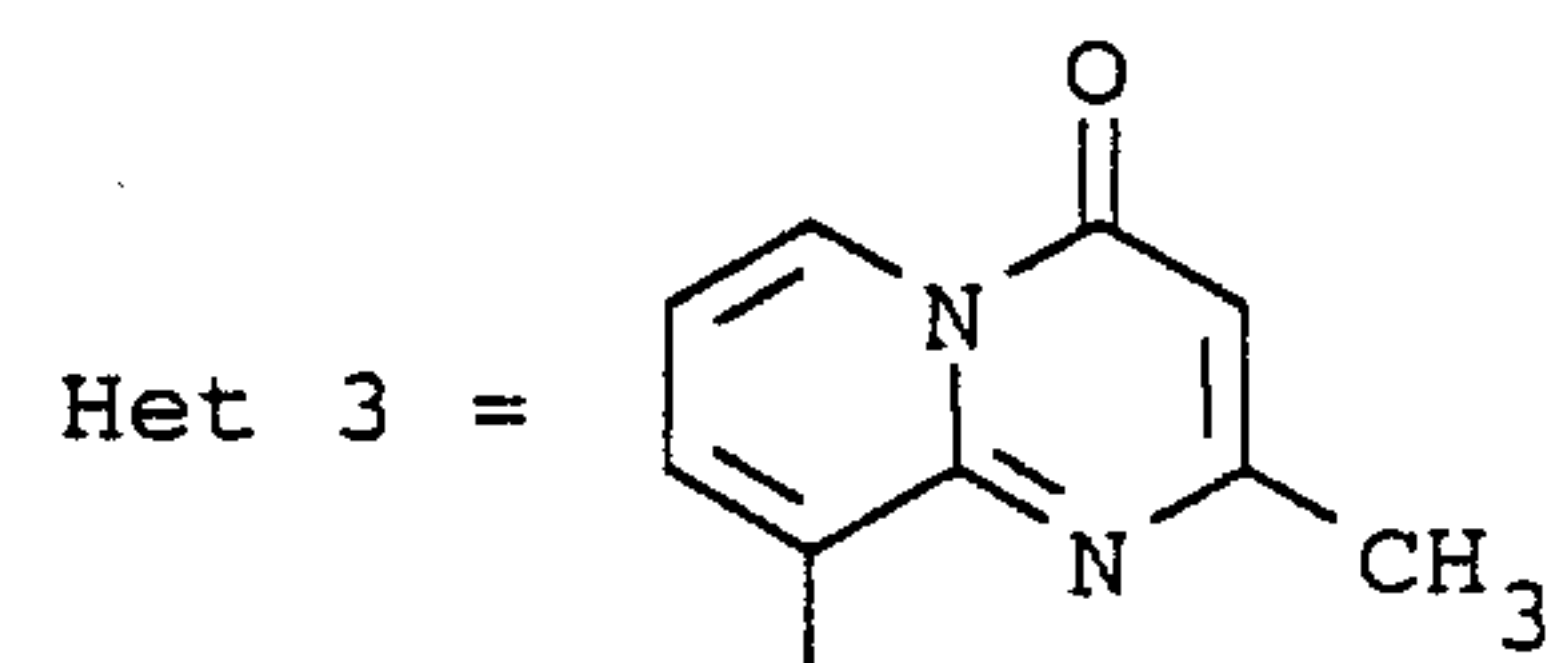
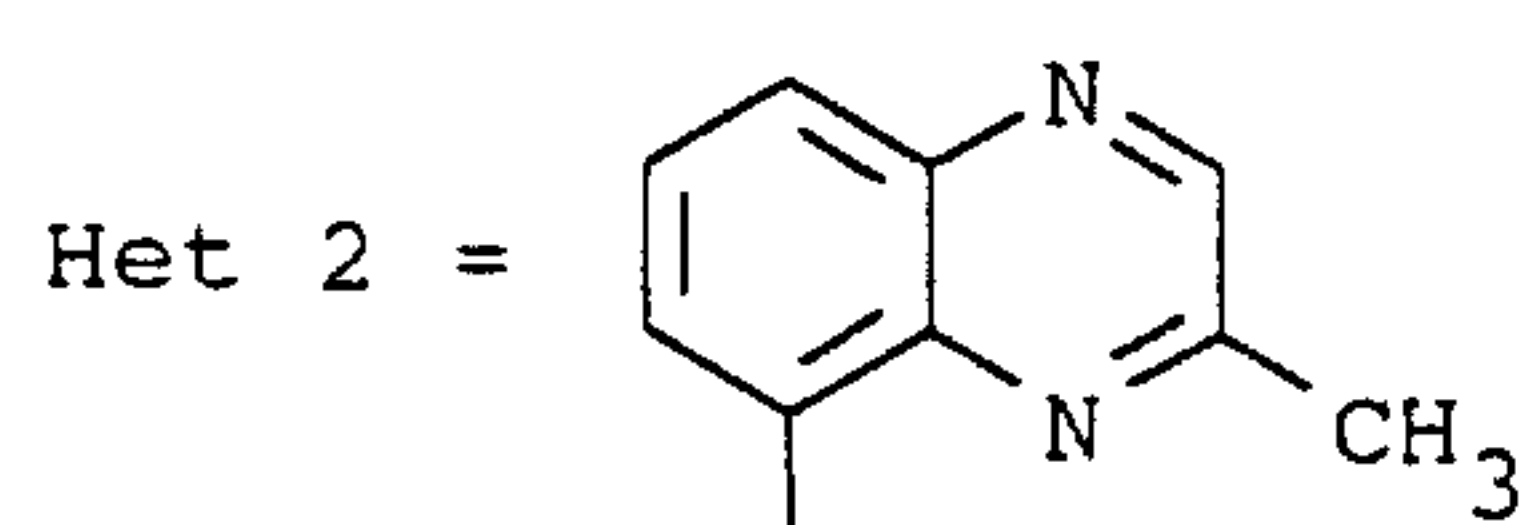
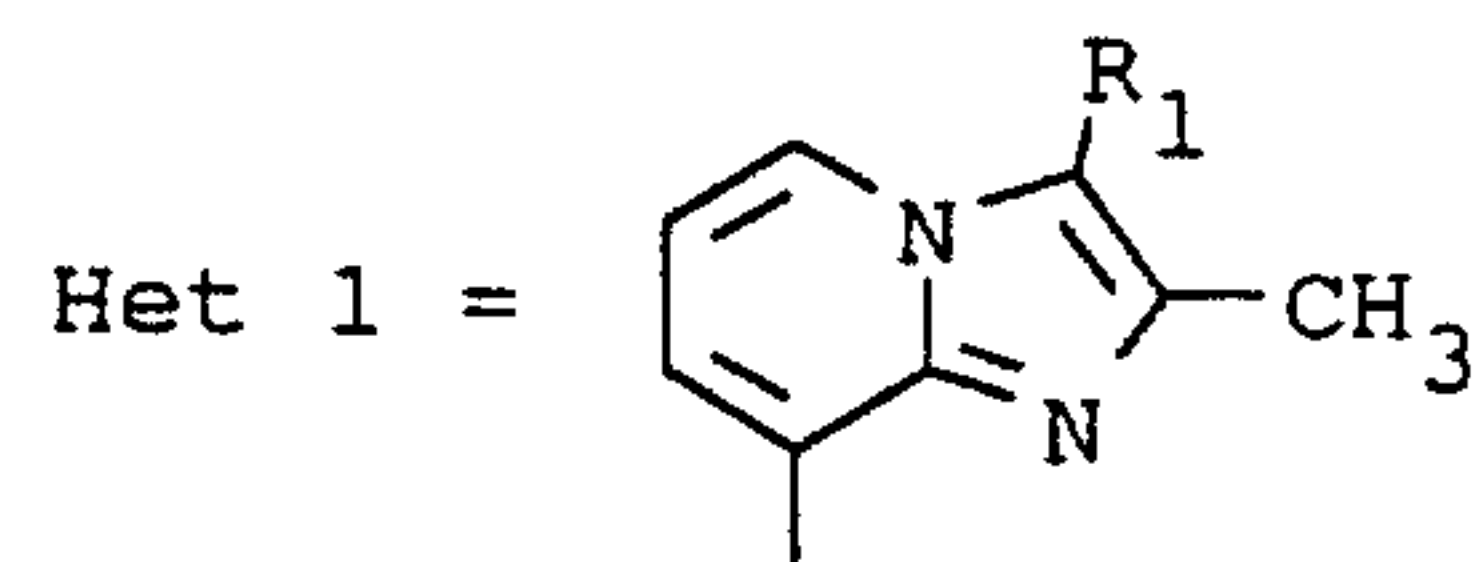
Ex.	Q	R ₁	A	R ₂	Salt	Activity %	pK _B
32	Het 3	-		H	-		
33	Het 3	-		H	Ms	96	7.8
34	Het 4	-	-NH-CH ₂ -	H	-		
35	Het 4	-	-NH-CH ₂ -	H	Chl		
36	Het 1	Cl	-NH-(CH ₂) ₃ -NH-CO-	OH	-		
37	Het 1	Cl	-NH-(CH ₂) ₃ -NH-CO-	H	-		
38	Het 1	Cl	-NH-(CH ₂) ₃ -NH-CO-	H	Ms	100	
39	Het 1	Cl		OH	-		
40	Het 1	Cl		H	-		
41	Het 1	Cl		H	Ms	100	

TABLE I (end)

Ex.	Q	R ₁	A	R ₂	Salt	Activity %	pK _B
42	Het 1	-CO-CH ₃	-NH-(CH ₂) ₃ -NH-CO-	OH	-		
43	Het 1	-CO-CH ₃	-NH-(CH ₂) ₃ -NH-CO-	H	-		
44	Het 1	-CO-CH ₃	-NH-(CH ₂) ₃ -NH-CO-	H	Ms	100	

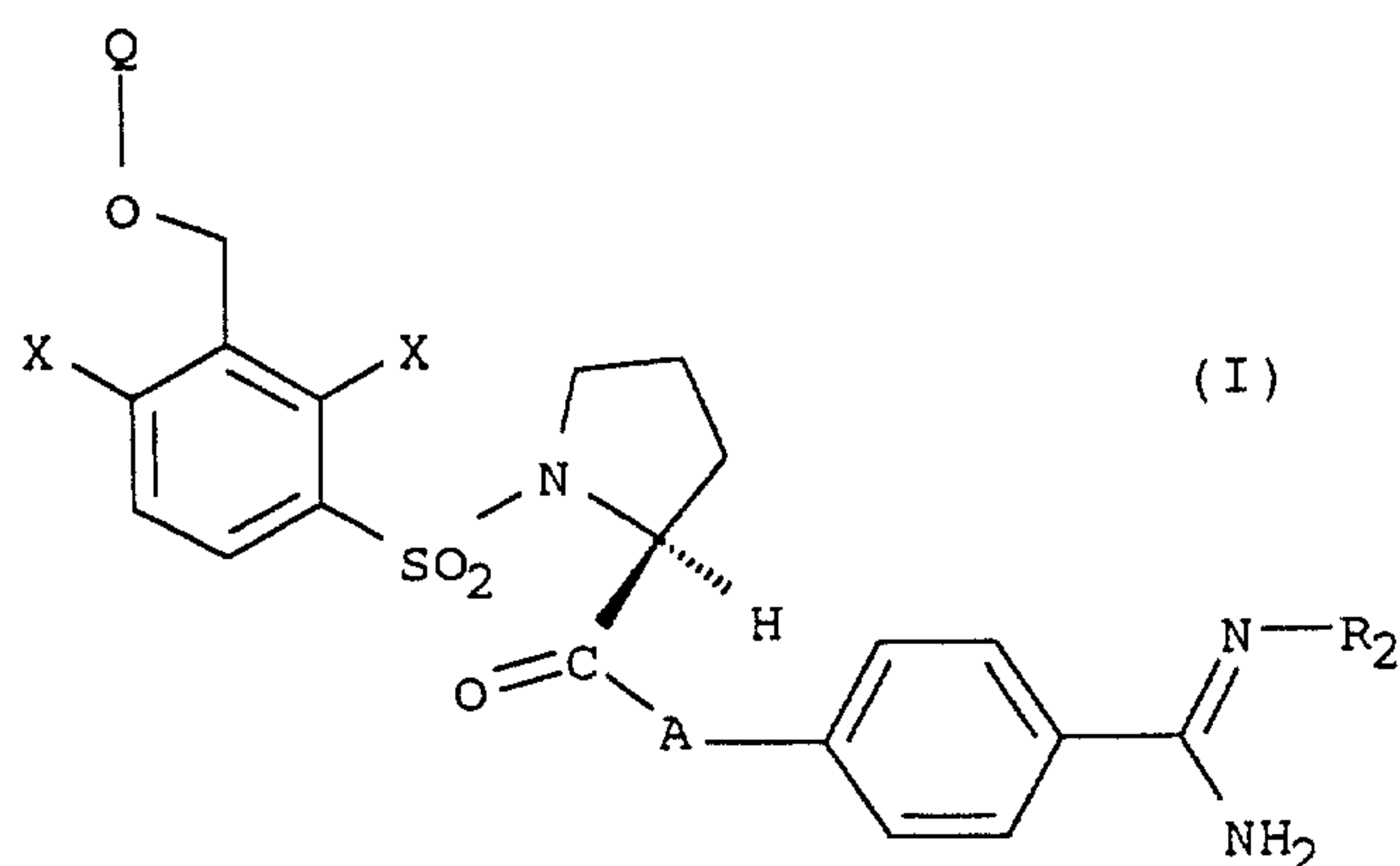
Notes:

Ms: addition salt with methanesulfonic acid

Chl: addition salt with hydrochloric acid

WHAT IS CLAIMED IS:

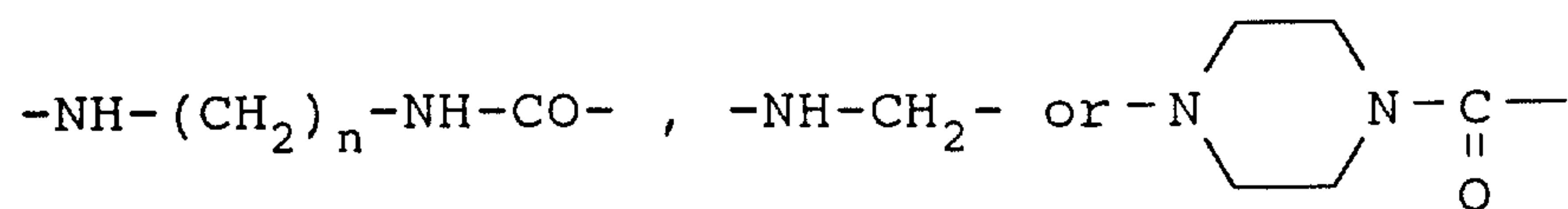
1. N-(Benzenesulfonyl)-L-proline compound selected from the group consisting of:
- 5 (i) the compounds of formula I:



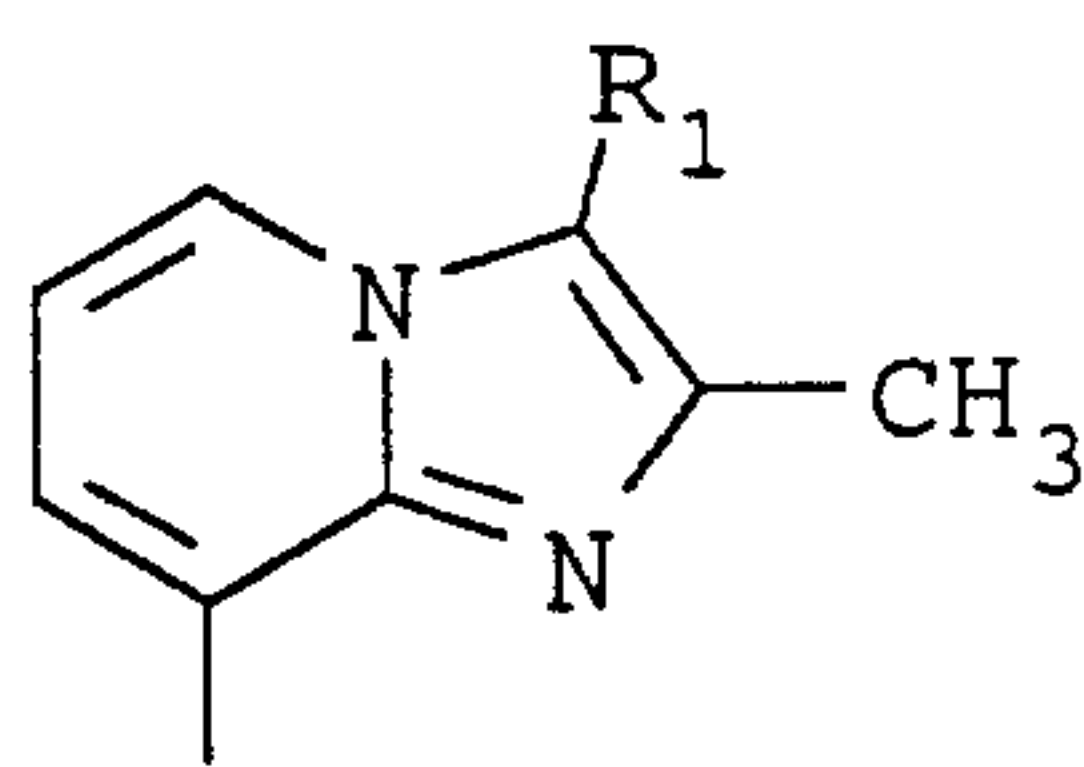
in which:

X is a halogen atom,

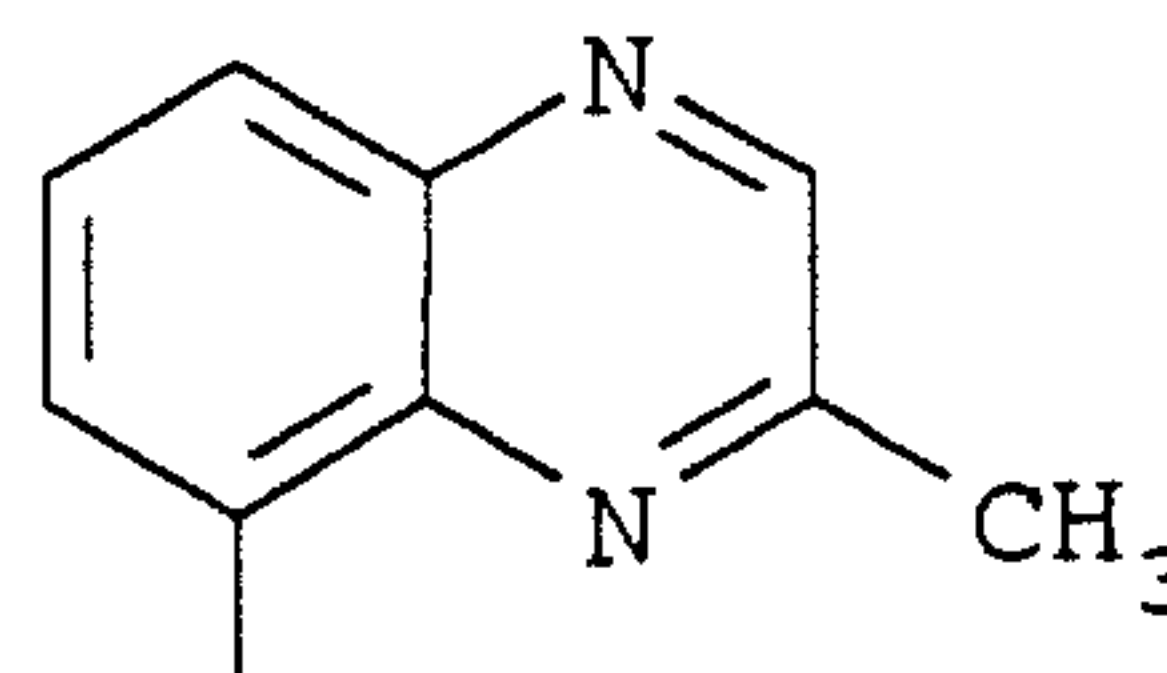
10 A is a divalent group



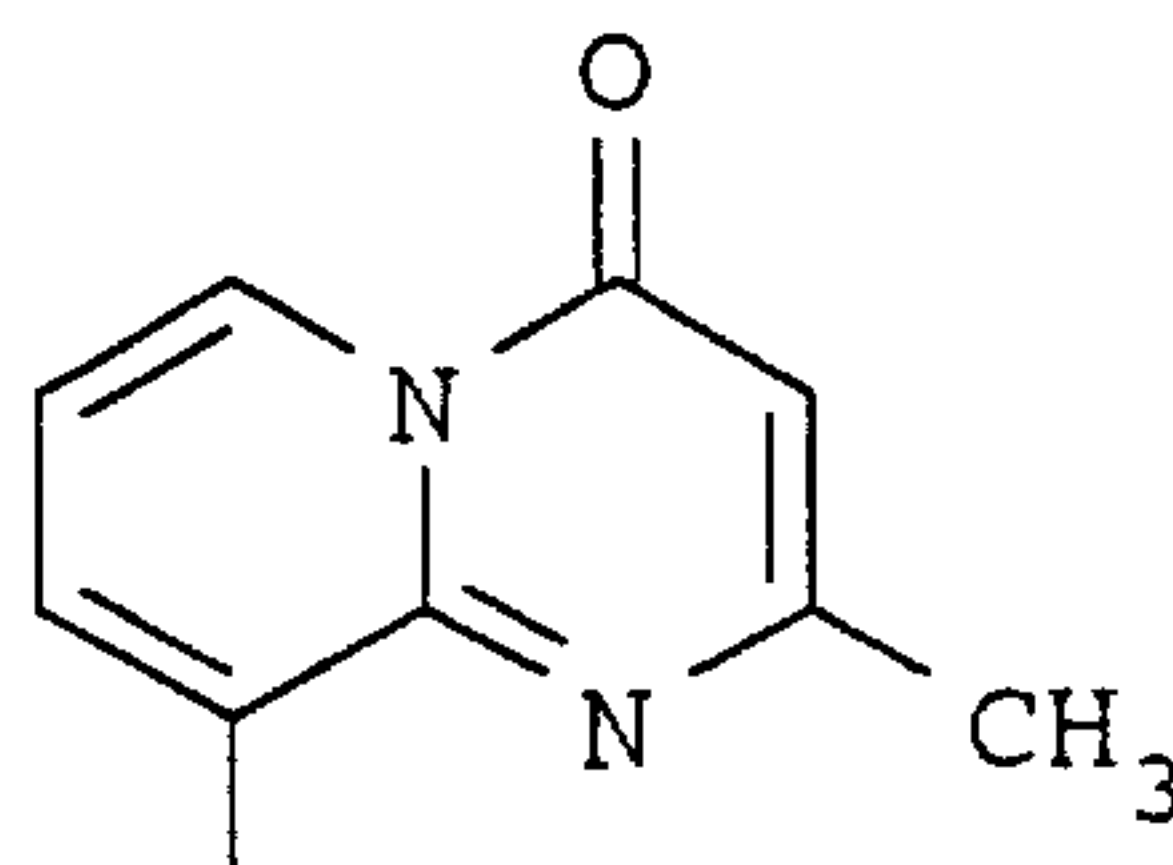
Q is a group



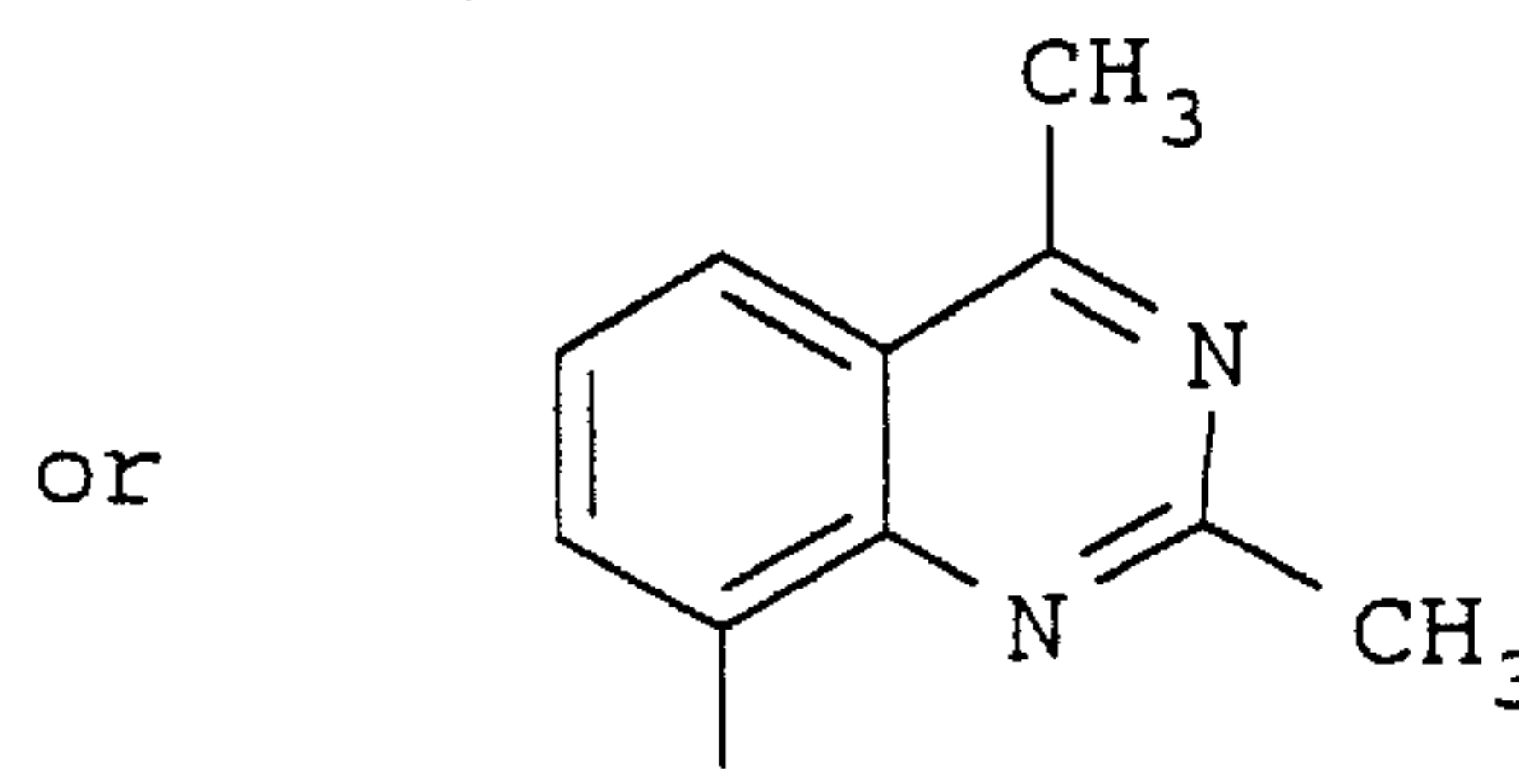
(Het 1)



(Het 2)



(Het 3)



(Het 4)

15

R₁ is a hydrogen atom, a halogen atom, a C₁-C₃ alkyl group with a linear or

branched hydrocarbon chain, or a C_1 - C_5 1-oxoalkyl group,

R_2 is a hydrogen atom or an OH group, and

n is 2, 3 or 4; and

(ii) their addition salts.

5 2. Compound according to claim 1 wherein X is Cl.

3. Process for the preparation of a compound of formula I, which comprises, according to a first variant A, the steps which consist in:

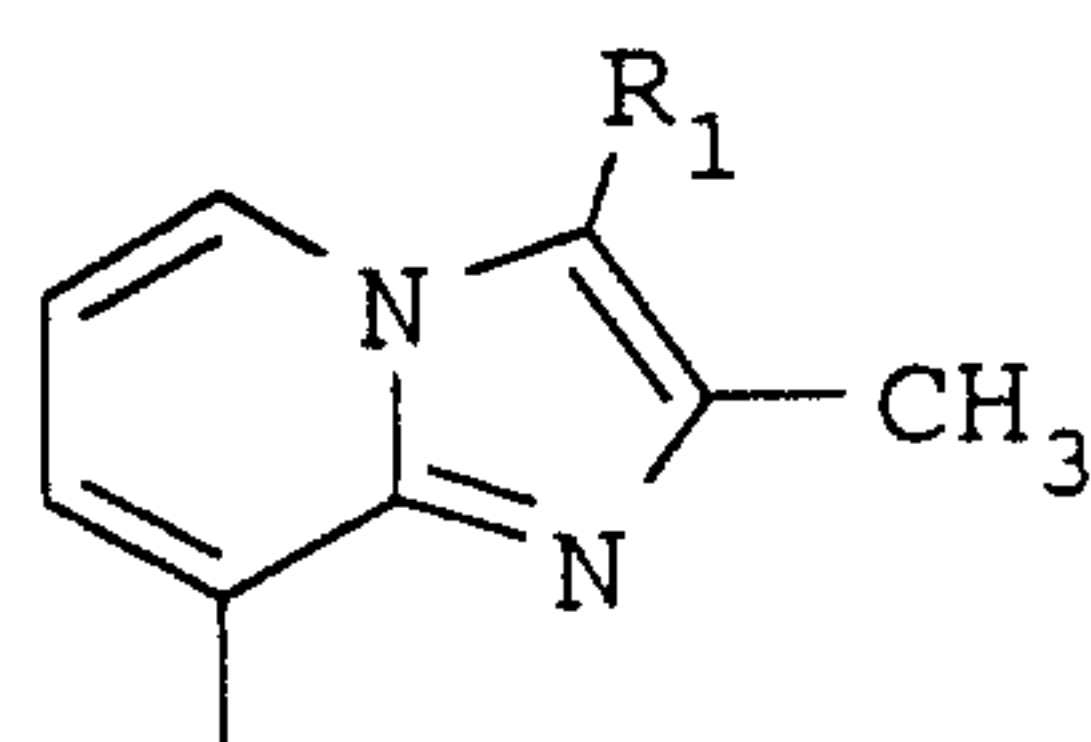
(1) reacting a hydroxylated heterocyclic compound of the formula



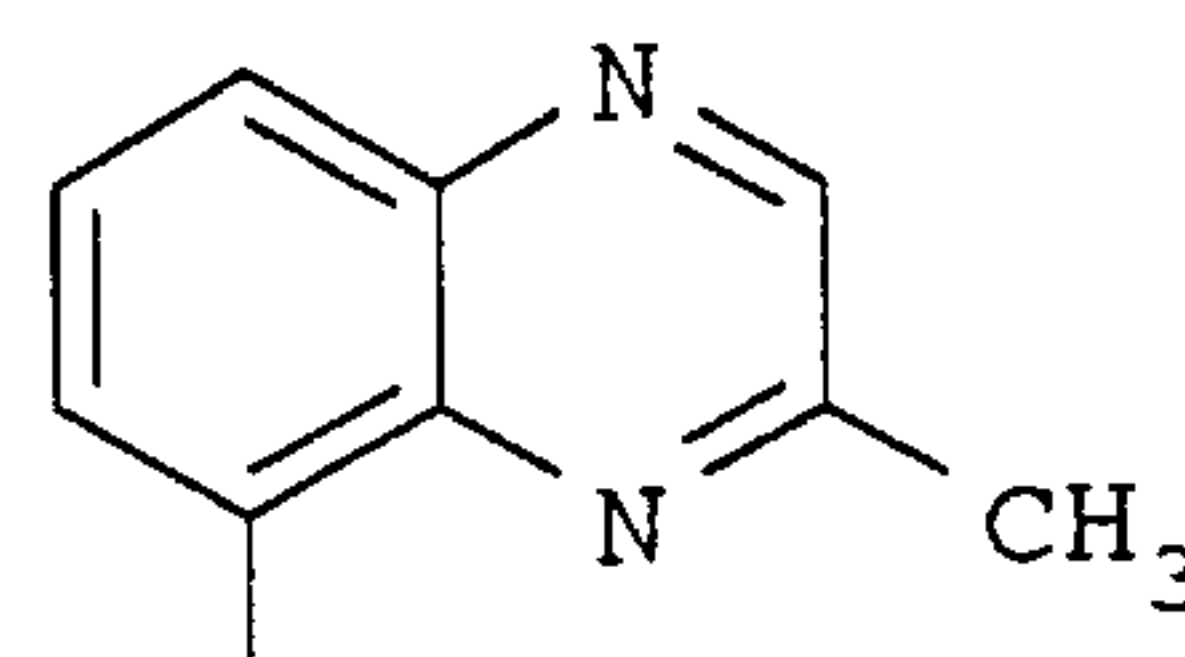
10 in which:

Met is an alkali metal, especially Na or K, and

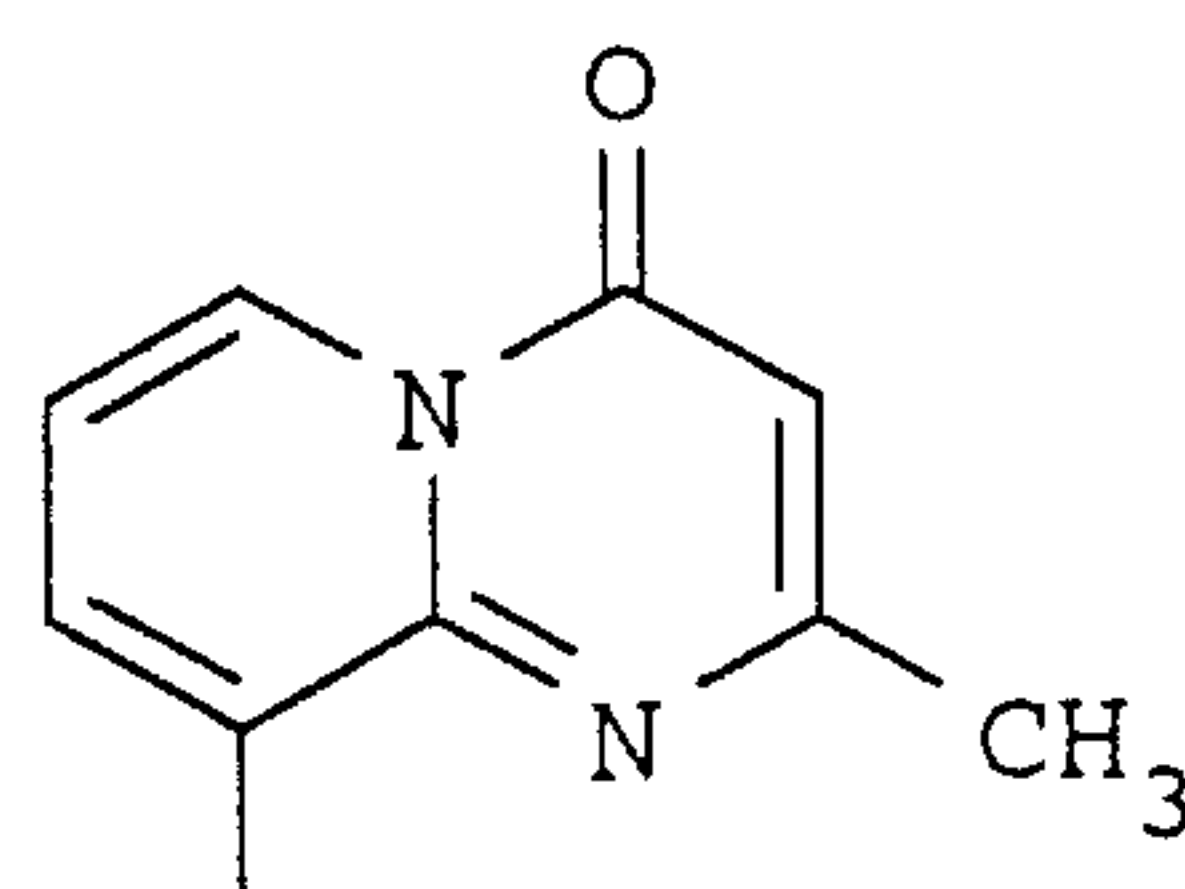
Q is a heterocyclic group selected from the structures Het 1, Het 2, Het 3 and Het 4:



(Het 1)

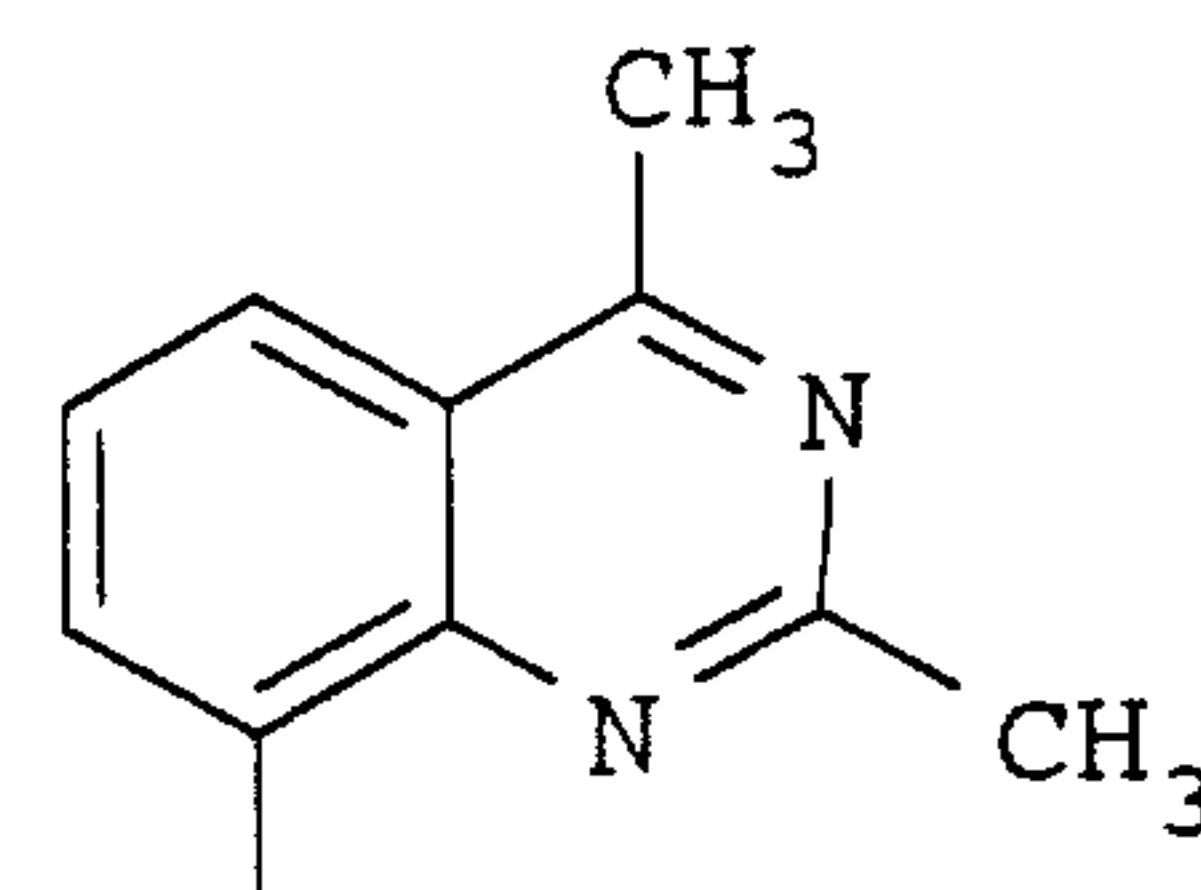


(Het 2)



(Het 3)

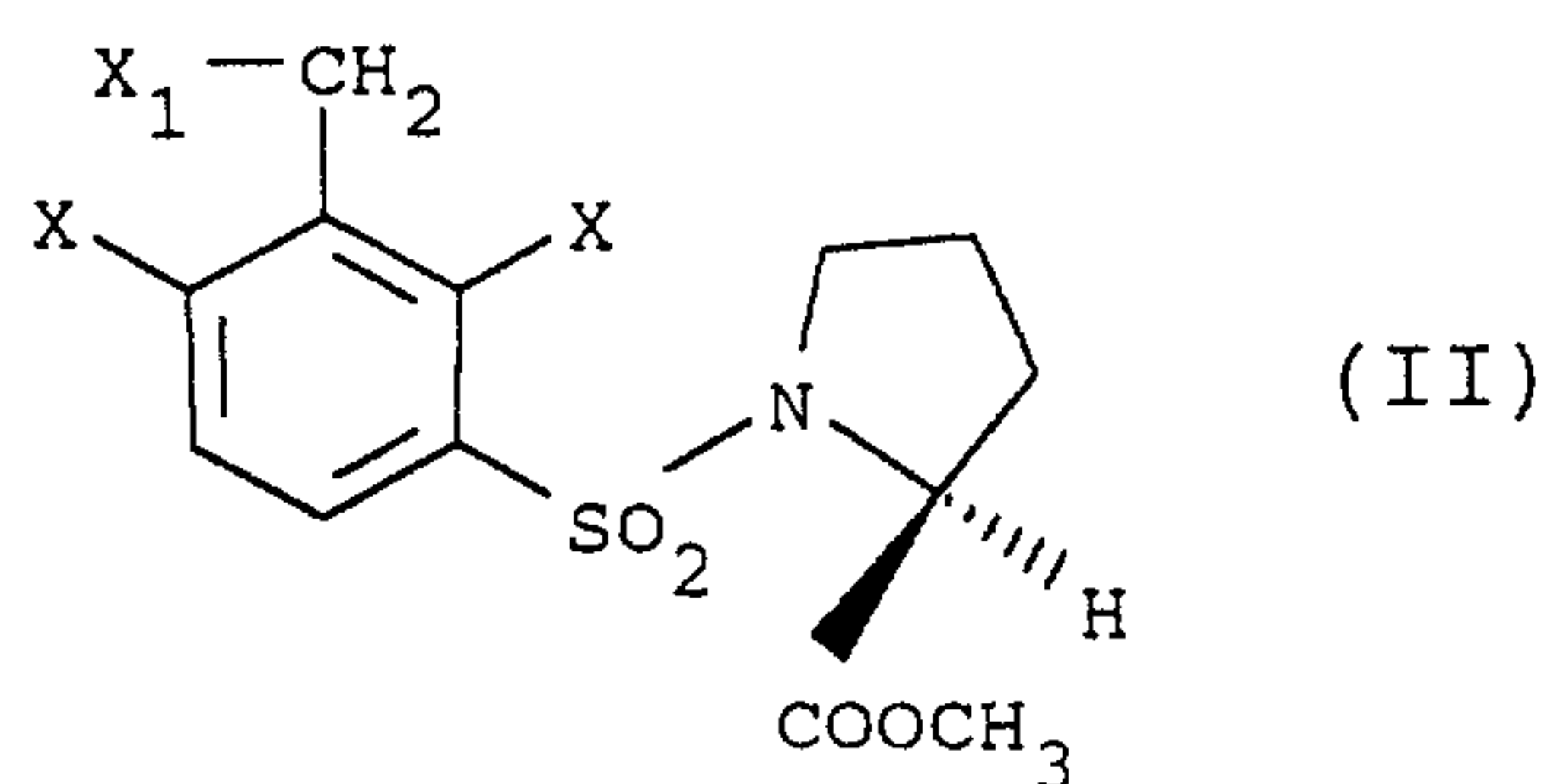
and



(Het 4)

15

R_1 being a hydrogen atom or a C_1 - C_3 alkyl group, with a compound of formula II:

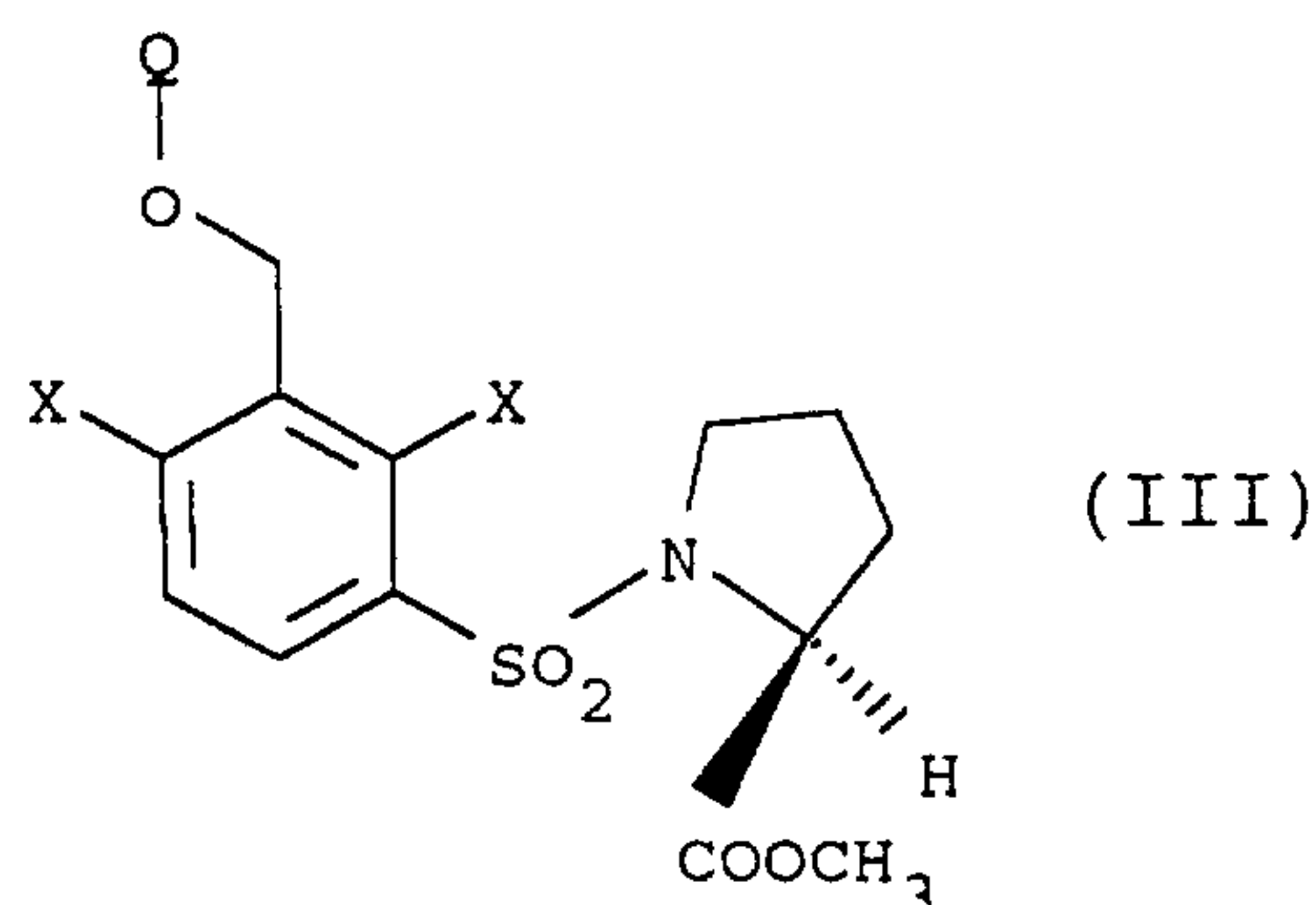


(II)

in which X is a halogen atom and X_1 is a halogen atom, preferably Br,

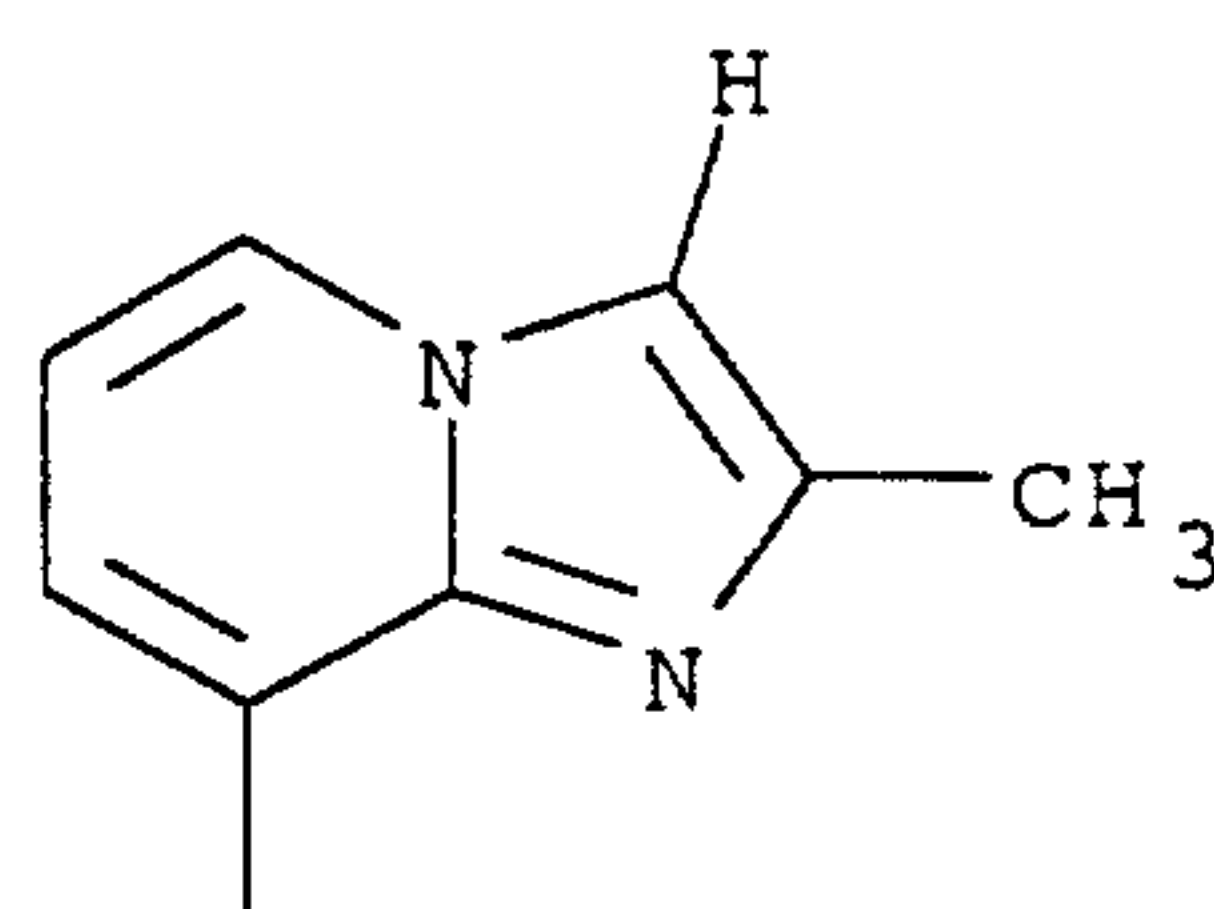
20 in an anhydrous solvent, at a temperature of between 0 and 50°C, for 0.5 to 10 hours, to give a compound of formula III:

50

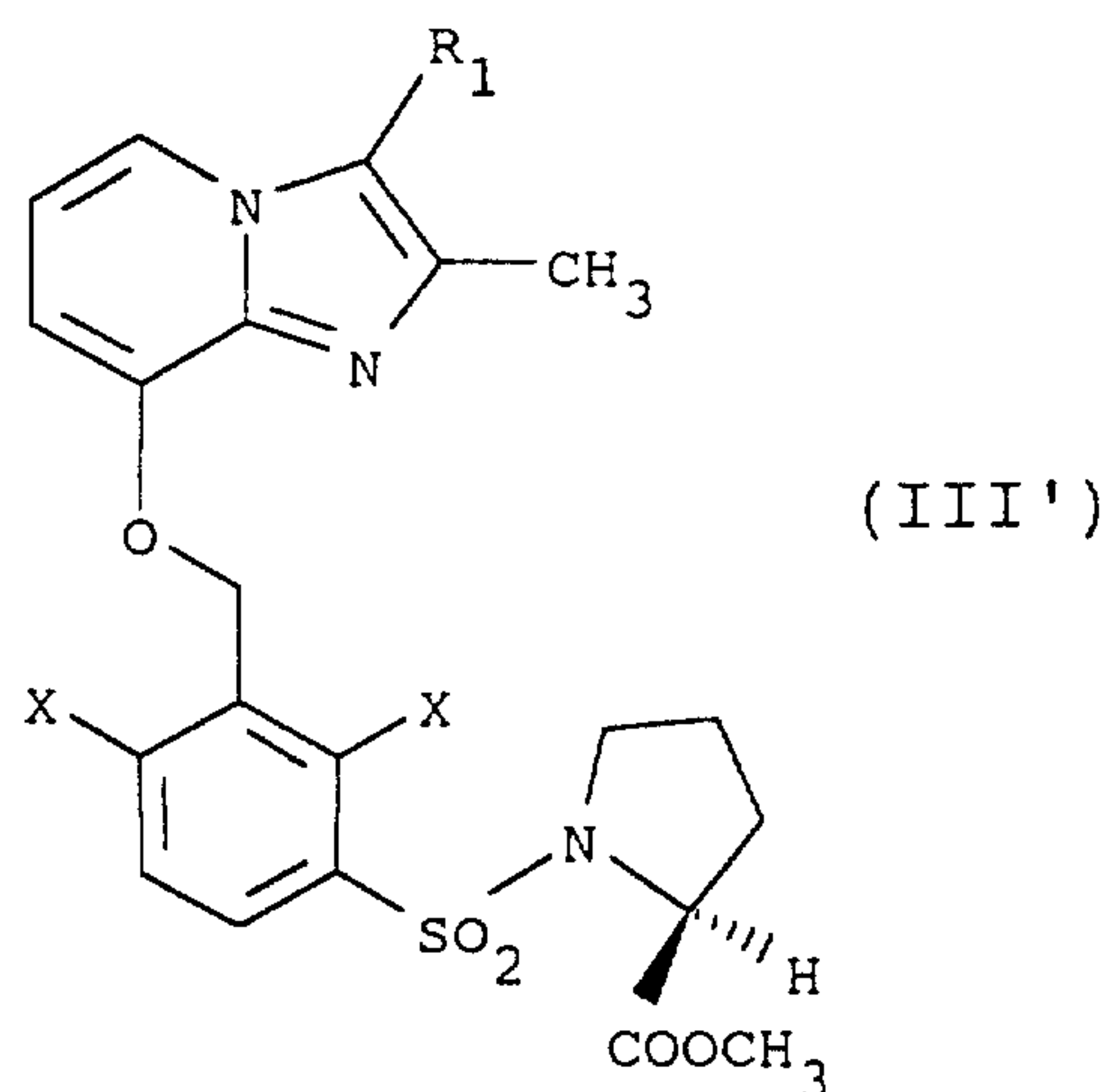


in which Q, X and R₁ are as defined above;

- (2) if necessary, if Q in the compound of formula III is the group Het 1 in which R₁ is a hydrogen atom:



reacting said compound of formula III with a halogenating agent in a solvent, at a temperature of between about 0 and 50°C, for 0.5 to 20 hours, to give a compound of formula III':

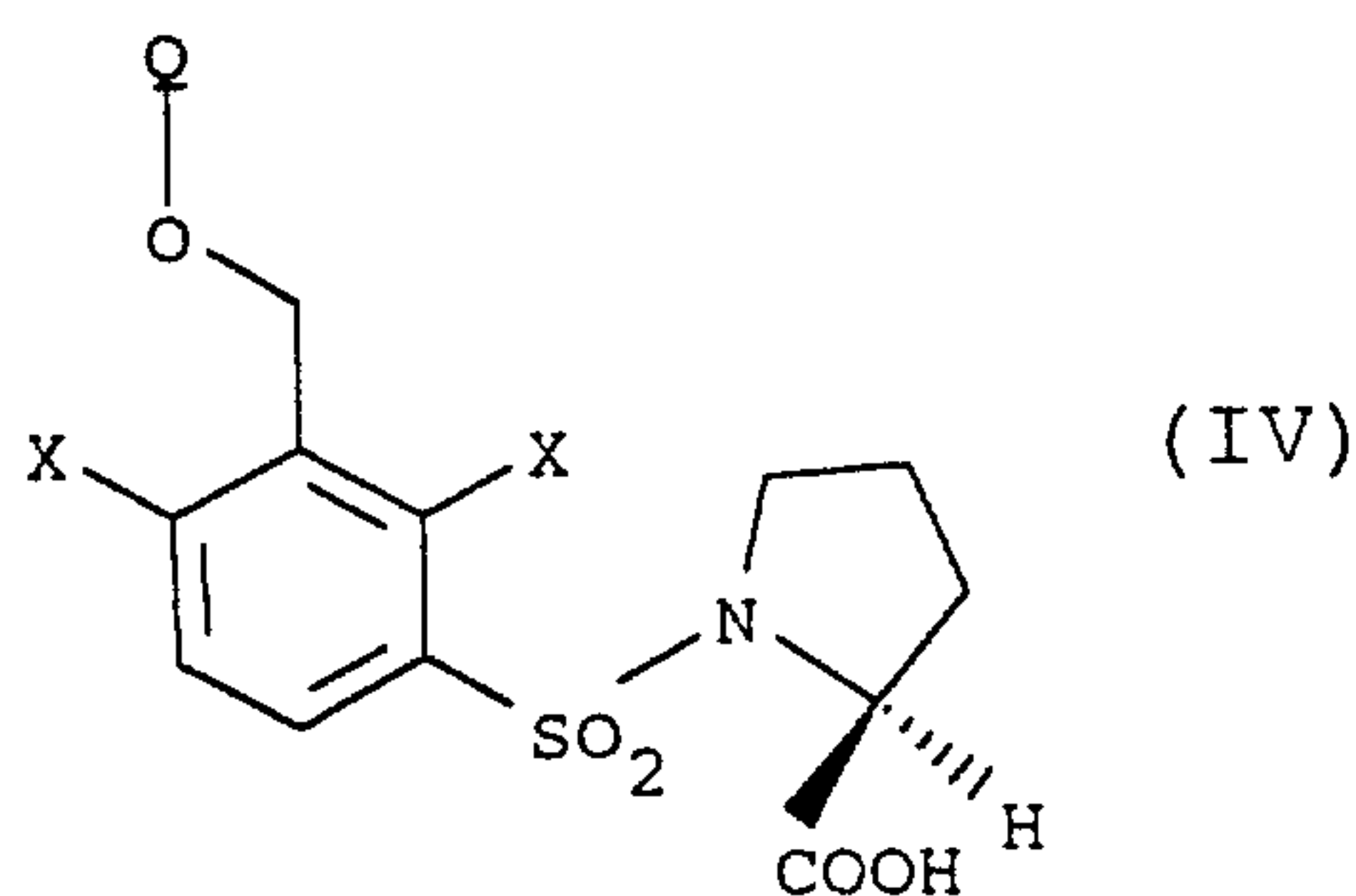


in which:

R₁ is a halogen atom, preferably Br or Cl;

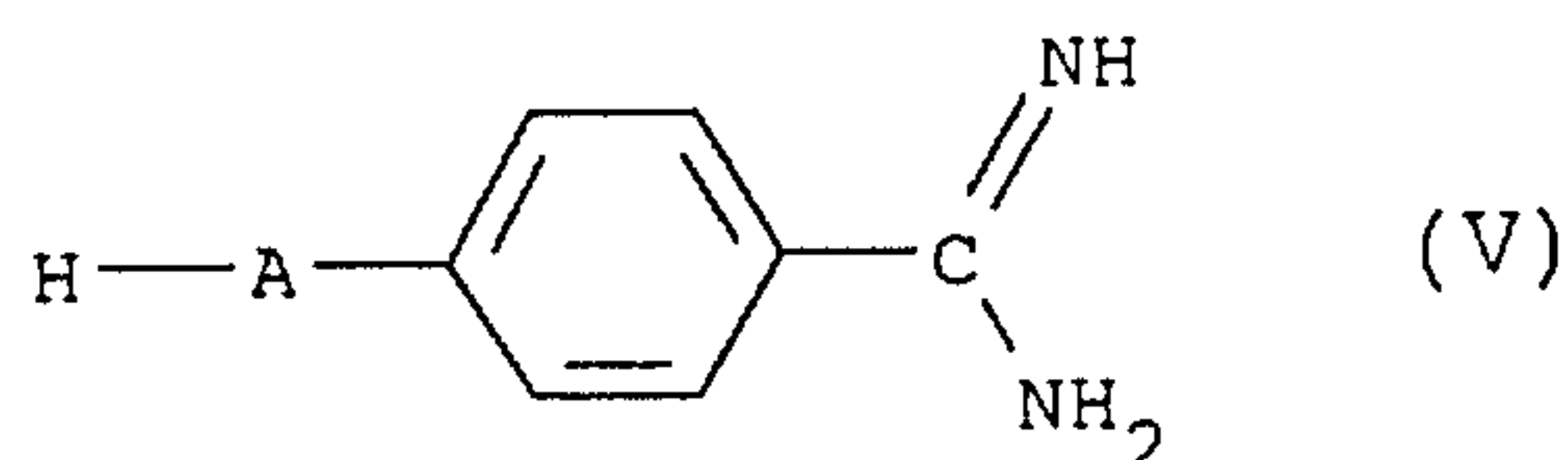
- (3) hydrolyzing the ester group of the compound of formula III or III' obtained according to one of steps (1) or (2) above, at a temperature of the order of 20 to 60°C, for 1 to 5 hours, to give a compound of formula IV:

51

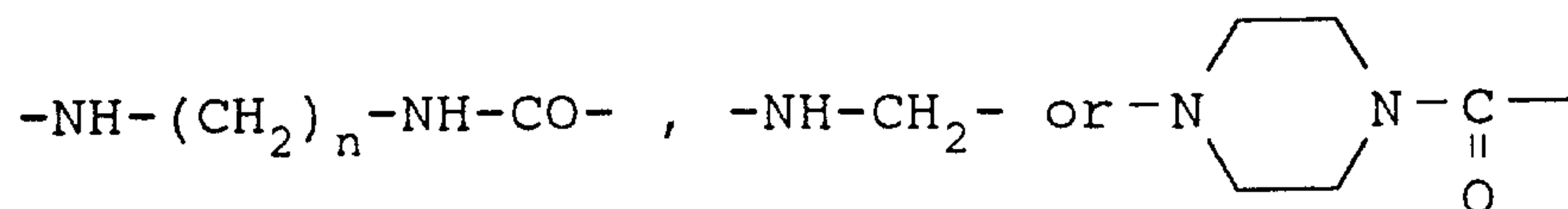


in which Q and X are as defined above and R_1 is a hydrogen atom, a halogen atom or a C_1 - C_3 alkyl group;

(4) reacting the resulting compound of formula IV with the salt of an amine of the
5 formula



in which A is a group

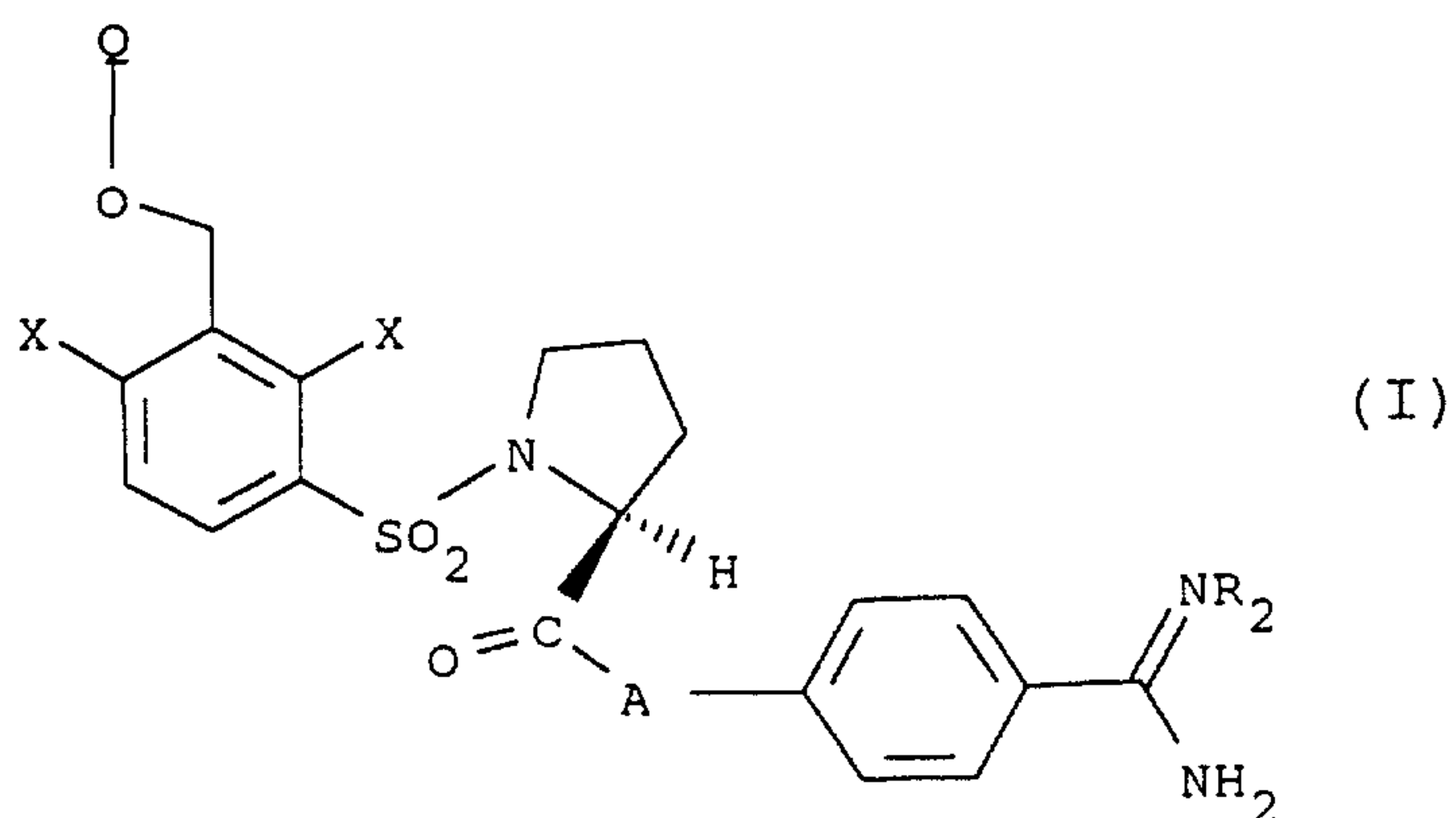


10

in which n is 2, 3 or 4,

in a solvent, in the presence of activators such as, in particular, 1-hydroxy-7-azabenzotriazole (HOAT) and 1-[3-(dimethylaminopropyl)-3-ethyl]carbodiimide (EDCI) hydrochloride, at a temperature close to room temperature ($10 - 35^\circ\text{C}$), for

15 2 to 50 hours, to give a compound of formula I in which R_2 is H:



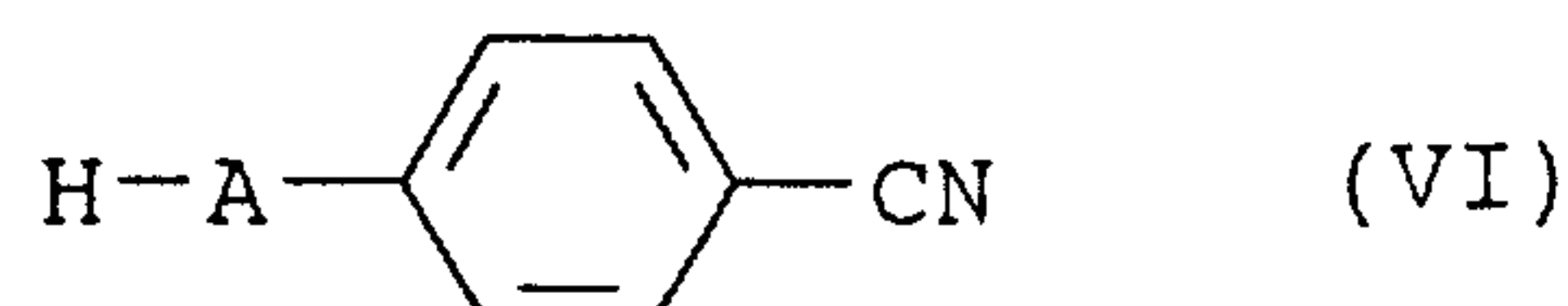
in which A, Q, X and R_1 are as defined above and R_2 is H; and

(5) if necessary, reacting the resulting compound of formula I with an acid to give

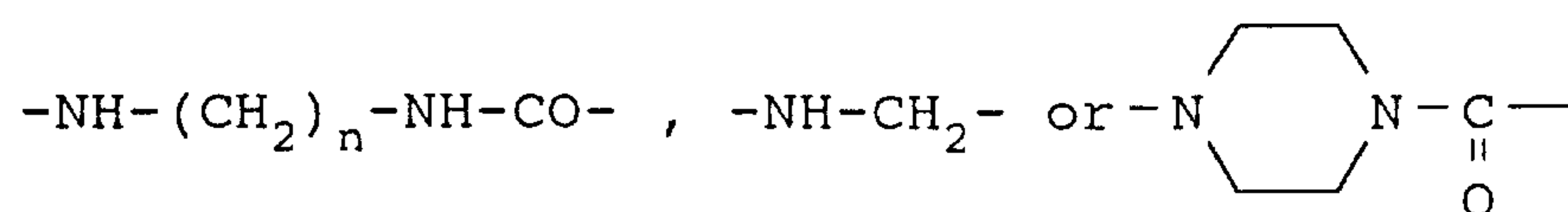
the corresponding acid addition salt;

according to a second variant B, the steps which consist in:

- (1) reacting the acid compound of formula IV, obtained for example in step (3) of variant A, in which R_1 is a hydrogen atom, a chlorine atom, a C_1 - C_3 alkyl group with a linear or branched hydrocarbon chain, or a C_1 - C_5 1-oxoalkyl group,
 5 with a compound of formula VI:

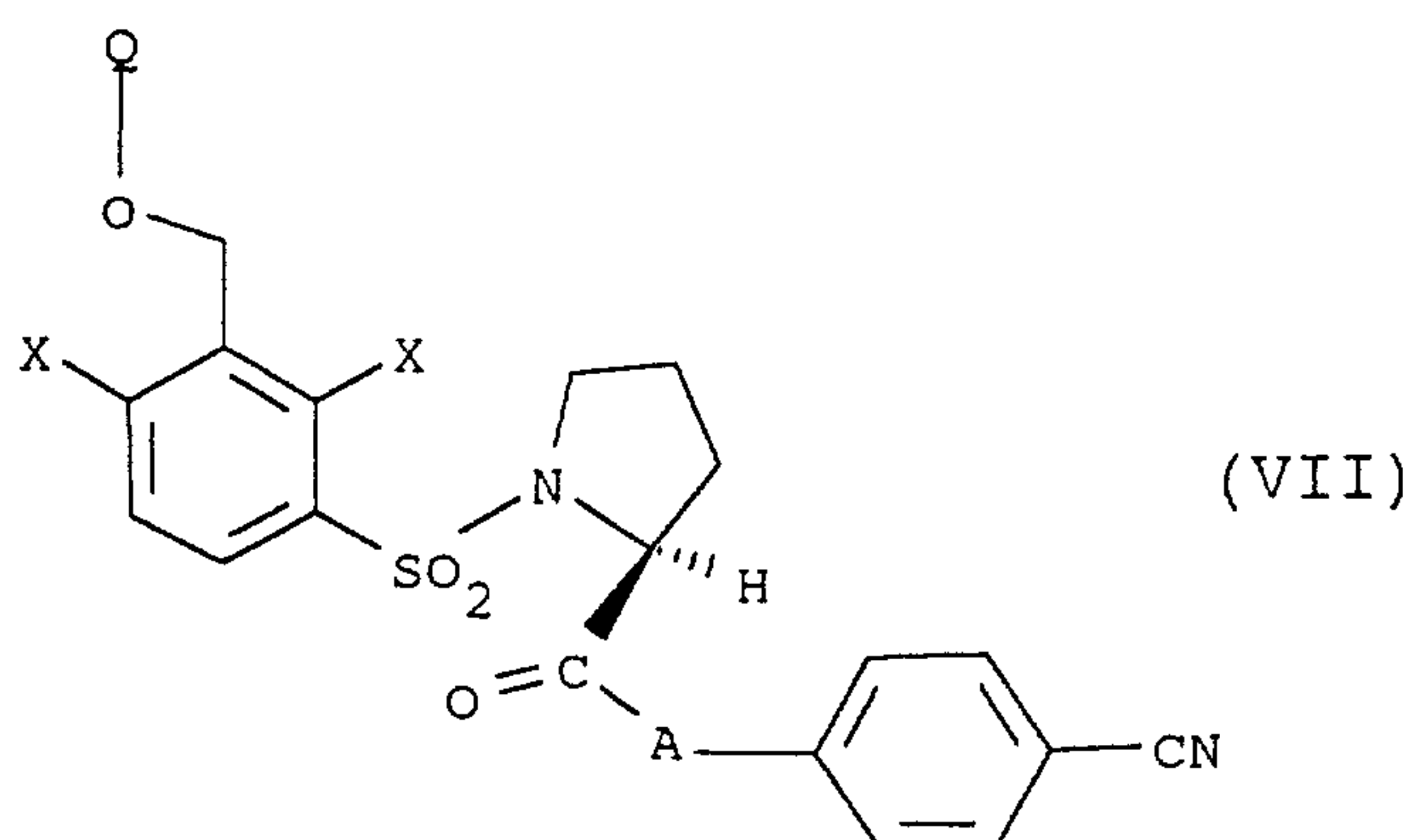


- 10 in which A is a group



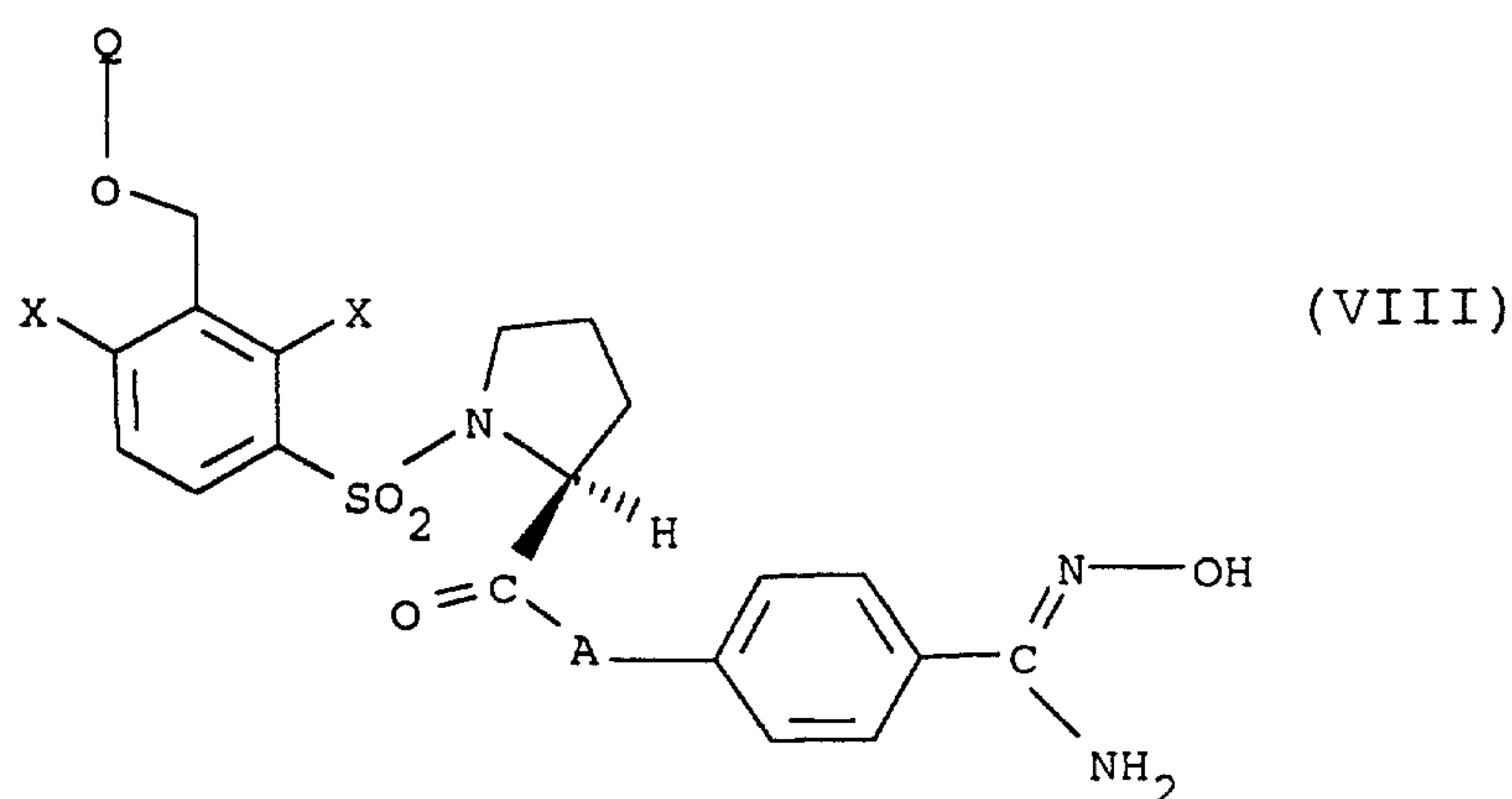
in which n is 2, 3 or 4,

- 15 under conditions analogous to those of step (4) of variant A above, to give a compound of formula VII:



- 20 in which Q, R_1 , X and A are as defined in the starting materials;

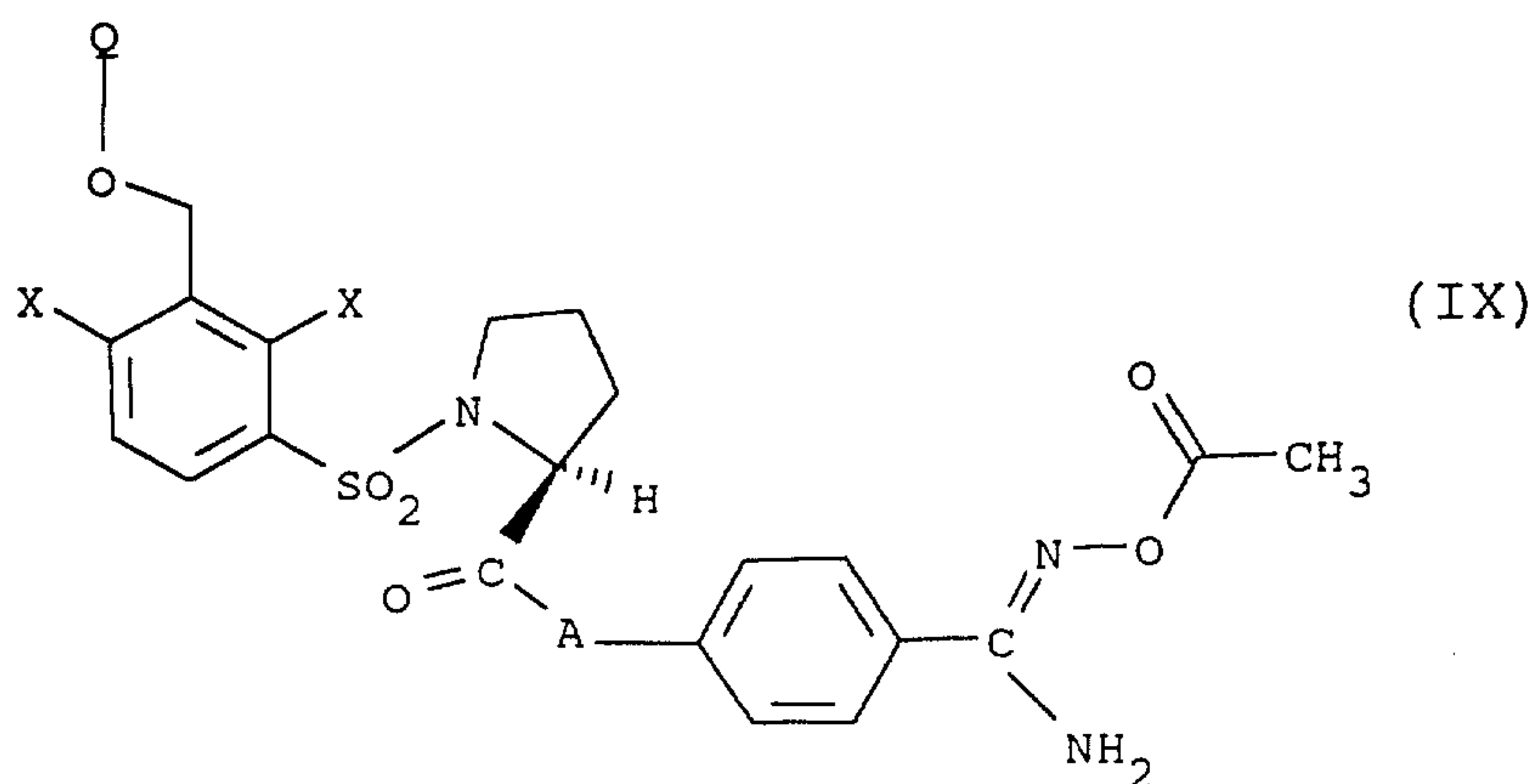
(2) reacting the resulting compound of formula VII with hydroxylamine in a solvent, at room temperature (15 - 25°C), for 1 to 12 hours, to give a compound of formula VIII:



in which Q, R₁, X and A are as defined above;

(3) acetylating the resulting compound of formula VIII, at a temperature close to room temperature, for 1 to 8 hours, to give the compound of formula IX:

5



in which Q, R₁, X and A are as defined above; and

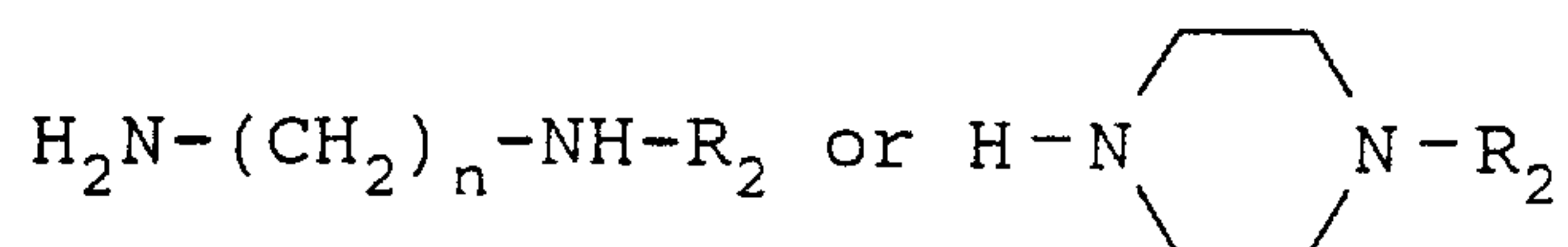
(4) reducing the resulting compound of formula IX by catalytic hydrogenation, at a temperature close to room temperature, under a hydrogen pressure of between 10⁵ and 10⁶ Pascals, to give the compound of formula I in which Q, R₁, X and A are as defined above and R₂ is H;

10

according to a third variant C, the steps which consist in:

(1) reacting the compound of formula V, obtained according to step (3) of variant A, with an amine of the formula

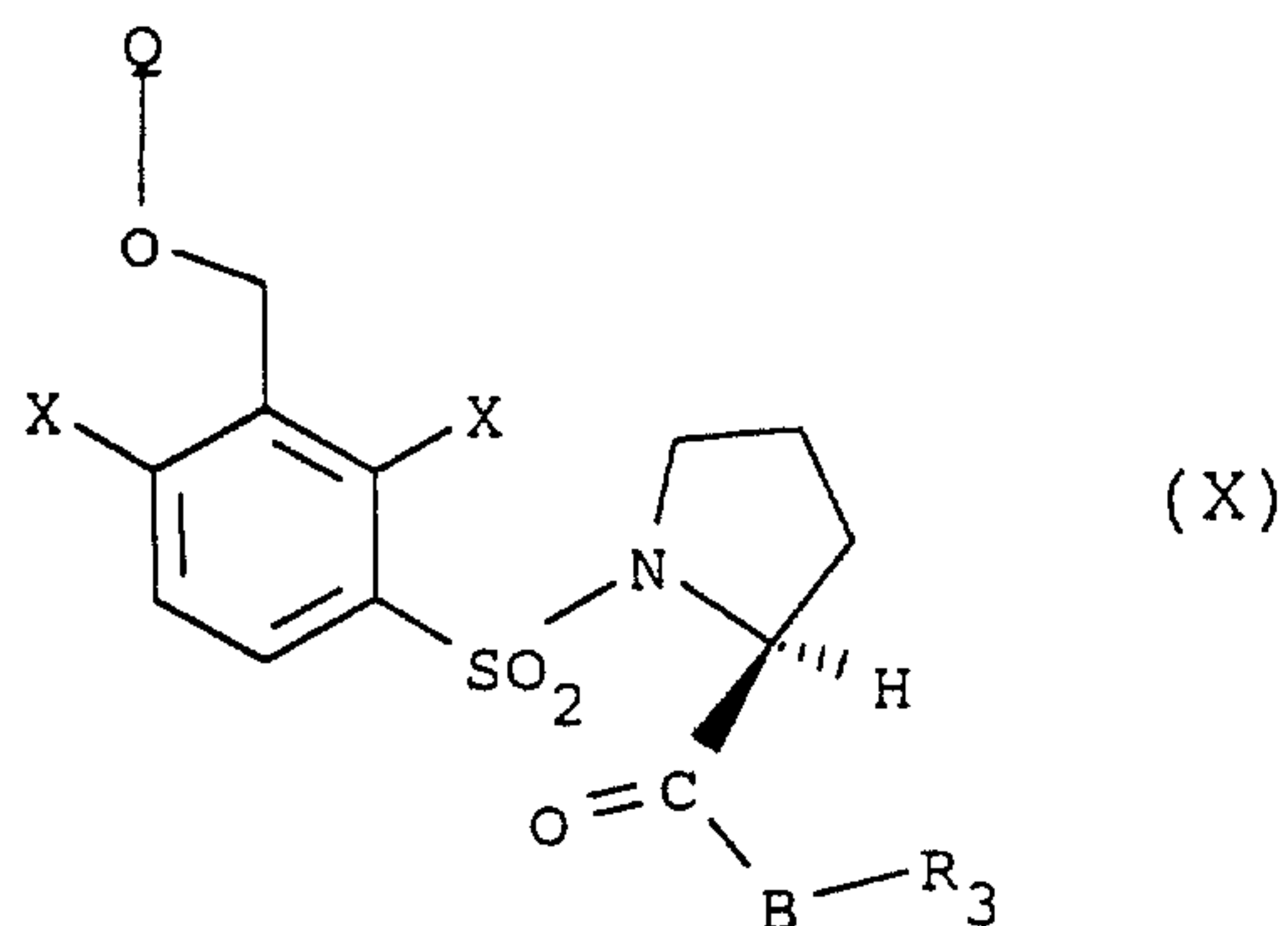
15



in which n is 2, 3 or 4 and R₂ is an amino-protecting group, especially the 1,1-dimethylethoxycarbonyl group,

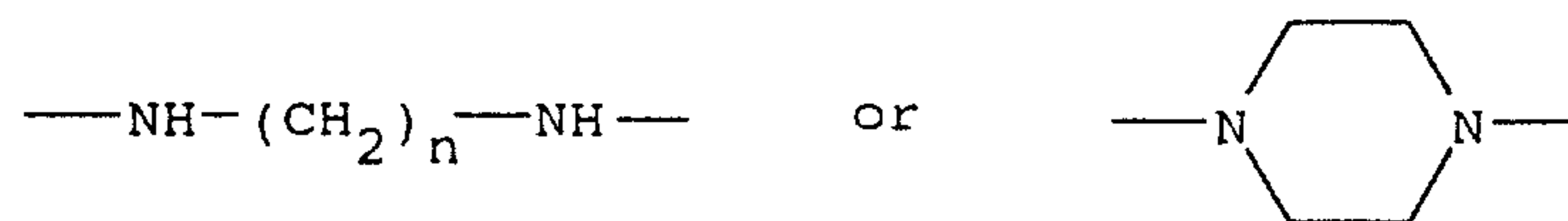
under operating conditions analogous to those of step (4) of variant A, to give a

compound of formula X:



in which B is

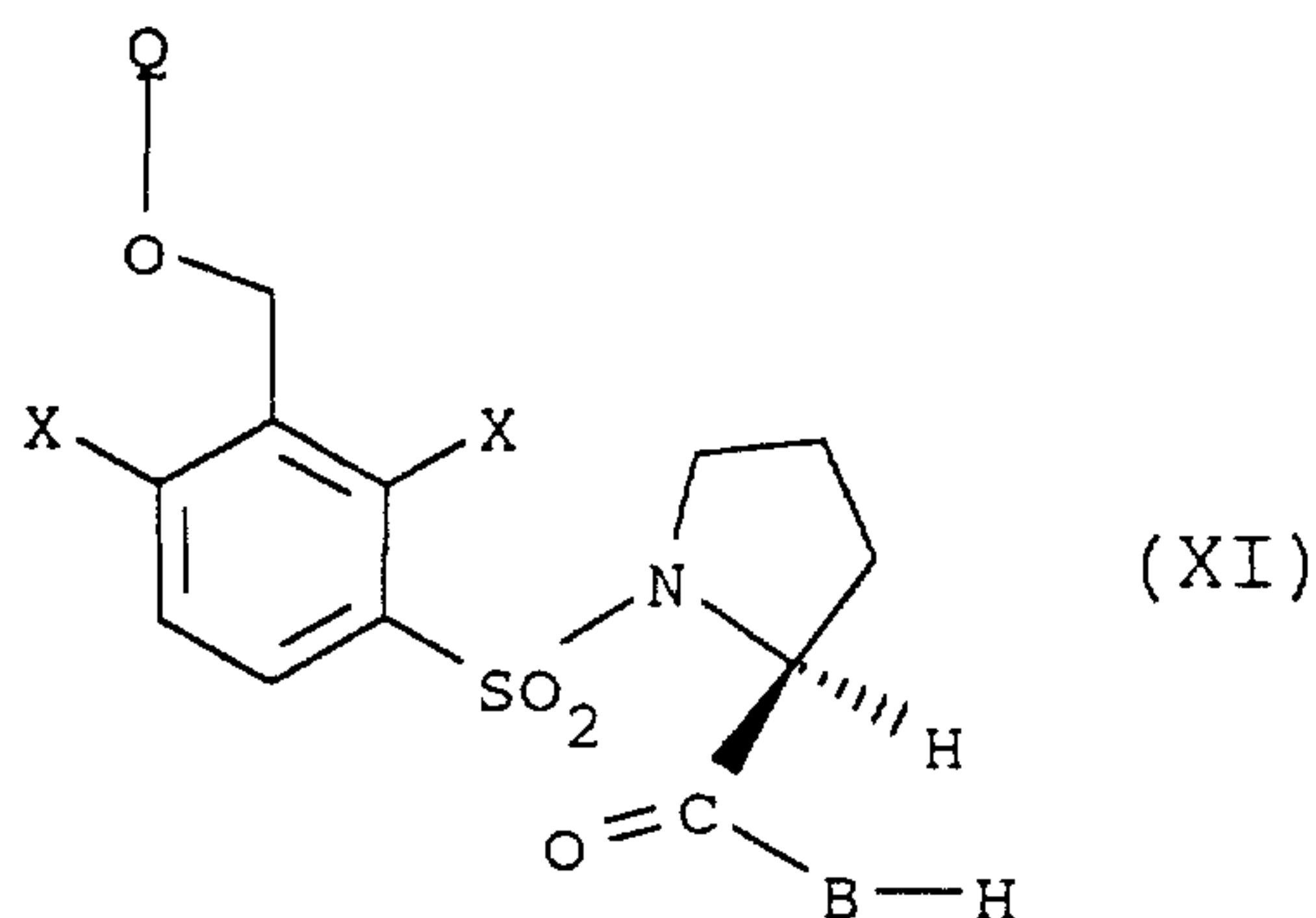
5



and Q, R₁ and X are as defined above;

(2) deprotecting the amine group of the resulting compound of formula X so as to replace the group R₂ with a hydrogen atom, to give the compound of formula XI:

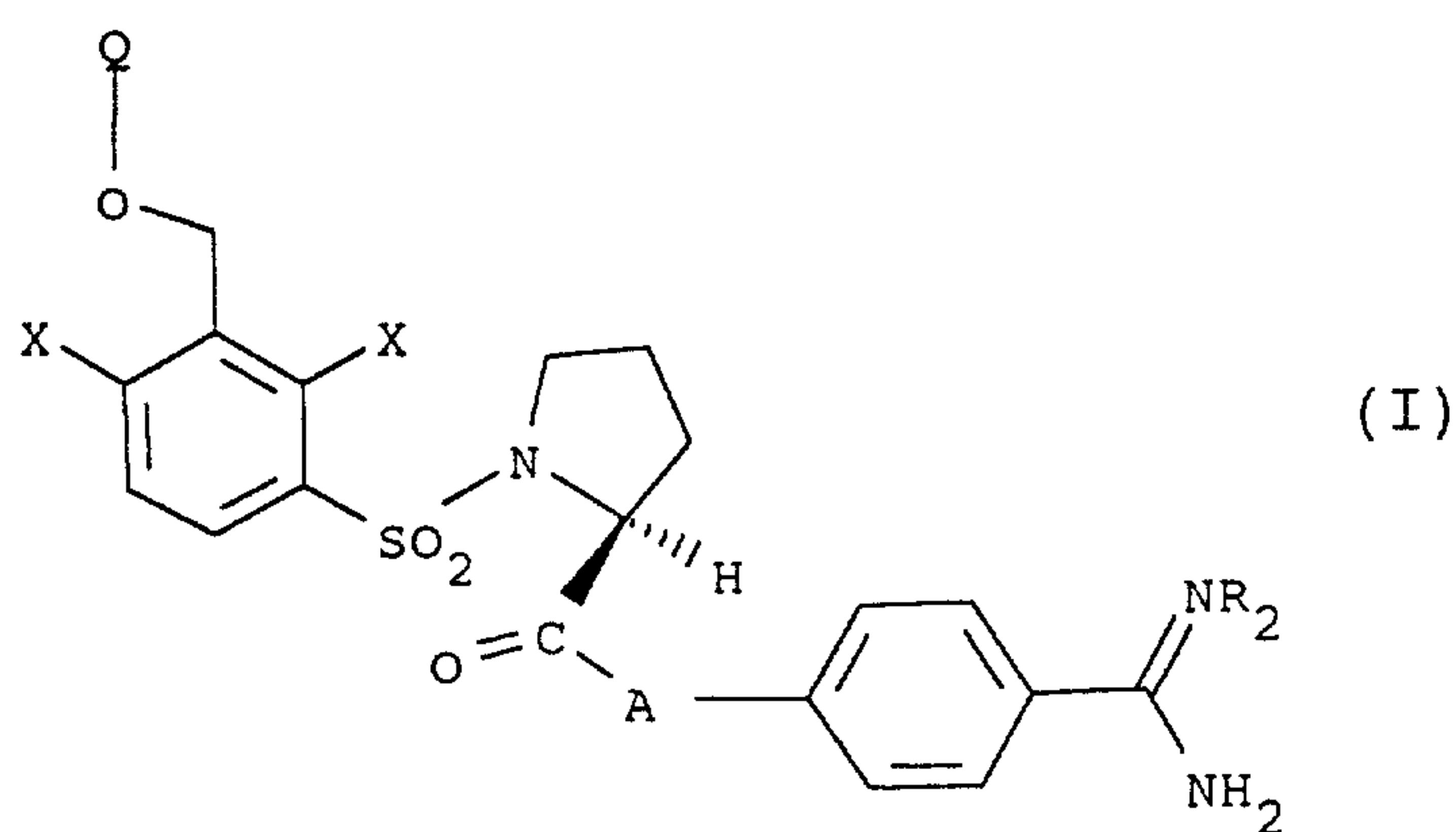
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in which B, Q, R₁ and X are as defined above; and

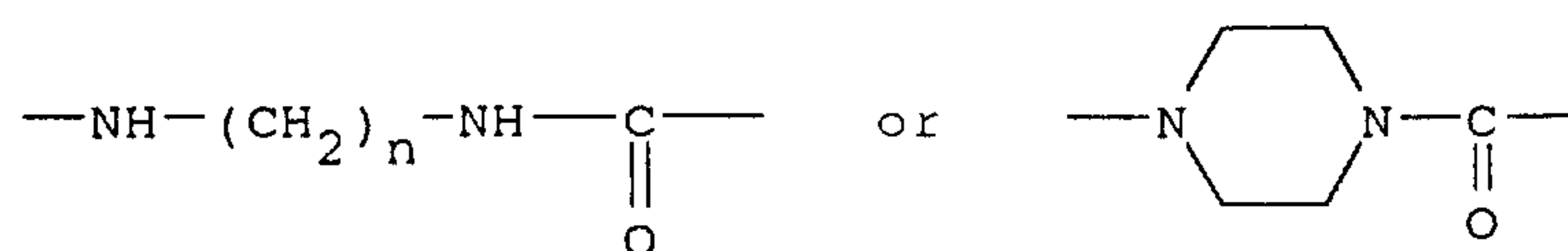
(3) reacting the resulting compound of formula XI with 4-(aminoiminomethyl)-benzoic acid, under conditions analogous to those of step (4) of variant A above, to give the compound of formula I in which R₂ is H:

15



in which:

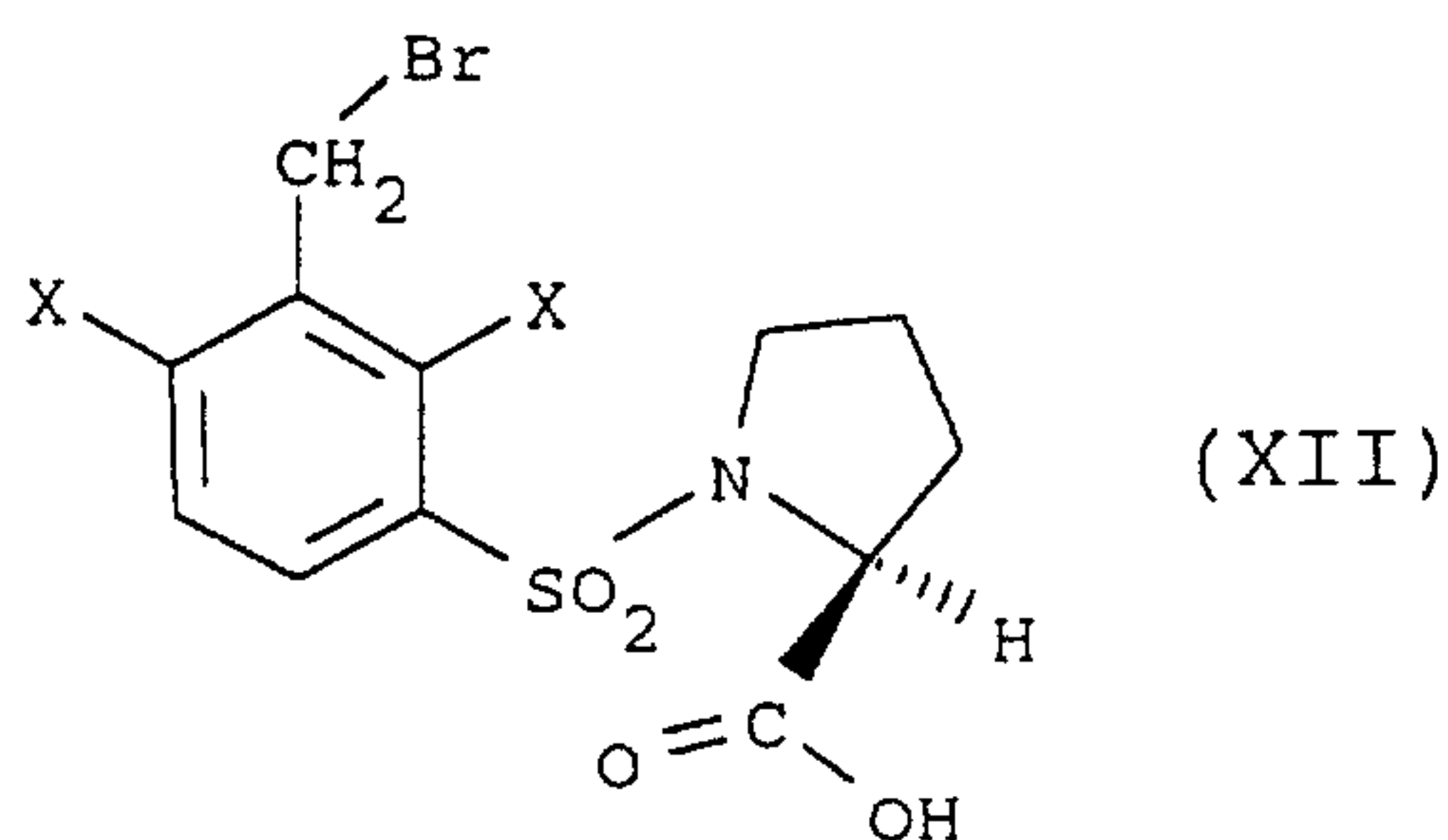
Q, R₁ and X are as defined above, R₂ is H and A is a group



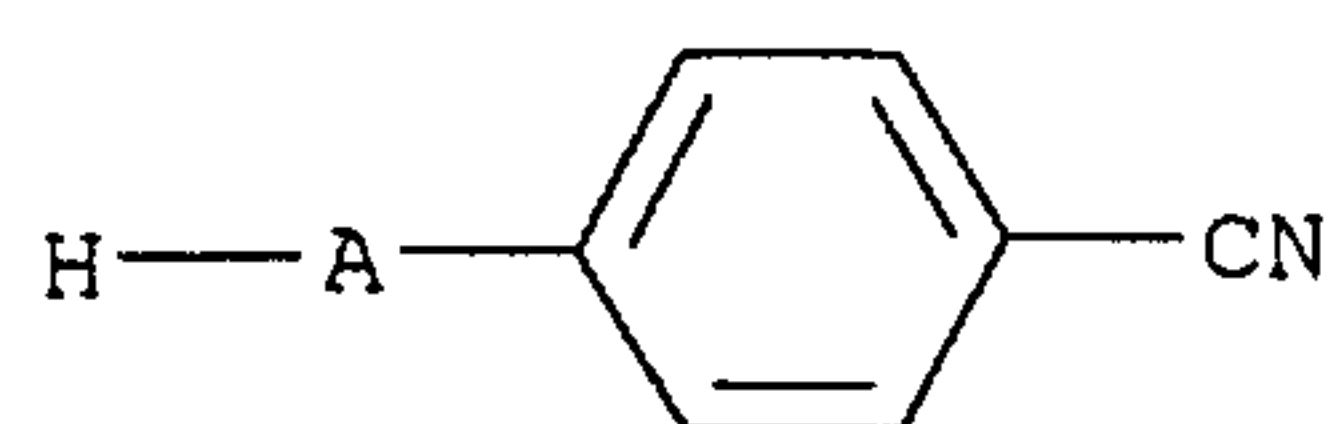
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and according to a fourth variant D, the steps which consist in:

(1) reacting the acid of the formula

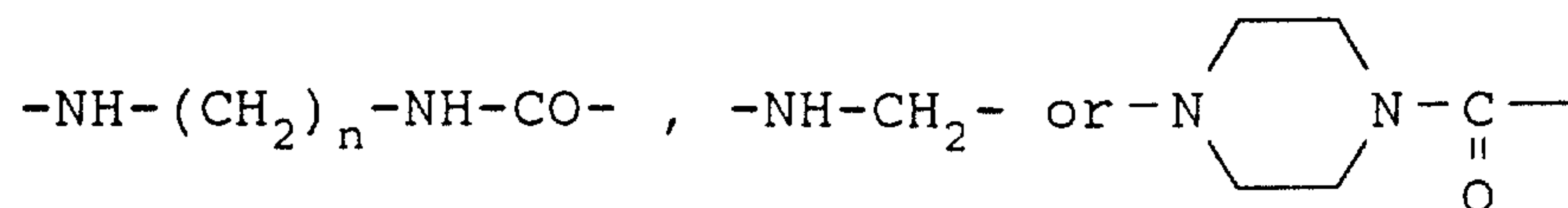


10 in which X is a halogen,
with a compound of the formula



in which A is a group

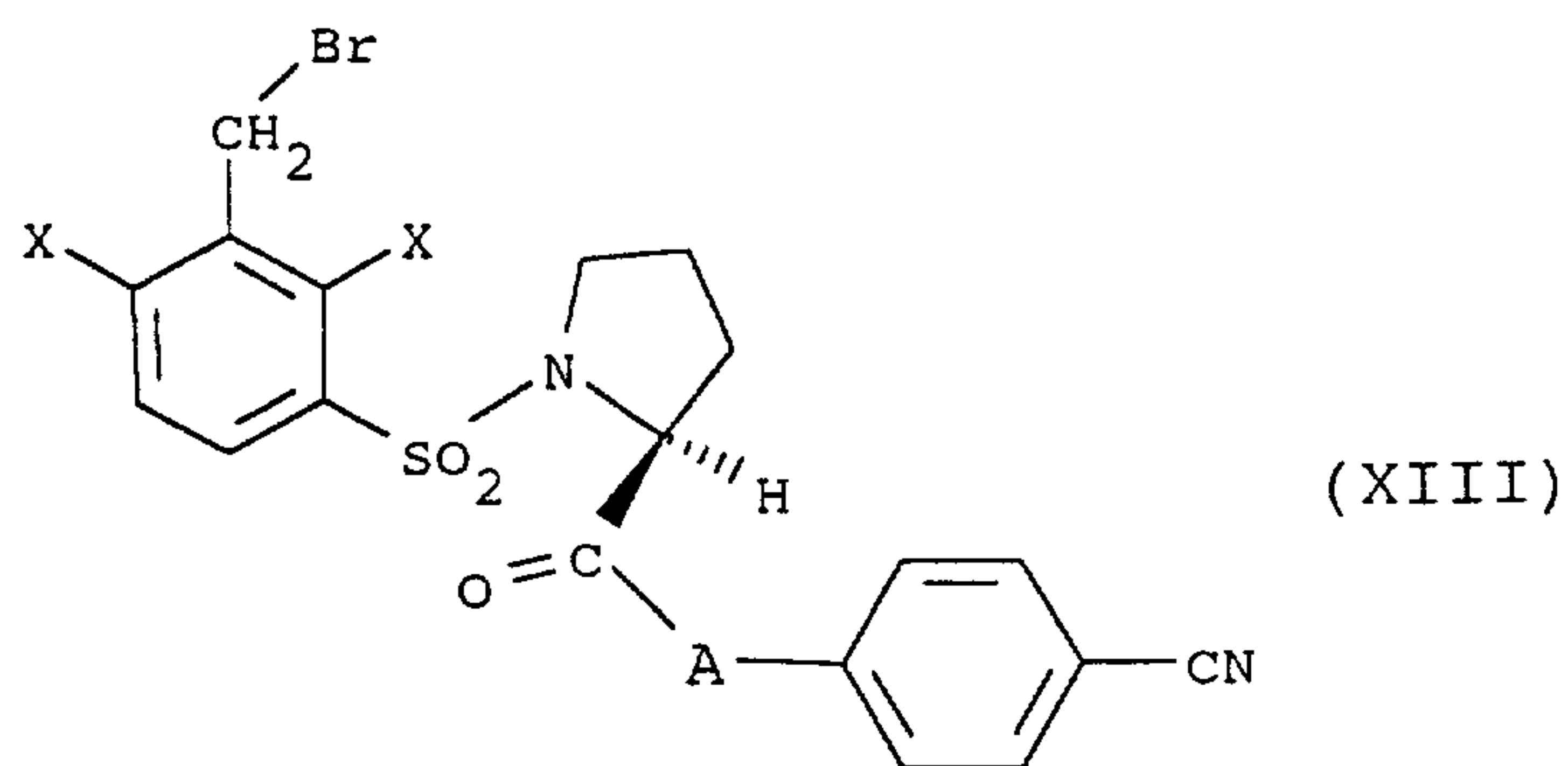
15



in which n is 2, 3 or 4,

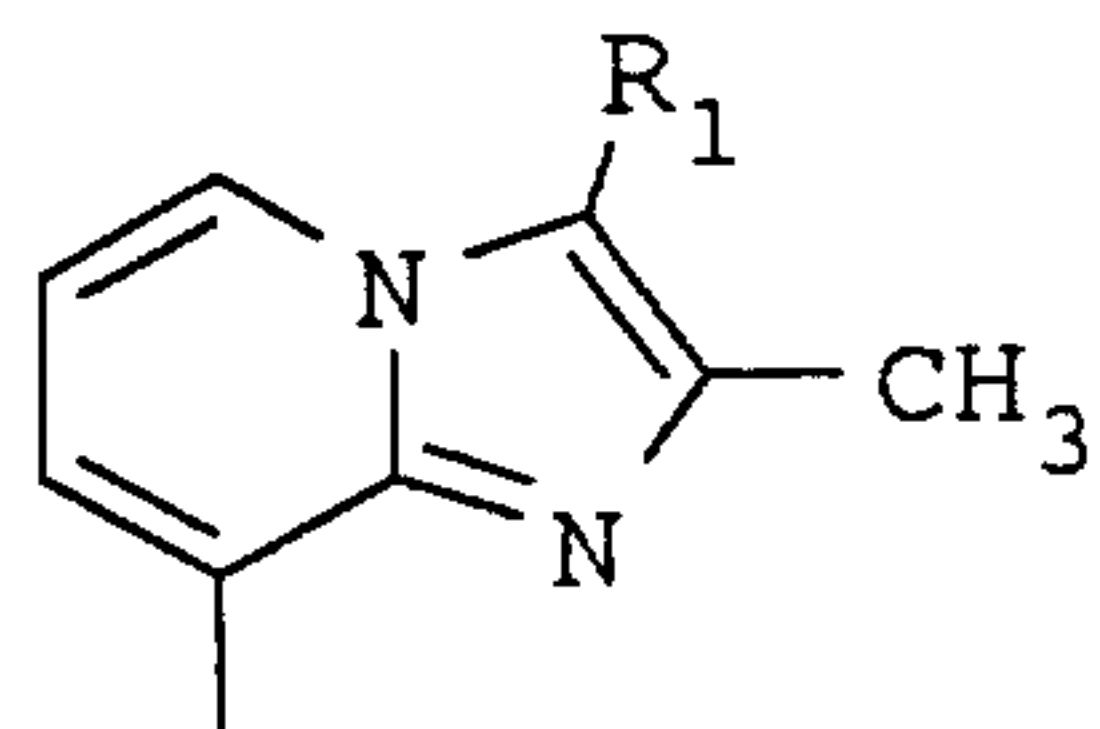
under conditions analogous to those of (4) of variant A above, to give the

compound of formula XIII:

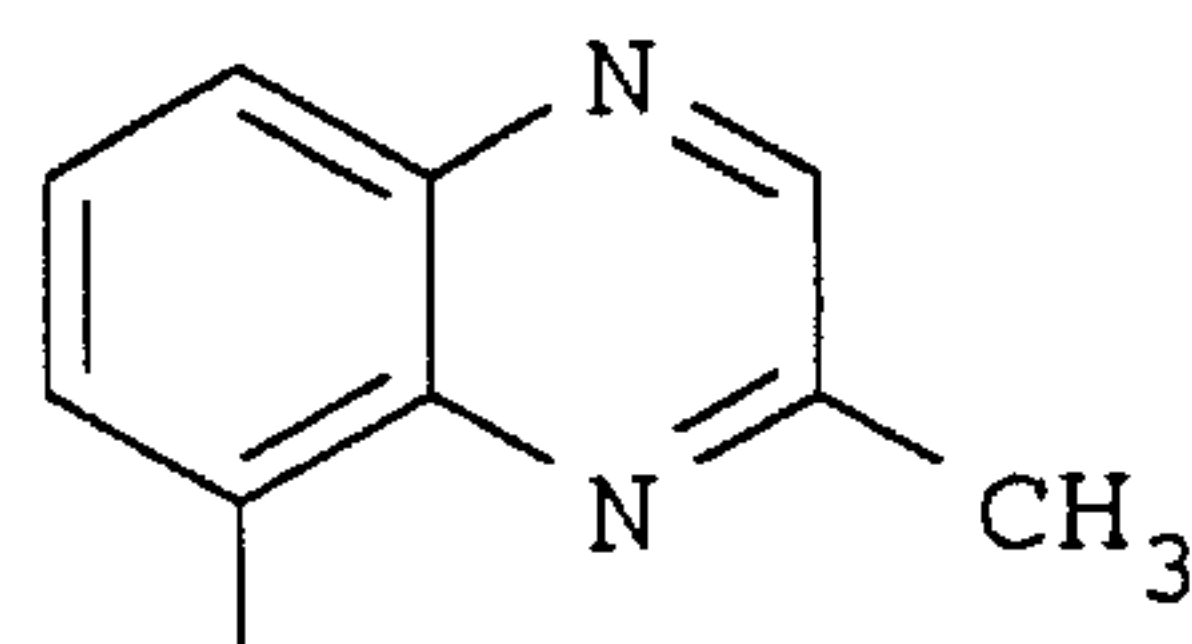


in which A and X are as defined above;

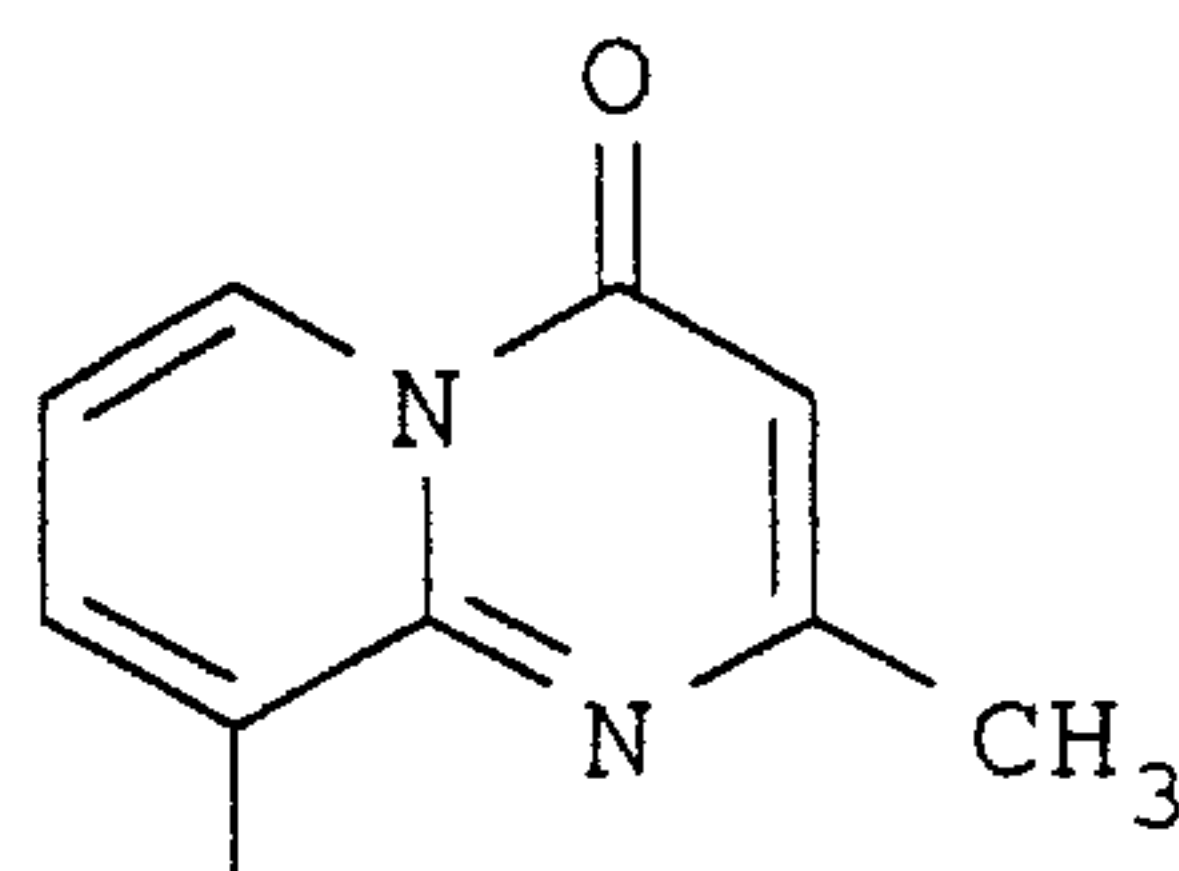
- 5 (2) reacting the resulting compound of formula XIII with a hydroxylated heterocyclic derivative of the general structure Q-OH, Q being selected from the structures



(Het 1)

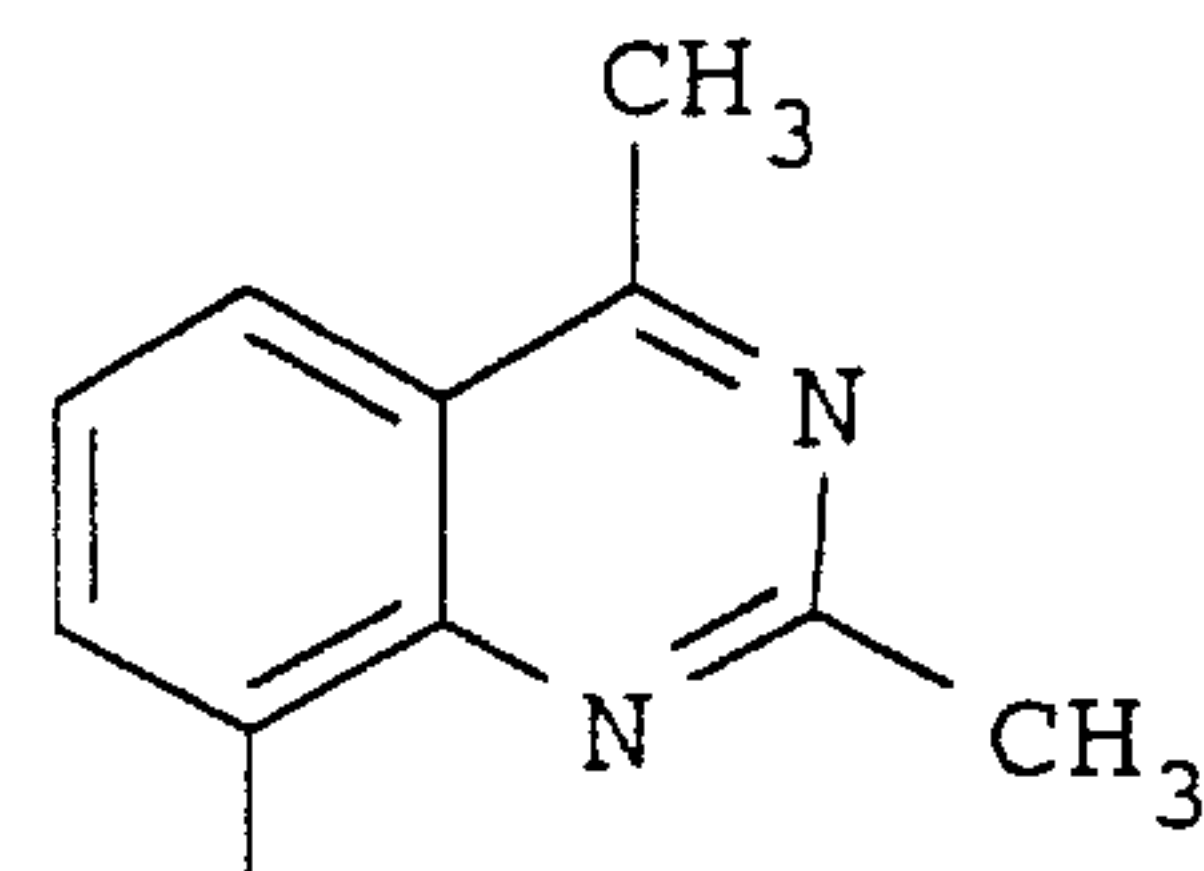


(Het 2)



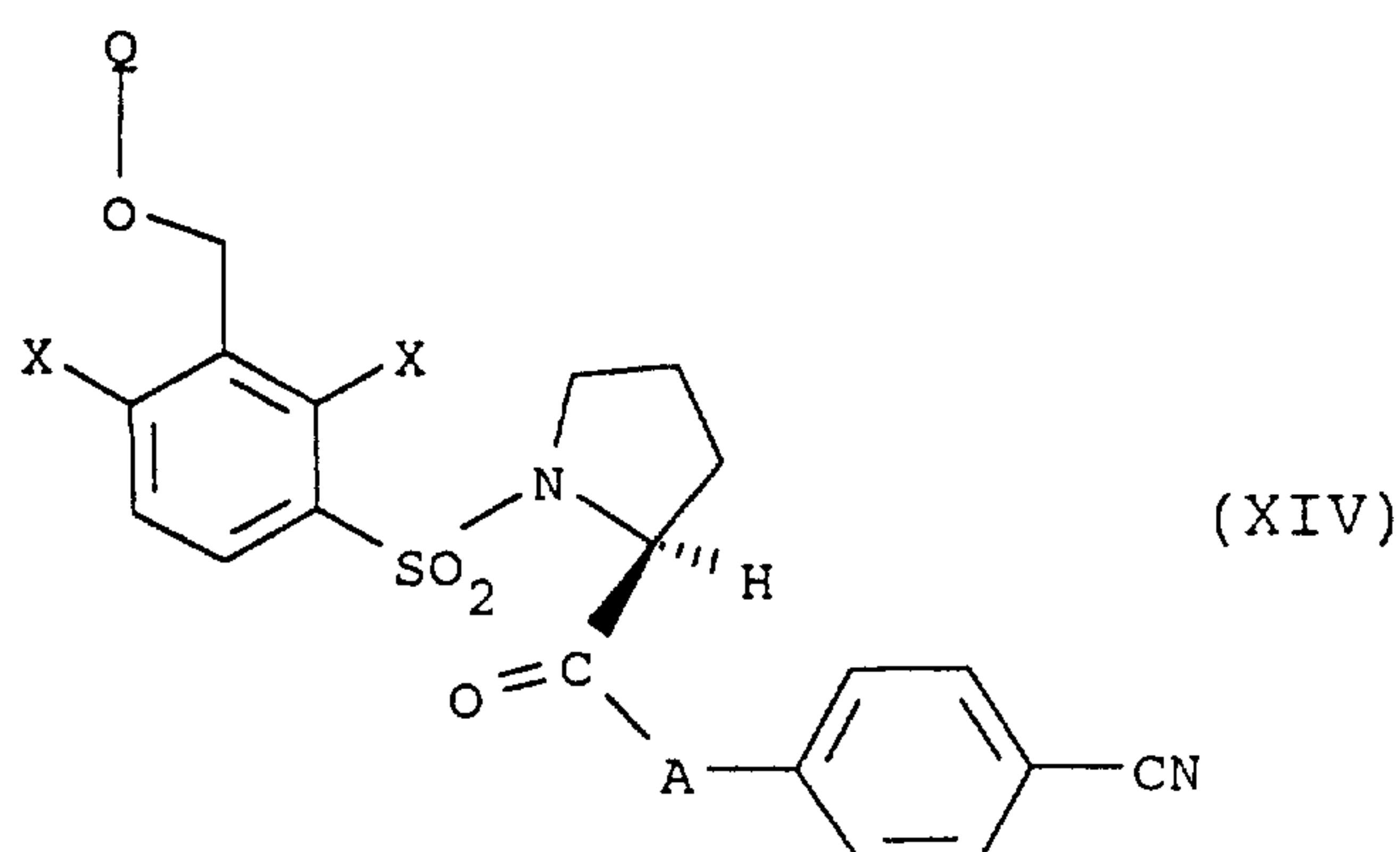
(Het 3)

and



(Het 4)

- 10 in which R₁ is a hydrogen atom, a halogen atom, a C₁-C₃ alkyl group or a C₁-C₅ 1-oxoalkyl group,
under conditions analogous to those of step (1) of variant A above, to give the compound of formula XIV:



in which Q, R₁, X and A are as defined in the starting materials; and

(3) then performing, on the resulting compound of formula XIV, a series of
 5 reactions analogous to those previously described in steps (2), (3) and (4) of variant B above, to give the compound of formula I in which Q, X, R₁ and A are as defined in the starting compounds.

4. Therapeutic composition which contains, in association with a physio-
 logically acceptable excipient, at least one compound selected from the group
 10 consisting of the compounds of formula I and their non-toxic addition salts according to claim 1.

5. Use of an antagonist of a receptor of bradykinin and analogous hormones,
 wherein a bradykinin B₂ receptor antagonist selected from the group consisting of
 the compounds of formula I and their non-toxic addition salts according to claim 1
 15 is used to obtain a drug intended for use in therapeutics to combat pathological conditions involving bradykinin or its homologs.

6. Use according to claim 5 of a substance selected from the group consisting
 of the compounds of formula I and their non-toxic addition salts according to claim
 1 for obtaining a drug intended for use in therapeutics for the treatment of painful
 20 states.

7. Use according to claim 5 of a substance selected from the group consisting
 of the compounds of formula I and their non-toxic addition salts according to claim
 1 for obtaining a drug intended for use in therapeutics for the treatment of
 inflammatory states.

25 8. Use of a compound of formula I or one of its addition salts according to claim 1 as a pharmacological reagent.