



AU9514573

(12) PATENT ABRIDGMENT (11) Document No. AU-B-14573/95
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 687152

(54) Title
NOVEL OPTIONALLY SUBSTITUTED PHENYLIMIDAZOLIDINES, INTERMEDIATES AND PROCESS FOR THEIR PREPARATION, THEIR USE AS DRUGS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

International Patent Classification(s)
(51)⁶ **C07D 233/78 C07D 235/02 A61K 031/415**

(21) Application No. : **14573/95** (22) Application Date : **04.01.95**

(87) PCT Publication Number : **WO95/18794**

(30) Priority Data

(31) Number	(32) Date	(33) Country
94 00042	05.01.94	FR FRANCE
94 10660	06.09.94	FR FRANCE

(43) Publication Date : **01.08.95**

(44) Publication Date of Accepted Application : **19.02.98**

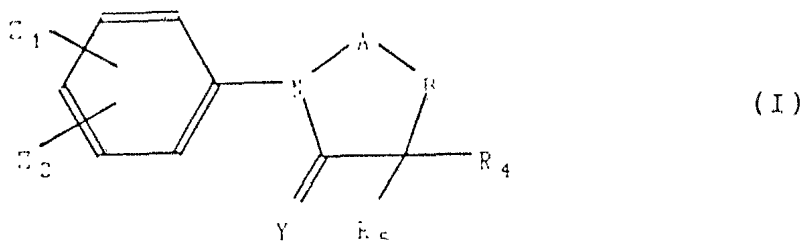
(71) Applicant(s)
ROUSSEL UCLAF

(72) Inventor(s)
ANDRE CLAUSSNER; FRANCOIS GOUBET; JEAN-GEORGES TEUTSCH

(74) Attorney or Agent
CALLINAN LAWRIE , Private Bag 7, KEW VIC 3101

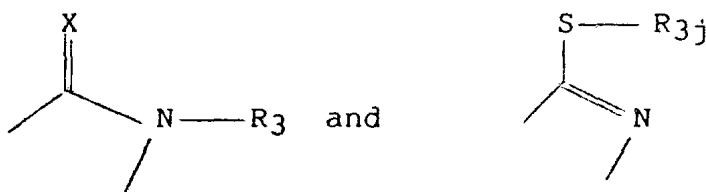
(57) Claim

1) The products of general formula (I):



in which:

Z_1 and Z_2 , identical or different, represent a cyano, nitro radical, a halogen atom, a trifluoromethyl radical or an esterified, amidified or salified free carboxy radical, the group $-A-B-$ is chosen from the radicals



in which X represents an oxygen or sulphur atom, R_3 represents R_3 with the exception of the hydrogen value and R_3 is chosen from the following radicals:

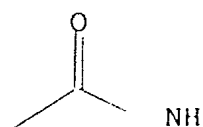
- a hydrogen atom,
- alkyl, alkenyl, alkynyl, aryl or arylalkyl radicals having at most 12 carbon atoms, these radicals being optionally substituted by one or more substituents chosen from halogen atoms and the following radicals: optionally esterified, etherified or protected hydroxy, alkoxy, hydroxyalkyl, alkenyloxy, alkynyloxy, trifluoromethyl, mercapto, cyano, acyl, acyloxy, aryl, optionally substituted S-alkyl, S-aryl, in which the sulphur atom is optionally oxidized in the form of the sulfoxide or sulphone, free, esterified, amidified or salified carboxy, amino, mono- or dialkylamino, a cyclic radical containing 3 to 6 members and optionally containing one or more heteroatoms chosen from sulphur, oxygen or nitrogen atoms and the $-O-\overset{\overset{O}{\parallel}}{C}-R_7$ radical in which R_7 represents

an alkyl, hydroxy, alkoxy, aryl or aryloxy radical, the alkyl, alkenyl or alkynyl radicals moreover being optionally interrupted by one or more atoms of oxygen, nitrogen or sulphur optionally oxidized in the form of the sulfoxide or sulphone, the nitrogen atoms being optionally oxidized,

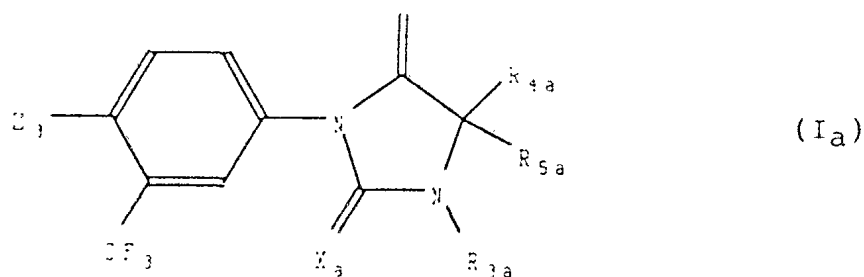
the aryl and aralkyl radicals moreover being optionally substituted by an alkyl, alkenyl or alkynyl, alkoxy, alkenyloxy, alkynyloxy or trifluoromethyl radical, Y represents an oxygen or sulphur atom or an NH radical, R_4 and R_5 , identical or different, represent a hydrogen atom or an alkyl radical having 1 to 12 carbon atoms optionally substituted by one or more substituents chosen from halogen atoms, the $-O-\overset{\overset{O}{\parallel}}{C}-R_7$ radical as defined above, the optionally

esterified, etherified or protected hydroxyl radical, linear or branched phenylthio and alkylthio radicals containing at most 8 carbon atoms, phenylthio and alkylthio radicals, in which the sulphur atom can be oxidized in the form of the sulfoxide or sulphone, themselves being optionally substituted by one or more radicals chosen from halogen

atoms, the optionally esterified, etherified or protected hydroxyl radical, the free, esterified, amidified or salified carboxy radical, amino, mono- or dialkylamino radicals, with the exception of the products in which R_4 and R_5 , identical or different, represent a hydrogen atom or an alkyl radical having 1 to 12 carbon atoms non-substituted or substituted by one or more halogen atoms, those in which one of R_4 or R_5 represents a methyl radical and the other represents a hydroxymethyl radical, Y represents an oxygen atom or an NH radical, the group $-AB-$ represents the radical



Z_1 in position 4 represents a nitro radical and Z_2 in position 3 represents a trifluoromethyl radical, those in which Z_1 and Z_2 both represent a halogen atom and those in which one of Z_1 and Z_2 represents a halogen atom, one of R_4 and R_5 represents an alkyl radical substituted by the group $-S-CH_3$ and R_3 represents a hydrogen atom or an alkyl radical, b) the products of formula (I_a):



in which Z_3 represents a cyano or nitro radical, R_{3a} represents a hydrogen atom or a linear or branched alkyl radical, containing at most 4 carbon atoms, optionally substituted by a fluorine atom, a cyano radical, R_{4a} and R_{5a} are such that one represents a methyl radical and the other represents a methyl radical substituted by a fluorine atom or R_{4a} and R_{5a} are identical and represent a methyl radical substituted by a fluorine atom, or R_{4a} and R_{5a}

form with the carbon atom to which they are linked a cyclopentyl radical,

X_a represents a sulphur or oxygen atom, with the exception of the product in which Z₃ represents a cyano radical, X_a represents a sulphur atom, R_{3a} represents a methyl radical and R_{4a} and R_{5a} form with the carbon atom to which they are linked a cyclopentyl radical,

and c) the following products:

- 4-(4,4-dimethyl 2,5-dioxo 3-(2-fluoroethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl 2,5-dioxo 3-(2,2,2-trifluoroethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl 3-(2-fluoroethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl 2,5-dioxo 3-(2-(2-hydroxyethoxy) ethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,

the said products of formula (I), (I_a) and the products mentioned being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products.

19. A method for the treatment of benign or malignant tumours possessing androgen receptors in the breast, skin, ovaries, bladder, lymphatic system, kidney or liver in a patient requiring said treatment, which method comprises administering to said patient an effective amount of the products of formula (I) according to any one of claims 1 to 6, 13 or 16 or of a pharmaceutical composition according to any one of claims 8, 10 or 17.



DEMANDA

f)

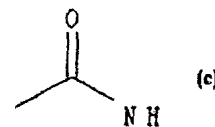
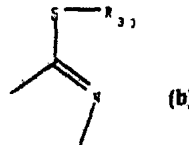
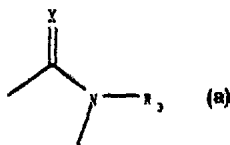
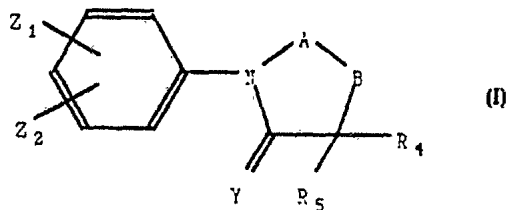
(51) Classification internationale des brevets : C07D 233/78, 235/02, A61K 31/415		A1	(11) Numéro de publication internationale: WO 95/18794
			(43) Date de publication internationale: 13 juillet 1995 (13.07.95)
(21) Numéro de la demande internationale: PCT/FR95/00004		(81) Etats désignés: AU, BR, CA, CN, FI, HU, JP, KR, RU, UA, US, brevet européen (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) Date de dépôt international: 4 janvier 1995 (04.01.95)		Publiée Avec rapport de recherche internationale.	
(30) Données relatives à la priorité: 94/00042 5 janvier 1994 (05.01.94) FR 94/10660 6 septembre 1994 (06.09.94) FR			
(71) Déposant (pour tous les Etats désignés sauf US): ROUSSEL UCLAF [FR/FR]; ~~95, boulevard des Invalides, F-75007 Paris (FR)~~ <i>102 Route De Noisy F-93230 Romainville France</i>		687152	
(72) Inventeurs; et			
(75) Inventeurs/Déposants (US seulement): CLAUSNER, André [FR/FR]; 62, rue Marc-Viéville, F-93250 Villemomble (FR). GOUBET, François [FR/FR]; 54, rue des Volontaires, F-75015 Paris (FR). TEUTSCH, Jean-Georges [FR/FR]; Bâtiment 3, Résidence Lavoisier, 3, rue Lavoisier, F-93500 Pantin (FR).			
(74) Mandataire: VIEILLEFOSSE, Jean-Claude; Roussel Uclaf, 111, route de Noisy, F-93235 Romainville Cédex (FR).			

(54) Title: NOVEL OPTIONALLY SUBSTITUTED PHENYLIMIDAZOLIDINES, INTERMEDIATES AND PROCESS FOR THEIR PREPARATION, THEIR USE AS DRUGS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(54) Titre: NOUVELLES PHENYLIMIDAZOLIDINES EVENTUELLEMENT SUBSTITUEES, LEUR PROCEDE ET DES INTERMEDIAIRES DE PREPARATION, LEUR APPLICATION COMME MEDICAMENTS ET LES COMPOSITIONS PHARMACEUTIQUES LES RENFERMANT

(57) Abstract

Products of general formula (I); wherein Z_1 and Z_2 , which are the same or different, are cyano, nitro, halogen, trifluoromethyl or free, esterified or salified carboxy; the group -A-B- is selected from radicals (a) and (b) wherein X is oxygen or sulphur, R_{3j} is R_3 except for the hydrogen value, R_3 is selected from the following radicals: hydrogen, optionally substituted alkyl, alkenyl, alkynyl, aryl or aryl-alkyl; Y is oxygen or sulphur or NH, R_4 and R_5 , which are the same or different, are chiefly hydroxyl-substituted alkyl, except for products wherein R_4 and R_5 , which are the same or different, are hydrogen or a (C_1-C_{12}) alkyl radical optionally substituted by one or more halogen atoms or R_4 and R_5 are a (C_1-C_7) cycloalkyl radical or one of R_4 or R_5 is methyl, the other being hydroxymethyl, Y is oxygen or NH, -A-B- is (c), Z_1 is a 4-nitro radical and Z_2 a 3- CF_3 radical.



(57) Abrégé

L'invention a notamment pour objet les produits de formule générale (I), dans laquelle: Z_1 et Z_2 identiques ou différents représentent cyano, nitro, halogène, trifluorométhyle ou carboxy libre estérifié ou salifié, le groupement -A-B est choisi parmi les radicaux (a) et (b) dans lesquels X représente oxygène ou soufre, R_3 représente R_3 à l'exception de la valeur hydrogène, R_3 est choisi parmi les radicaux suivants: hydrogène; alkyle, alcényle, alkynyle, aryle ou aryl-alkyle, éventuellement substitués; Y représente oxygène ou soufre ou NH, R_4 et R_5 identiques ou différents représentent notamment alkyle substitué par hydroxyle, à l'exception des produits dans lesquels R_4 et R_5 identiques ou différents, représentent hydrogène ou un radical alkyle (C_1 - C_{12}) éventuellement substitué par un ou plusieurs atomes d'halogène ou R_4 et R_5 représentent un radical cycloalkyle (C_1 - C_7) ou l'un de R_4 ou R_5 représente méthyle, l'autre hydroxyméthyle, Y représente oxygène ou NH, -A-B- représente (c), Z_1 est un radical 4-nitro et Z_2 un radical 3- CF_3 .

UNIQUEMENT A TITRE D'INFORMATION

Codes utilisés pour identifier les Etats parties au PCT, sur les pages de couverture des brochures publiant des demandes internationales en vertu du PCT.

AT	Autriche	GB	Royaume-Uni	MR	Mauritanie
AU	Australie	GE	Géorgie	MW	Malawi
BB	Barbade	GN	Guinée	NE	Niger
BE	Belgique	GR	Grèce	NL	Pays-Bas
BF	Burkina Faso	HU	Hongrie	NO	Norvège
BG	Bulgarie	IE	Irlande	NZ	Nouvelle-Zélande
BJ	Bénin	IT	Italie	PL	Pologne
BR	Brazil	JP	Japon	PT	Portugal
BY	Bélarus	KE	Kenya	RO	Roumanie
CA	Canada	KG	Kirghizistan	RU	Fédération de Russie
CF	République centrafricaine	KP	République populaire démocratique de Corée	SD	Soudan
CG	Congo	KR	République de Corée	SE	Suède
CH	Suisse	KZ	Kazakhstan	SI	Slovénie
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovaquie
CM	Cameroun	LK	Sri Lanka	SN	Sénégal
CN	Chine	LU	Luxembourg	TD	Tchad
CS	Tchécoslovaquie	LV	Lettonie	TG	Togo
CZ	République tchèque	MC	Monaco	TJ	Tadjikistan
DE	Allemagne	MD	République de Moldova	TT	Trinité-et-Tobago
DK	Danemark	MG	Madagascar	UA	Ukraine
ES	Espagne	ML	Mali	US	Etats-Unis d'Amérique
FI	Finlande	MN	Mongolie	UZ	Ouzbékistan
FR	France			VN	Viet Nam
GA	Gabon				

New optionally substituted phenylimidazolidines, their preparation process and intermediates, their use as medicaments and the pharmaceutical compositions containing them.

5

The present invention relates to new optionally substituted phenylimidazolidines, their preparation process and intermediates, their use as medicaments and the pharmaceutical compositions containing them.

10

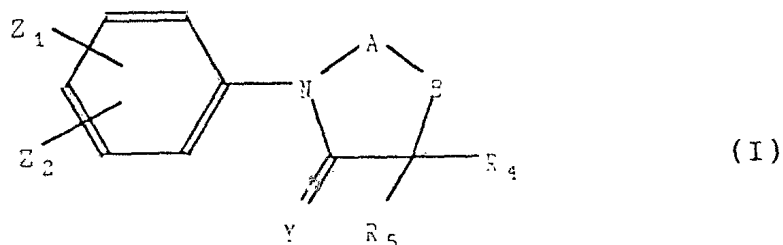
In the Japanese Application J 48087030 3-phenyl 2-thiohydantoins are described which are presented as inhibiting the germination of certain plants.

15

In European Patent Applications 0,494,819 and 0,578,516 imidazolidines are described which are presented as possessing an anti-androgenic activity. The products of this Patent are however different from the products of the following Patent Application.

Therefore a subject of the present invention is the products of general formula (I):

20

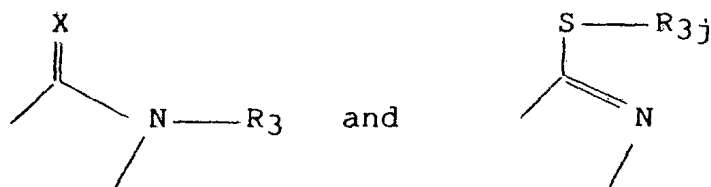


25

in which:

Z₁ and Z₂, identical or different, represent a cyano, nitro radical, a halogen atom, a trifluoromethyl radical or an esterified, amidified or salified free carboxy radical, the group -A-B- is chosen from the radicals

35



in which X represents an oxygen or sulphur atom, R_3j represents R_3 with the exception of the hydrogen value and R_3 is chosen from the following radicals:

- a hydrogen atom,

- 5 - alkyl, alkenyl, alkynyl, aryl or arylalkyl radicals having at most 12 carbon atoms, these radicals being optionally substituted by one or more substituents chosen from halogen atoms and the following radicals: optionally esterified, etherified or protected hydroxy, alkoxy, hydroxyalkyl, alkenyloxy, alkynyloxy, trifluoromethyl, mercapto, cyano, acyl, acyloxy, aryl, optionally substituted S-alkyl, S-aryl, in which the sulphur atom is optionally oxidized in the form of the sulfoxide or sulphone, free, esterified, amidified or salified carboxy, amino, mono- or dialkylamino, a cyclic radical containing 3 to 6 members and optionally containing one or more heteroatoms chosen from sulphur, oxygen or nitrogen atoms and the $-O-\overset{\overset{O}{\parallel}}{C}-R_7$ radical in which R_7 represents
- 10
- 15

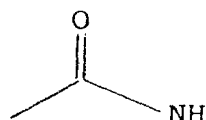
an alkyl, hydroxy, alkoxy, aryl or aryloxy radical,

- 20 the alkyl, alkenyl or alkynyl radicals moreover being optionally interrupted by one or more atoms of oxygen, nitrogen or sulphur optionally oxidized in the form of the sulfoxide or sulphone, the nitrogen atoms being optionally oxidized,
- 25 the aryl and aralkyl radicals moreover being optionally substituted by an alkyl, alkenyl or alkynyl, alkoxy, alkenyloxy, alkynyloxy or trifluoromethyl radical, Y represents an oxygen or sulphur atom or an NH radical, R_4 and R_5 , identical or different, represent a hydrogen atom or an alkyl radical having 1 to 12 carbon atoms optionally substituted by one or more substituents chosen from halogen atoms, the $-O-\overset{\overset{O}{\parallel}}{C}-R_7$ radical as defined above, the optionally
- 30

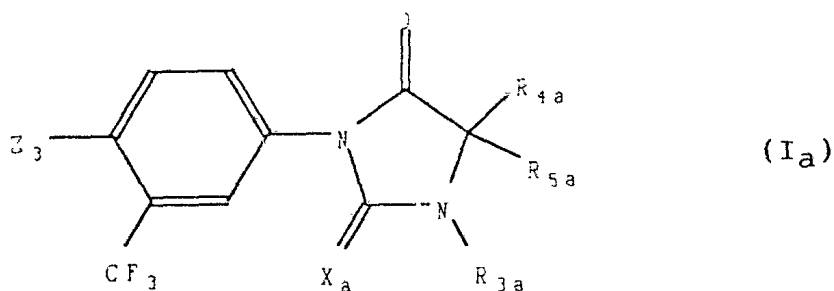
- 35 esterified, etherified or protected hydroxyl radical, linear or branched phenylthio and alkylthio radicals containing at most 8 carbon atoms, phenylthio and alkylthio radicals, in which the sulphur atom can be oxidized in the form of the sulfoxide or sulphone, themselves being optionally



substituted by one or more radicals chosen from halogen atoms, the optionally esterified, etherified or protected hydroxyl radical, the free, esterified, amidified or salified carboxy radical, amino, mono- or dialkylamino radicals, with the exception of the products in which R_4 and R_5 , identical or different, represent a hydrogen atom or an alkyl radical having 1 to 12 carbon atoms non-substituted or substituted by one or more halogen atoms, those in which one of R_4 or R_5 represents a methyl radical and the other represents a hydroxymethyl radical, Y represents an oxygen atom or an NH radical, the group -AB- represents the radical



Z_1 in position 4 represents a nitro radical and Z_2 in position 3 represents a trifluoromethyl radical, those in which Z_1 and Z_2 both represent a halogen atom and those in which one of Z_1 and Z_2 represents a halogen atom, one of R_4 and R_5 represents an alkyl radical substituted by the group -S-CH₃ and R_3 represents a hydrogen atom or an alkyl radical, b) the products of formula (I_a):



in which Z_3 represents a cyano or nitro radical, R_{3a} represents a hydrogen atom or a linear or branched alkyl radical, containing at most 4 carbon atoms, optionally substituted by a fluorine atom, a cyano radical, R_{4a} and R_{5a} are such that one represents a methyl radical and the other represents a methyl radical substituted by a fluorine atom or R_{4a} and R_{5a} are identical and represent a



methyl radical substituted by a fluorine atom, or R_{4a} and R_{5a} form with the carbon atom to which they are linked a cyclopentyl radical,

X_a represents a sulphur or oxygen atom, with the exception of
5 the product in which Z₃ represents a cyano radical, X_a represents a sulphur atom, R_{3a} represents a methyl radical and R_{4a} and R_{5a} form with the carbon atom to which they are linked a cyclopentyl radical,
and c) the following products:

- 10 - 4-(4,4-dimethyl 2,5-dioxo 3-(2-fluoroethyl) 1-imidazol-
idiny) 2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl 2,5-dioxo 3-(2,2,2-trifluoroethyl) 1-
imidazolidiny) 2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl 3-(2-fluoroethyl) 5-oxo 2-thioxo 1-
15 imidazolidiny) 2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl 2,5-dioxo 3-(2-(2-hydroxyethoxy) ethyl) 1-
imidazolidiny) 2-(trifluoromethyl) benzonitrile,
the said products of formula (I), (I_a) and the products
mentioned being in all the possible racemic, enantiomeric and
20 diastereoisomeric isomer forms, as well as the addition salts
with mineral and organic acids or with mineral and organic
bases of the said products.

For the definition of the substituents indicated above
and in what follows, the definitions used can have the
25 following values:

The term alkyl designates a linear or branched radical
having at most 12 carbon atoms such as for example methyl,
ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-
butyl, pentyl, isopentyl, sec-pentyl, tert-pentyl, neo-
30 pentyl, hexyl, isohexyl, sec-hexyl, tert-hexyl, heptyl,
octyl, decyl, undecyl, dodecyl.

Alkyl radicals having at most 4 carbon atoms are
preferred and notably the methyl, ethyl, propyl, isopropyl
and n-butyl radicals.

35 The term alkenyl designates a linear or branched radical
having at most 12 carbon atoms such as for example vinyl,
allyl, 1-propenyl, butenyl, pentenyl, hexenyl.

Among the alkenyl radicals, the radicals having at most



4 carbon atoms are preferred and notably the allyl or butenyl radical.

The term alkynyl designates a linear or branched radical having at most 12 carbon atoms such as for example ethynyl,
5 propargyl, butynyl, pentynyl or hexynyl.

Among the alkynyl radicals, the radicals having at most 4 carbon atoms are preferred and notably the propargyl radical.

By aryl is meant the carbocyclic aryl radicals such as
10 phenyl or naphthyl or the monocyclic heterocyclic aryl radicals with 5 or 6 members or the heterocyclic aryl radicals constituted by condensed rings, containing one or more heteroatoms preferably chosen from oxygen, sulphur and nitrogen. Among the heterocyclic aryls with 5 members, the
15 following radicals can be mentioned: furyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, thiadiazolyl, pyrazolyl, isoxazolyl, tetrazolyl.

Among the heterocyclic aryl radicals with 6 members, the pyridyl, pyrimidinyl, pyridazinyl and pyrazinyl radicals can
20 be mentioned.

Among the condensed aryl radicals, the indolyl, benzofurannyl, benzothienyl and quinolinyl radicals can be mentioned.

The phenyl, tetrazolyl and pyridyl radicals are
25 preferred.

By arylalkyl is meant the radicals resulting from the combination of the alkyl radicals and the aryl radicals mentioned above.

The benzyl, phenylethyl, pyridylmethyl, pyridylethyl or
30 tetrazolylmethyl radicals are preferred.

By halogen is meant, of course, the fluorine, chlorine, bromine or iodine atoms.

The fluorine, chlorine or bromine atoms are preferred.

As particular examples of alkyl radicals substituted by
35 one or more halogens, the following radicals can be mentioned: monofluoro, chloro, bromo or iodomethyl, difluoro, dichloro or dibromomethyl and trifluoromethyl.

As particular examples of substituted aryl or aralkyl



radicals, there can be mentioned those in which the phenyl radical is substituted in the para position by a fluorine atom or by a methoxy or trifluoromethyl radical.

By acyl radical is preferably meant a radical having at most 7 carbon atoms such as the acetyl, propionyl, butyryl or benzoyl radical, but it can also represent a valeryl, hexanoyl, acryloyl, crotonoyl or carbamoyl radical: the formyl radical can also be mentioned.

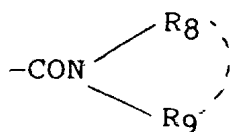
By acyloxy radical is meant the radicals in which the acyl radicals have the meaning indicated above and for example the acetoxy or propionyloxy radicals.

By esterified carboxy is meant for example the radicals such as the alkyloxy-carbonyl radicals, for example methoxy-carbonyl, ethoxycarbonyl, propoxycarbonyl, butyl or tert-butyl oxycarbonyl.

There can also be mentioned the radicals formed with the easily cleavable ester remainders such as the methoxymethyl, ethoxymethyl radicals; the acyloxyalkyl radicals such as pivaloyloxymethyl, pivaloyloxyethyl, acetoxymethyl or acetoxylethyl; the alkyloxy-carbonyloxy alkyl radicals such as the methoxycarbonyloxy methyl or ethyl radicals, the isopropyl oxycarbonyloxy methyl or ethyl radicals.

A list of such ester radicals can be found for example in the European Patent EP 0,034,536.

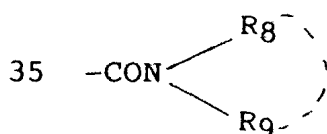
By amidified carboxy is meant the groups of



type in which the R₈ and R₉ radicals,

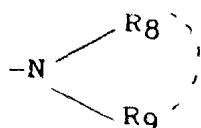
identical or different, represent a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl radicals.

In the groups



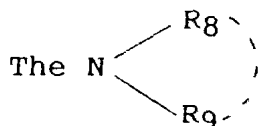
defined above, those in which the





radical represents the amino, mono- or dimethylamino radical are preferred.

5



radical can also represent a heterocycle which may contain an additional heteroatom. The pyrrolyl, imidazolyl, indolyl, piperidino, morpholino, piperazinyl radicals can be mentioned. The piperidino or morpholino radicals are preferred.

10

By salified carboxy is meant the salts formed for example with an equivalent of sodium, potassium, lithium, calcium, magnesium or ammonium. The salts formed with the organic bases such as methylamine, propylamine, trimethyl-

15

amine, diethylamine, triethylamine, can also be mentioned. The sodium salt is preferred.

By alkylamino radical is preferably meant the radicals in which the alkyl contains at most 4 carbon atoms. The methylamino, ethylamino, propylamino or butyl (linear or branched) amino radicals can be mentioned.

20

Similarly, by dialkylamino radical is preferably meant the radicals in which the alkyl contains at most 4 carbon atoms. For example the dimethylamino, diethylamino, methylethylamino radicals can be mentioned.

25

By heterocyclic radical containing one or more heteroatoms is meant for example the saturated heterocyclic, monocyclic radicals such as the following radicals: oxirannyl, oxolannyl, dioxolannyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl or morpholinyl.

30

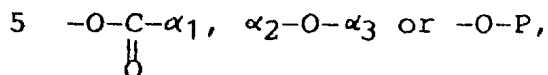
By alkyl, alkenyl, or alkynyl radicals optionally interrupted by a heteroatom chosen from sulphur, oxygen or nitrogen atoms is meant the radicals containing one or more of these atoms, identical or different in their structure, these heteroatoms obviously not being able to be situated at the end of the radical. There can be mentioned for example the alkoxyalkyl radicals such as methoxymethyl or

35



methoxyethyl or also the alkoxy alkoxyalkyl radicals such as methoxyethoxymethyl.

By esterified, etherified or protected hydroxyl radical is meant respectively the radicals



formed from a hydroxyl radical, according to the usual methods known to a man skilled in the art and in which P represents a protective group,

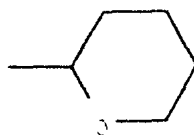
10 α_1 , α_2 and α_3 represent in particular an alkyl, akenyl, alkynyl, aryl or arylalkyl radical, having at most 12 carbon atoms and optionally substituted as defined above in particular for R_3 .

Examples of the protective group P, as well as the
15 formation of the protected hydroxyl radical, are given in particular in the common book for a man skilled in the art: Protective Groups in Organic Synthesis, Theodora W. Greene, Harvard University, printed in 1981 by Wiley-Interscience Publishers, John Wiley & Sons.

20 The protective group of the hydroxyl radical that can be represented by P, can be chosen from the following list: for example formyl, acetyl, chloroacetyl, bromoacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, benzoylformyl, p-
25 nitrobenzoyl. The following groups can also be mentioned: ethoxycarbonyl, methoxycarbonyl, propoxycarbonyl, $\beta\beta\beta$ -trichloroethoxycarbonyl, benzyloxycarbonyl, tert-butoxycarbonyl, 1-cyclo propylethoxycarbonyl, tetrahydro-pyrannyl, tetrahydrothiopyrannyl, methoxytetrahydropyrannyl,
30 trityl, benzyl, 4-methoxybenzyl, benzhydryl, trichloroethyl, 1-methyl 1-methoxyethyl, phthaloyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl and pivaloyl, phenylacetyl, phenylpropionyl, mesyl, chlorobenzoyl, para-nitrobenzoyl, para-tert-butylbenzoyl,
35 caprylyl, acryloyl, methylcarbamoyl, phenylcarbamoyl, naphthylcarbamoyl.

P can in particular represent the radical





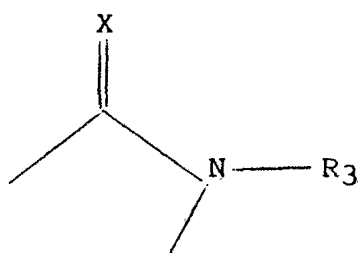
5

or also a silicon derivative such as trimethylsilyl.

When the products of formulae (I) and (I_a) as defined above contain an amino radical salifiable by an acid it is understood that these acid salts are also part of the
10 invention. There can be mentioned the salts formed with hydrochloric or methanesulphonic acids for example.

A particular subject of the invention is the products of formula (I) as defined above, in which Z₁ and Z₂ represent a trifluoromethyl, nitro or cyano radical, Y represents an
15 oxygen atom or an NH radical, the group -A-B- represents the radical:

20



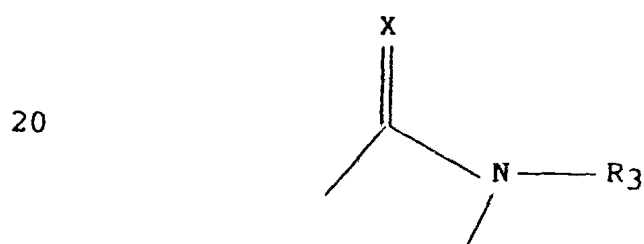
in which X represents an oxygen or sulphur atom,
25 R₃ represents a hydrogen atom, a linear or branched alkyl radical containing at most 6 carbon atoms, optionally interrupted by one or more oxygen or sulphur atoms, a phenyl or pyridyl radical, these radicals being optionally substituted by one or more radicals chosen from halogen
30 atoms, the following radicals: phenyl, optionally esterified, etherified or protected hydroxyl, alkoxy, cyano, trifluoromethyl, hydroxyalkyl, free, esterified, amidified or salified carboxy, amino, mono- or dialkylamino, the nitrogen atom of the pyridyl radical being optionally oxidized,
35 R₄ and R₅ represent a linear or branched alkyl radical containing at most 6 carbon atoms, optionally substituted by one or more radicals chosen from optionally esterified, etherified or protected hydroxyl radicals, halogen atoms, the



-O-C-R_7 radical in which R_7 represents a linear or branched
 ||
 O

alkyl or alkoxy radical and alkylthio and phenylthio
radicals, themselves optionally substituted by one or more
5 radicals chosen from halogen atoms and the free, esterified,
etherified or protected hydroxyl radical,
the said products of formula (I) being in all the possible
racemic, enantiomeric and diastereoisomeric isomer forms, as
well as the addition salts with mineral and organic acids or
10 with mineral and organic bases of the said products of
formula (I).

Among these products, a particular subject of the
invention is the products of formula (I) as defined above, in
which Z_1 and Z_2 represent a trifluoromethyl, nitro or cyano
15 radical, Y represents an oxygen atom or an NH radical, the
group -A-B- represents the group:



in which X represents an oxygen or sulphur atom, R_3
25 represents a hydrogen atom or an alkyl radical having 1 to 6
carbon atoms optionally substituted by one or more radicals
chosen from halogen atoms and the optionally esterified,
etherified or protected hydroxyl radical, the free,
esterified, amidified or salified carboxy radical and the
30 cyano radical, the alkyl radical being optionally interrupted
by one or more oxygen or sulphur atoms,
 R_4 and R_5 represent an alkyl radical containing at most 6
carbon atoms optionally substituted by one or more radicals
chosen from the optionally esterified, etherified or
35 protected hydroxyl radical, halogen atoms and alkylthio and
phenylthio radicals themselves optionally substituted by one
or more radicals chosen from halogen atoms and the hydroxyl
radical, the said products of formula (I) being in all the



possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

- 5 Among these products, a more particular subject of the invention is the products of formula (I) as defined above, in which Y represents an oxygen atom or an NH radical, Z₂ in position 3 represents a trifluoromethyl radical and Z₁ in position 4 represents a cyano or nitro radical,
- 10 X represents an oxygen or sulphur atom,
R₃ represents a hydrogen atom or an alkyl radical having at most 4 carbon atoms, optionally substituted by one or more radicals chosen from halogen atoms or the cyano radical,
R₄ and R₅, identical or different, represent a linear or
- 15 branched alkyl radical containing at most 4 carbon atoms optionally substituted by a free, esterified, etherified or protected hydroxyl radical, a halogen atom, or a phenylthio radical optionally substituted by a halogen atom or a free, esterified, etherified or protected hydroxyl radical,
- 20 the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).
- 25 Among the preferred products of the invention, there can be mentioned more particularly the products of formula (I) as defined above the names of which follow:
- 2-(trifluoromethyl) 4-(4-(hydroxymethyl) 4-methyl 2,5-dioxo 1-imidazolidinyl) benzonitrile,
- 30 - 4-(3,4-dimethyl) 4-(hydroxymethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 2-(trifluoromethyl) 4-(4-(hydroxymethyl) 3,4-dimethyl 2,5-dioxo 1-imidazolidinyl) benzonitrile,
- 4-(2,5-dioxo 3-(2-fluoroethyl) 4-(hydroxymethyl) 4-methyl
- 35 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 1,5-dimethyl 5-(hydroxymethyl) 3-(4-nitro 3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione,
- 4-(4,4-bis(hydroxymethyl)-2,5-dioxo-1-imidazolidinyl)-2-



(trifluoromethyl)-benzonitrile

the said products of formula (I) being in all their racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with
5 mineral and organic bases of the said products of formula (I).

Also a quite particular subject of the invention is the products of formula (I_a) as defined above, the names of which follow:

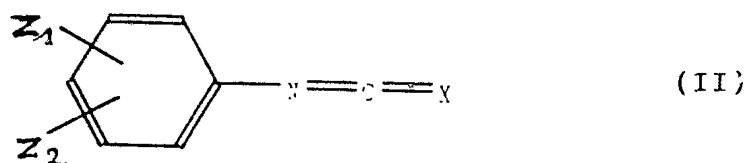
- 10 - 4-(4-(fluoromethyl) 3,4-dimethyl) 2,5-dioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 4-(3,4-dimethyl) 4-(fluoromethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 4-(2,5-dioxo 3-(2-fluoroethyl) 4-(fluoromethyl) 4-methyl 1-
15 imidazolidinyl) 2-trifluoromethyl) benzonitrile,
- 4-(2,4-dioxo 1,3-diazaspiro(4.4)nonan-3-yl) 2-(trifluoromethyl) benzonitrile,
- 4-(2,4-dioxo 1-(2-fluoroethyl) 1,3-diazaspiro(4.4)nonan-3-yl) 2-(trifluoromethyl) benzonitrile,
20 - 1,5-dimethyl 5-(fluoromethyl) 3-(4-nitro 3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione,
- 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 5-(fluoromethyl) 5-methyl 1-imidazolidinacetonitrile,
- 4-(4,4-bis-(fluoromethyl) 3-methyl 5-oxo 2-thioxo 1-
25 imidazolidinyl) 2-(trifluoromethyl) benzonitrile,

the said products of formula (I_a) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of
30 formula (I_a).

Also a subject of the invention is a preparation process for the products of formula (I), (I_a) and cited products as defined above characterized in that:

either a product of formula (II):





5

in which Z_1 , Z_2 and X have the meaning indicated above, is reacted in the presence of a tertiary base with a product of formula (III):

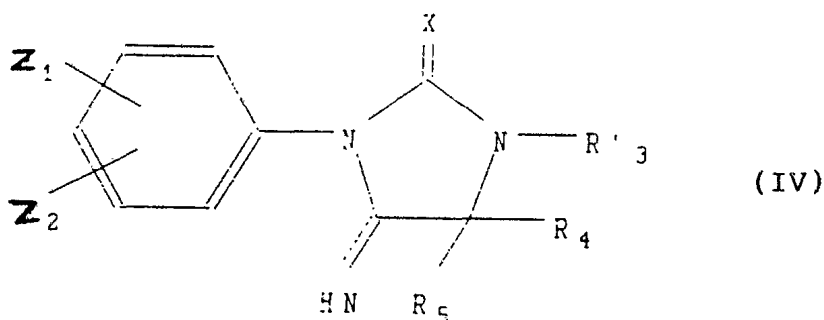
10



15

in which R_4 and R_5 have the meaning indicated above and R'_3 has the values indicated above for R_3 in which the optional reactive functions are optionally protected and it being understood that R_4 and R_5 do not represent simultaneously a methyl radical and that if Z_1 represents an NO_2 radical in position 4, Z_2 represents a CF_3 radical in position 3, X represents an oxygen atom and R'_3 represents a hydrogen atom, then one of R_4 or R_5 does not represent a CH_3 radical and the other a CH_2OH radical, in order to obtain a product of formula (IV):

20

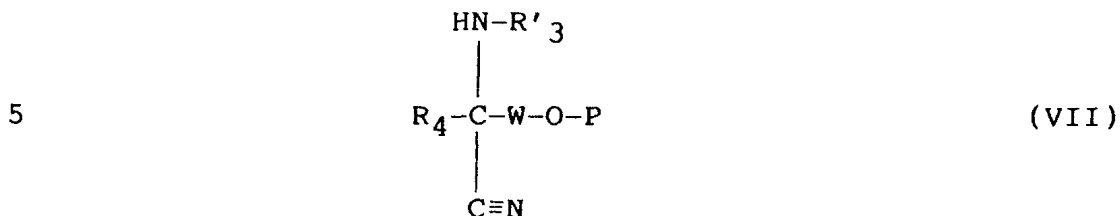


30

in which Z_1 , Z_2 , X , R'_3 , R_4 and R_5 have the previous meaning, or the product of formula (II), as defined above, is reacted in the presence of a tertiary base with a product of formula

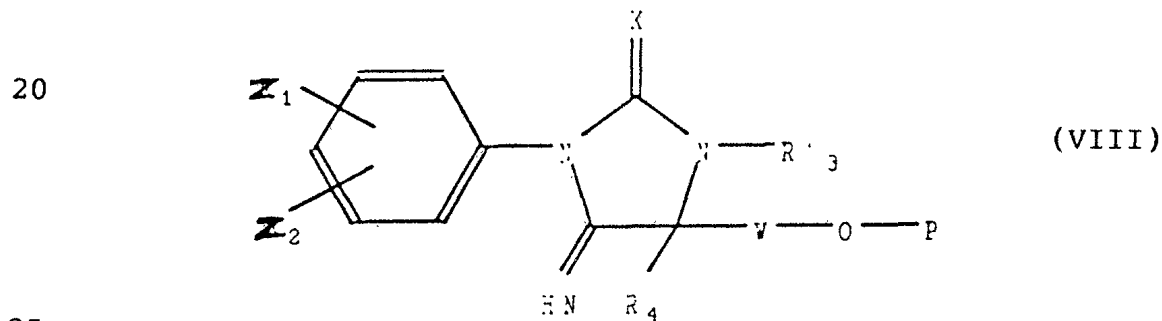


(VII):



in which W has the meaning indicated above for R₅ with the
10 exception of the hydrogen atom, the alkyl radical substituted
by a free, esterified, etherified or protected hydroxyl

radical and the value $-O-C-R_7$ as defined above, and P represents a protective group of OH or a radical such that -
15 O-P represents an etherified hydroxyl radical and R'_3 and R_4 have the meaning indicated above, in order to obtain a product of formula (VIII);



in which X, Z₁, Z₂, R'₃, R₄, W and P have the meaning indicated above,
of which product of formula (VIII) if necessary and if desired, the OH radical can be released from OP which can
30 then if necessary and if desired, be esterified or converted into a halogen radical,
which products of formulae (IV) and (VIII), if necessary or if desired, are subjected to any one or more of the following reactions, in any order:

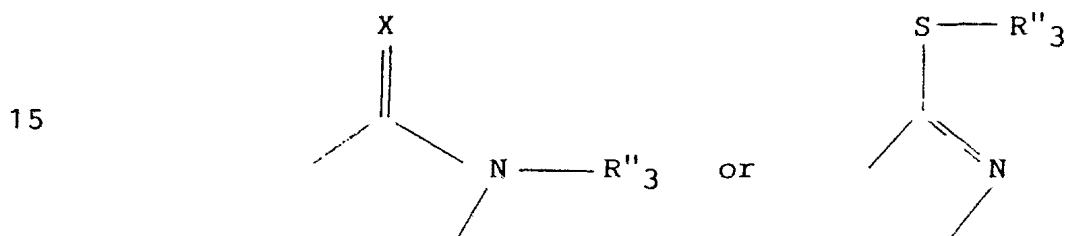
- 35 a) elimination reaction of the optional protective groups that can be carried by R'₃;
b) hydrolysis reaction of the >C=NH group into a carbonyl function and if appropriate conversion of the >C=S group into



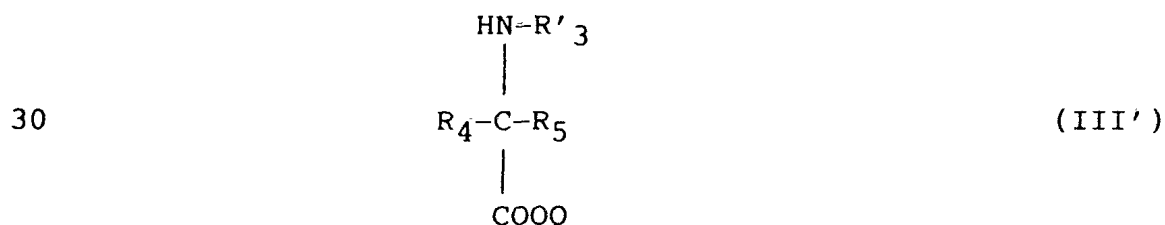
the $>C=O$ group;

c) conversion reaction of the $>C=O$ group or groups into the $>C=S$ group;

d) action on the products of formula (IV) or (VIII) in which
 5 R'_3 represents a hydrogen atom, and after hydrolysis of the
 $>C=NH$ group into a carbonyl function, of a reagent of formula
 $Hal-R''_3$ in which R''_3 has the values of R'_3 with the exception
 of the hydrogen value and Hal represents a halogen atom, in
 order to obtain products of formulae (I), (I_a) and cited
 10 products as defined above, in which the A-B- group
 represents the group



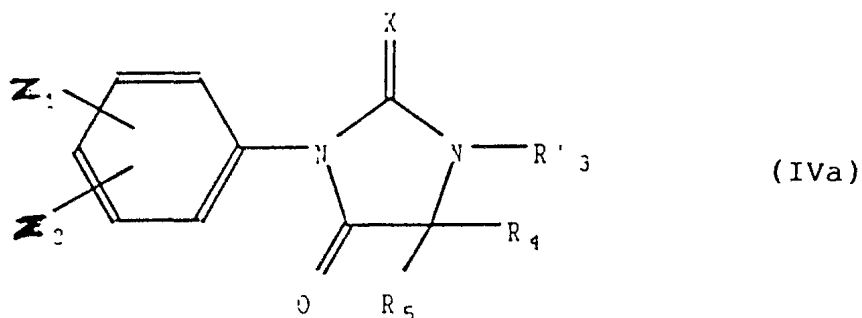
in which R''_3 has the meaning indicated previously then, if
 20 desired, action on these products, of an elimination agent of
 the optional protective groups that can be carried by R''_3 or
 if appropriate, action of an esterification, amidification or
 salification agent,
or a product of formula (II) as defined above is reacted in
 25 the presence of a tertiary base with a product of formula
 (III'):



in which R'_3 , R_4 and R_5 have the meaning indicated above and
 35 Q represents either an alkali metal atom or an alkyl radical
 containing 1 to 6 carbon atoms, in order to obtain a product
 of formula (IVa):

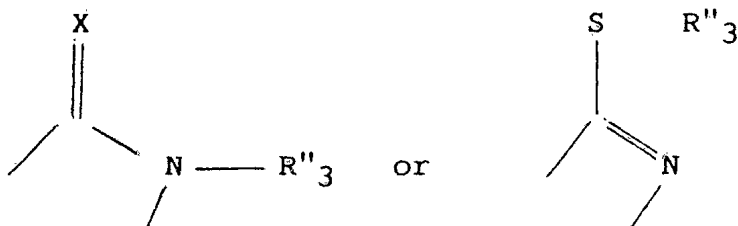


5



- 10 in which X, Z₁, Z₂, R'₃, R₄ and R₅ have the meaning indicated above, which if desired is subjected to any one or more of the following reactions, in any order:
- a) elimination reaction of the optional protective groups that can be carried by R'₃;
- 15 b) conversion reaction of the >C=O group or groups into the >C=S group or if appropriate of the >C=S group into the >C=O group;
- c) action on the products of formula (IVa) in which R'₃ represents a hydrogen atom of a reagent of formula Hal-R''₃ in
- 20 which R''₃ has the values of R'₃ with the exception of the hydrogen value and Hal represents a halogen atom, in order to obtain products of formulae (I), (Ia) and cited products as defined above, in which the A-B- group represents the group

25

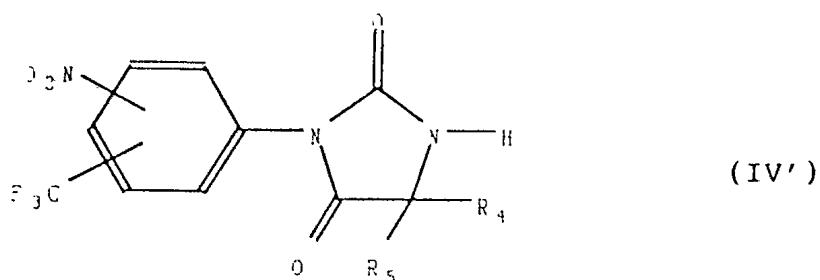


30

- in which R''₃ has the meaning indicated previously then, if desired, action on these products of an elimination agent of the optional protective groups that can be carried by R''₃ or if appropriate, action of an esterification, amidification or
- 35 salification agent,
- or a reagent of formula Hal-R''₃ in which Hal and R''₃ have the values indicated previously is reacted on a product of formula (IV'):



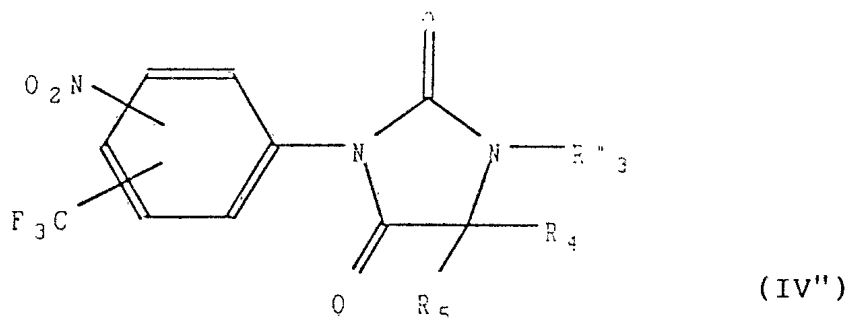
5



in order to obtain a product of formula (IV''):

10

15



20

which product of formula (IV), (IVa), (IV'), (IV'') or (VIII) represents or does not represent a product of formula (I) and which, in order to obtain if necessary or if desired a product of formula (I), is subjected to any one or more of the following reactions in any order:

25

a) elimination reaction of the optional protective groups that can be carried by R'3 then if appropriate action of an esterification, amidification or salification agent;

b) conversion reaction of the >C=O group or groups into

30

>C=S groups, the said products of formula (I) thus obtained being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms.

The action of the products of formula (II) with the products of formula (III) is preferably carried out in an organic solvent such as tetrahydrofuran or dichloroethane but ethyl ether or isopropyl ether can also be used.

35

The operation is carried out in the presence of a tertiary base such as triethylamine or also pyridine or



methylethylpyridine.

The optional reactive functions that can be contained by R_3 and that are optionally protected, are hydroxy or amino functions. The usual protective groups are used to protect
5 these functions. There can be mentioned for example the following protective groups of the amino radical: tert-butyl, tert-amyl, trichloroacetyl, chloroacetyl, benzhydryl, trityl, formyl, benzyloxycarbonyl.

As protective group of the hydroxy radical there can be
10 mentioned the radicals such as formyl, chloroacetyl, tetrahydropyrannyl, trimethylsilyl, tert-butyl dimethylsilyl.

It is well understood that the above list is not limitative and that other protective groups, for example known in the chemistry of the peptides, can be used. A list
15 of such protective groups is found for example in the French Patent BF 2,499,995 whose content is incorporated here by way of reference.

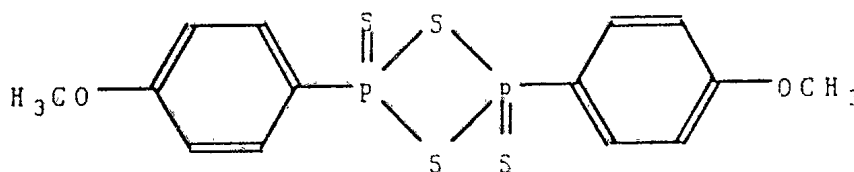
The optional elimination reactions of the protective groups are carried out as indicated in the said Patent BF
20 2,499.995. The preferred method of elimination is acid hydrolysis using acids chosen from hydrochloric, benzene sulphonic or paratoluene sulphonic, formic or trifluoroacetic acids. Hydrochloric acid is preferred.

The optional hydrolysis reaction of the $>C=NH$ group into
25 the ketone group is also preferably carried out using an acid such as aqueous hydrochloric acid for example under reflux.

When the hydrolysis of the $>C=NH$ group into the carbonyl group is carried out on a molecule also containing a $>C=S$ group, this can be converted into the $>C=O$ group. The free
30 OH radical that can optionally be contained by R_3 can then be converted into the SH radical.

The conversion reaction of the $>C=O$ group or groups into the $>C=S$ group is carried out using the so-called Lawesson reagent of formula:

35



which is a product marketed for example by the FLUKA company and whose use is described for example in the publication: Bull. Soc. Chim. Belg. Vol. 87, No. 3, (1987) p. 229.

When it is desired to convert two $>C=O$ functions into
5 two $>C=S$ functions the operation is carried out in the presence of an excess of Lawesson reagent. The same goes when one starts with a molecule containing a $>C=S$ function and a $>C=O$ function and it is desired to convert the said $>C=O$ function into a $>C=S$ function.

10 On the other hand when one starts with a molecule containing two $>C=O$ functions and it is desired to obtain a product containing only a single $>C=S$ function. The operation is carried out in the presence of a deficit of Lawesson reagent. Then in general a mixture of three
15 products is obtained: each of the two products containing a $>C=O$ function and a $>C=S$ function and the product containing two $>C=S$ functions. These products can then be separated by the usual methods such as chromatography.

The action on the product of formula (IV), (IVa), (IV')
20 or (VIII) of the reagent of formula $Hal-R''_3$ is carried out in the presence of a strong base such as sodium or potassium hydride. The operation can be carried out by phase transfer reaction in the presence of quaternary ammonium salts such as tert-butyl ammonium.

25 - The protective groups that can be carried by the R''_3 substituent can be for example one of those previously mentioned for R_3 . The elimination reactions of the protective groups are carried out under the conditions indicated above.

30 An example of the elimination of the terbutyldimethylsilyl group by means of hydrochloric acid is given hereafter in the examples.

- The optional esterification of the products of formulae (I), (Ia) and as defined above, in which R''_3 contains a free
35 OH radical is carried out under standard conditions. There can be used an acid or a functional derivative, for example an anhydride such as acetic anhydride in the presence of a base such as pyridine.

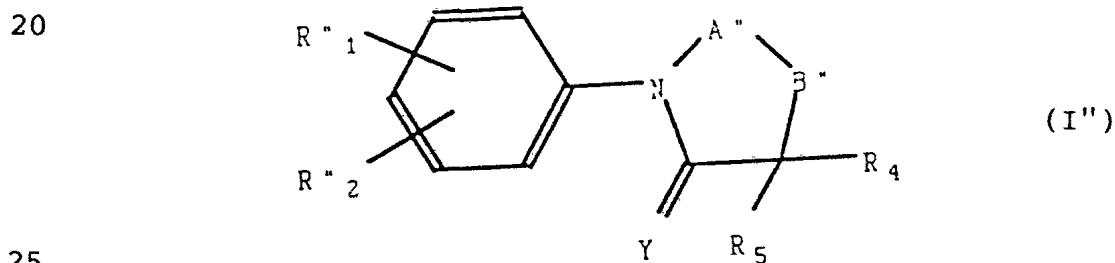


The optional esterification or salification of the products of formulae (I), (Ia) and the cited products as defined above, in which R''_3 represents a COOH group, is carried out under standard conditions known to a man skilled in the art.

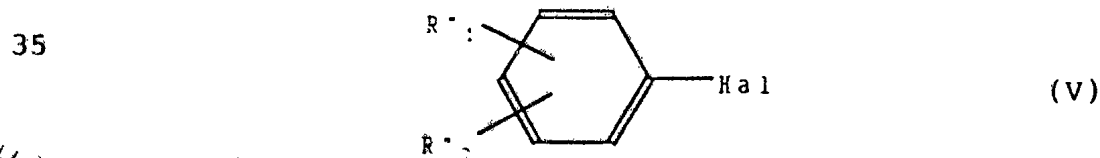
- The optional amidification of the products of formulae (I), (Ia) and as defined above, in which R''_3 contains a COOH radical, is carried out under standard conditions. A primary or secondary amine can be used on a functional derivative of the acid for example a symmetrical or mixed anhydride.

The reaction of the product of formula (II) as defined above with the product of formula (VII) as defined above to give the product of formula (VIII) as defined above, can be carried out notably in the presence of methylene chloride at a temperature of approximately -30°C .

Also a subject of the present invention is a preparation process for the products of formula (I''):

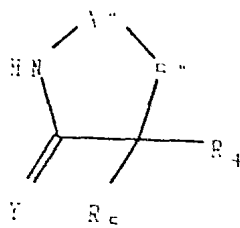


in which R_4 and R_5 are defined as above and R''_1 , R''_2 , $-A''-B''-$ have the meanings indicated above for Z_1 , Z_2 and $-A-B-$, it being understood that when $-A''-B''-$ represents a $-\text{CO}-\text{N}(\text{R}''_3)-$ group in which R''_3 represents a hydrogen atom or a linear or branched alkyl radical having at most 7 carbon atoms and Y represents an oxygen atom, R''_1 represents a cyano radical, process characterized in that a product of formula (V):



in which R''_1 and R''_2 have the previous meanings and Hal represents a halogen atom, is reacted with a product of formula (VI):

5



(VI)

10 in which $-A''-B''-$, R_4 , R_5 and Y have the meaning indicated above, the reaction being carried out in the presence of a catalyst and optionally of a solvent.

With regard to the products of formula (V), the term Hal preferably designates the chlorine atom, but can also
15 represent a bromine or iodine atom.

The rôle of the catalyst is probably to trap the hydrogen halide which is released and thus to facilitate the condensation reaction of the product of formula (V) with the product of formula (VI) to give the desired product.

20 A more particular subject of the invention is a process as defined above in which the catalyst is a metal in native or oxidized form or a base.

When the catalyst used is a metal, this metal can be copper or nickel. It can be in native form, in the form of
25 the metal oxide or also in the form of the metal salts.

The metal salts can be a chloride or an acetate.

When the catalyst is a base, this base can be for example soda or potash and, if desired, dimethylsulphoxide can be added to the reaction medium.

30 A more particular subject of the invention is a process as defined above in which the catalyst is chosen from cuprous oxide, cupric oxide, copper in the native form and a base such as soda or potash.

The copper in native form used as catalyst is preferably
35 in powdered form.

A particular subject of the invention is a process as defined above in which the catalyst is cuprous oxide.

The solvent used is preferably chosen from ethers with a



high boiling point such as, for example, phenyl oxide, diglyme, triglyme and dimethylsulphoxide but can also be, for example, an oil with a high boiling point such as paraffin or vaseline.

5 A more particular subject of the invention is a process as defined above characterized in that the operation is carried out in the presence of a solvent of ether type such as phenyl oxide, diglyme, triglyme or dimethylsulphoxide.

10 A quite particular subject of the invention is a process as defined above in which the solvent used is phenyl oxide or triglyme.

 The preparation process of the desired product defined above can be carried out under pressure or at atmospheric pressure, preferably at a high temperature.

15 Therefore a subject of the invention is a process as defined above characterized in that the reaction is carried out at a temperature higher than 100°C and preferably higher than 150°C.

20 A more particular subject of the invention is a process as defined above characterized in that the reaction is carried out for more than 2 hours.

25 A very particular subject of the invention is a process as defined above characterized in that the reaction is carried out in the presence of cuprous oxide, in triglyme, at a temperature higher than or equal to 200°C and for more than 3 hours.

30 The products which are a subject of the present invention possess useful pharmacological properties, in particular they fix on the androgen receptor and they present an anti-androgenic activity.

 Tests given in the experimental part illustrate these properties.

35 These properties make the products of formula (I) as defined above of the present invention of use as medicaments mainly for:

- the treatment of adenomas and neoplasias of the prostate as well as benign hypertrophy of the prostate, alone or in combination with analogues of LHRH. They can also be used in



the treatment of benign or malignant tumours possessing androgen receptors and more particularly cancers of the breast, skin, ovaries, bladder, lymphatic system, kidney and liver,

- 5 - the treatment of cutaneous affections such as acne, hyperseborrhea, alopecia or hirsutism. These products can therefore be used in dermatology alone or in combination with antibiotics such as derivatives of azelaic and fusidic acids, erythromycin, as well as derivatives of retinoic acid or an
10 inhibitor of 5α -reductase such as (5α , 17β)-1,1-dimethylethyl 3-oxo 4-aza-androst-1-ene 17-carboxamide (or Finasteride, Merck 11th Ed.) for the treatment of acne, alopecia or hirsutism. They can also be combined with a product stimulating hair growth such as Minoxidil for the treatment
15 of alopecia.

The products of formulae (I), (I_a) and the cited products as defined above, in radioactive form (tritium, carbon 14, iodine 125 or fluorine 18) can also be used as a specific marker for the androgen receptors. They can also be
20 used in diagnostics in medical imaging.

The products of formulae (I), (I_a) and the cited products as defined above can also be used in the veterinary domain for the treatment of behavioural disorders such as aggressiveness, androgen-dependent affections, such as circum
25 anum in dogs, and tumours having androgen receptors. They can also be used to bring about a chemical castration in animals.

Therefore a subject of the invention is the use, as medicaments, of the pharmaceutically acceptable products of
30 formulae (I) and (I_a) as defined above.

Also a subject of the invention is the use, as medicaments, of the following products:

- 4-(4,4-dimethyl 2,5-dioxo 3-(2-fluoroethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 35 - 4-(4,4-dimethyl 2,5-dioxo 3-(2,2,2-trifluoroethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl 3-(2-fluoroethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,



- 4-(4,4-dimethyl 2,5-dioxo 3-(2-(2-hydroxyethoxy) ethyl) 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile.

A particular subject of the invention is the use, as medicaments, of the following products:

- 5 - 2-(trifluoromethyl) 4-(4-(hydroxymethyl) 4-methyl 2,5-dioxo 1-imidazolidinyl) benzonitrile,
- 4-(3,4-dimethyl) 4-(hydroxymethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 2-(trifluoromethyl) 4-(4-(hydroxymethyl) 3,4-dimethyl 2,5-
10 dioxo 1-imidazolidinyl) benzonitrile,
- 4-(2,5-dioxo 3-(2-fluoroethyl) 4-(hydroxymethyl) 4-methyl 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 1,5-dimethyl 5-(hydroxymethyl) 3-(4-nitro 3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione,
15 - 4-(4,4-bis (hydroxymethyl) 2,5-dioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile.

Also a particular subject of the invention is the use, as medicaments, of the following products of formula (I_a):

- 4-(4-(fluoromethyl) 3,4-dimethyl) 2,5-dioxo 1-
20 imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 4-(3,4-dimethyl) 4-(fluoromethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 4-(2,5-dioxo 3-(2-fluoroethyl) 4-(4-(fluoromethyl) 4-methyl 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
25 - 4-(2,4-dioxo 1,3-diazaspiro(4.4)nonan-3-yl) 2-(trifluoromethyl) benzonitrile,
- 4-(2,4-dioxo 1-(2-fluoroethyl) 1,3-diazaspiro(4.4)nonan-3-yl) 2-(trifluoromethyl) benzonitrile,
- 1,5-dimethyl 5-(fluoromethyl) 3-(4-nitro 3-(trifluoro-
30 methyl) phenyl) 2,4-imidazolidinedione,
- 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 5-(fluoromethyl) 5-methyl 1-imidazolidinacetonitrile,
- 4-(4,4-bis-(fluoromethyl) 3-methyl 5-oxo 2-thioxo 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile.

35 The products can be administered by parenteral, buccal, perlingual, rectal or topical route.

Also a subject of the invention is the pharmaceutical compositions, characterized in that they contain, as active

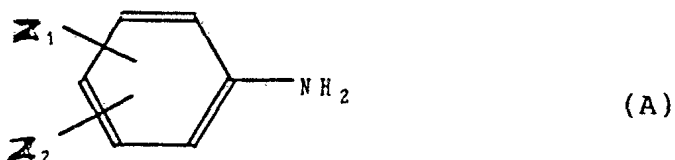


ingredient, at least one of the medicaments of formulae (I), (Ia) and the cited products as defined above.

These compositions can be presented in the form of injectable solutions or suspensions, tablets, sugar-coated
5 tablets, capsules, syrups, suppositories, creams, ointments and lotions. These pharmaceutical forms are prepared according to the usual methods. The active ingredient can be incorporated with excipients usually employed in these compositions, such as aqueous or non-aqueous vehicles, talc,
10 gum arabic, lactose, starch, magnesium stearate, cocoa butter, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents, preservatives.

The usual dose, variable according to the patient being
15 treated and the affection in question, can be, for example, from 10 mg to 500 mg per day for man, by oral route.

The products of formula (II) used at the start of the invention can be obtained by the action of phosgene when X represents an oxygen atom or thiophosgene when X represents a
20 sulphur atom on the corresponding amine of formula (A):



25

An example of such a preparation is given hereafter in the experimental part. A product of this type is also described in the French Patent BF 2,329,276.

30 The amines of formula (A) are described in the European Patent EP 0,002,892 or the French Patent BF 2,142,804.

The products of formula (III) or (III') are known or can be prepared from the corresponding cyanhydrin according to the process described in the publications: J. Am. Chem. Soc.
35 (1953), 75, 4841, BEIL I 4 526 or J. Org. Chem. 27 2901 (1962).

The products of formula (III) in which R'₃ is different from a hydrogen atom can be obtained by the action of a



product of formula $R''_3 \text{ Hal}$ on 2-cyano 2-amino propane under the conditions set out above for the action of $R''_3 \text{ Hal}$ on the products of formula (IV). An example of this type of preparation is described in the reference:

- 5 - Jilek et al. Collect. Czech. Chem. Comm. 54(8) 2248 (1989).

The products of formula (IV') are described in the French Patent BF 2,329,276.

10 The products of formulae (V) and (VI), used at the start of a process which is a subject of the invention, for obtaining the products of formulae (I), (I_a) as defined above, are known and commercially available or can be prepared according to methods known to a man skilled in the art.

15 The preparation of products of formula (VI) is described in particular in the following publications:

- Zhur. Preklad. Khim. 28, 969-75 (1955) (CA 50, 4881a, 1956)
 - Tetrahedron 43, 1753 (1987)
 - J. Org. 52, 2407 (1987)
 - 20 - Zh. Org. Khim. 21, 2006 (1985)
 - J. Fluor. Chem. 17, 345 (1981)
- or in the Patents:
- German Patent DRP 637,318 (1935)
 - European Patent EP 0,130.875
 - 25 - Japanese Patent JP 81,121,524.

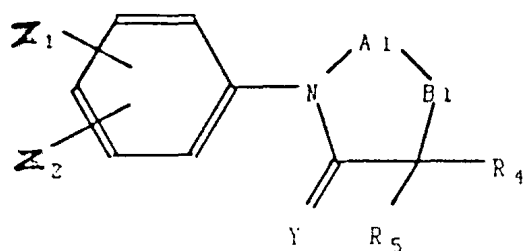
The products of formula (VI) which are derivatives of hydantoin are widely used and mentioned in the literature such as for example in the following articles:

- J. Pharm. Pharmacol., 67, Vol. 19(4), p. 209-16 (1967)
- 30 - Khim. Farm. Zh., 67, Vol. 1(5) p. 51-2
- German Patent 2,217,914
- European Patent 0,091,596
- J. Chem. Soc. Perkin. Trans. 1, p. 219-21 (1974).

35 Also a subject of the invention is, as new industrial products and notably as new industrial products which can be used as intermediates for the preparation of the products of formulae (I), (I_a) and the cited products as defined above, the products of formula (IVi):



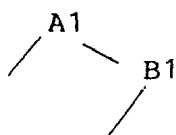
5



(IVi)

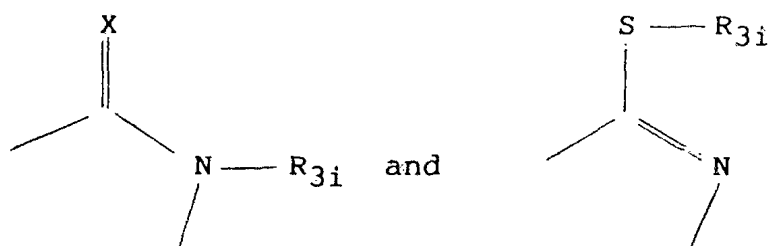
in which Z_1 , Z_2 , R_4 , R_5 and Y have the meanings indicated
10 above and the group:

15



is chosen from the radicals:

20



in which X represents an oxygen or sulphur atom and R_{3i} is
25 chosen from the values of R_3 containing a protected reactive
function, with the exception of the products in which R_4 and
 R_5 , identical or different, represent a hydrogen atom or an
alkyl radical having 1 to 12 carbon atoms optionally
substituted by one or more halogen atoms.

30 Among the reactive functions which can be protected the
hydroxyl and amino functions can be mentioned. These
functions can be protected as indicated above for the
substituent R_3 .

The following examples illustrate the invention without
35 however limiting it.

EXAMPLE 1: 2-(trifluoromethyl) 4-(4-(hydroxymethyl) 4-methyl
2,5-dioxo 1-imidazolidinyl) benzonitrile

Stage A: 1-(tetrahydro 2H-pyran-2-yl) oxy) 2-propanone



50 g of hydroxyacetone, 100 cm³ of methylene chloride and 0.5 g of 1% monohydrated paratoluene sulphonic acid are introduced together. Then over 5 hours at 20°C, 62.44 g of 3,4-dihydro 2-pyran is added. After 2 hours 30 minutes of introduction, 0.5 g of paratoluene sulphonic acid is added then the mixture is agitated for one hour 30 minutes and 100 cm³ of water saturated with sodium bicarbonate is added. Agitation is carried out for 5 minutes at an alkaline pH then the reaction medium is decanted and extraction is carried out with methylene chloride, then the extracts are washed with water, the organic phases are dried, filtered and brought to dryness. 101.8 g of expected product is obtained (pale yellow oil).

Stage B: 2-amino 2-methyl 3-((tetrahydro 2H-pyran 2-yl) oxy) propanenitrile

77.3 g of potassium cyanide, 178.1 g of alumina and 70 g of ammonium chloride in 1 litre of acetonitrile are agitated under ultrasound for one hour while maintaining the temperature at 40°C.

Next 95 g of the product obtained in Stage A) above is added, then the mixture is rinsed with 0.2 l of acetonitrile and agitated for about 21 hours.

Filtration is carried out, followed by rinsing with acetonitrile and drying. Purification is carried out on silica (eluant: cyclohexane - ethyl acetate 1-1) and 65.5 g of expected product (yellow oil) is collected.

IR Spectrum: CHCl₃

C≡N 2230

NH 3393

3330

Stage C: 2-(trifluoromethyl) 4-(4-(hydroxymethyl) 4-methyl 2,5-dioxo 1-imidazolidinyl) benzonitrile

a) Condensation 2-(trifluoromethyl) 4-[5-imino 4-methyl 2-oxo 4-[[[(tetrahydro 2-H-pyran 2-yl) oxy] methyl] 1-imidazolidinyl] benzonitrile

12.77 g of the product obtained in Stage B above is introduced at 20°C ± 2°C into 127.7 ml of methylene chloride. Then over about 1 hour 30 minutes, under agitation at -30°C



± 3°C, a previously-filtered solution of 11.4 g of the product obtained in the preparation of Example 7 of the European Patent Application EP 0,494,819 in 171 ml of methylene chloride is added and agitation is carried out for about one hour at -30°C ± 3° then the solvent is evaporated off under reduced pressure at 40°C. 24.7 g of the expected condensation product is obtained, used as it is for the methanolic hydrolysis.

b) Hydrolysis 2-(trifluoromethyl) 4-(4-(hydroxymethyl) 4-methyl 2,5-dioxo 1-imidazolidinyl) benzonitrile

21.3 g of the product obtained above in a is introduced under agitation at 20° ± 2°, into 213 ml of methanol. Then 67 ml of 2N hydrochloric acid is added over 2 minutes. The mixture is taken to reflux for one hour then left to cool under agitation. After concentration by distilling off about 100 ml of methanol, the reaction medium is placed under magnetic stirring for about one hour at a temperature of 0°/+5°C then separated.

The crystals obtained are purified, 3 volumes of methanol are added, followed by taking to reflux for 15 minutes, then leaving to cool down under agitation at 20-25° and separating. 10.7 g of expected product (white crystals) is obtained. M.p. = 218°C.

Microanalysis:

	Theoretical	Product dried at 60°C
C%	49.85	49.7
N%	13.4	13.4
F%	18.19	18.0
H%	3.22	3.2
IR complex absorption OH/NH region		
-C≡N		approx. 2230 cm ⁻¹
>=O		1780 - 1735 cm ⁻¹
Aromatics		1604 - 1575 - 1503 cm ⁻¹

EXAMPLE 2: 2-(trifluoromethyl) 4-(4-(hydroxymethyl) 3,4-dimethyl 2,5-dioxo 1-imidazolidinyl) benzonitrile

1) Formation of tetrahydropyranic ether

626 mg of the product of Example 1, 10 ml of tetrahydrofuran, 30 mg of paratoluene sulphonic acid, H₂O and



2 ml of dihydropyran are introduced together. At end of about 30 minutes, the mixture is poured into 10 ml of sodium bicarbonate and 1 ml of triethylamine and extracted with chloroform. The organic phase is washed with salt water, dried and the solvent is evaporated off. Purification is carried out on silica (eluant: CH_2Cl_2 , MeOH). 830 mg of the expected ether is obtained.

2) Methylation of the nitrogen

103 mg of 50% sodium hydride is introduced and 830 mg of the ether obtained above in 1) in 7 ml dimethylformamide is added over about 40 minutes, then 10 minutes after the cessation of the release of hydrogen, the reaction medium is placed in a water bath and 0.18 ml of methyl iodide and 0.5 ml of dimethylformamide are added. After reaction for 30 minutes, the medium is poured into 40 ml of water containing about 0.5 g of monopotassium phosphate and extracted with ether, then the organic phase is washed with salt water, dried and the solvent is evaporated off under reduced pressure. Purification is carried out on silica (eluant: CH_2Cl_2 -Me₂CO (95-5)). 770 mg of product is obtained, used as it is for the following stage.

3) Hydrolysis of the tetrahydropyranic ether

770 mg of the N-methylated ether obtained above in 2) is introduced into 10 ml of methanol, 1.5 ml of 2N hydrochloric acid and heated at about 40°C.

After 30 minutes, the mixture is taken to ambient temperature, poured into 20 ml of sodium bicarbonate, extraction is carried out with chloroform, the extracts are washed with salt water, dried and the solvent is evaporated off under reduced pressure. Purification is carried out on silica (eluant: CH_2Cl_2 -Me₂CO (3-1)). 111 mg of the crude product obtained above is recrystallized from 5 ml of hot isopropanol, concentrated to about 1 ml and ice-cooled for 16 hours. After filtration and drying, 90 mg of the expected product is obtained (white crystals) M.p. = 178-179°C.

Microanalysis

	C	H	F	N
% calculated	51.38	3.70	17.41	12.84



% found 51.5 3.7 17.5 12.8

IR CHCl₃

OH 3620 cm⁻¹

>=O 1781 - 1728 cm⁻¹

5 C≡N 2235 cm⁻¹

Aromatics 1615 - 1576 - 1505 cm⁻¹

UV EtOH

Max 262 nm ε = 13900

Infl 278 nm ε = 7200

10 Infl 286 nm ε = 3800

EXAMPLE 3: 4-(2,5-dioxo 3-(2-fluoroethyl) 4-(hydroxymethyl) 4-methyl 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

a) Alkylation with 1,2-bromofluoroethane

830 mg of the ether obtained in Stage 1) of Example 2
15 and 7.5 ml of dimethylsulphoxide are added drop by drop to
104 mg of 5% sodium hydride. About 20 minutes after
cessation of the release of hydrogen, 0.22 ml of 1,2-
bromofluoroethane is added in one lot. After about one hour
of reaction, the medium is poured into 5 ml of water
20 containing 500 mg of monopotassium phosphate and extracted
with ether. The organic phase is washed with water then with
salt water, dried and the solvent is evaporated off under
reduced pressure. Purification is carried out on silica
(eluant: CH₂Cl₂-Me₂CO (97.5-2.5)) and 743 mg of expected
25 product is obtained.

b) Hydrolysis of the tetrahydropyranic ether

743 mg of the product obtained above in 1) is introduced
into 10 ml of methanol, 1.5 ml of 2N hydrochloric acid and
the mixture is taken to 40°C then after 45 minutes is poured
30 into 20 ml of sodium bicarbonate and extracted with
chloroform. The organic phase is washed with salt water,
dried and the solvent is evaporated off under reduced
pressure. Purification is carried out on silica (eluant:
CH₂Cl₂-Me₂CO (9-1)) then the crystals obtained are dissolved
35 in 20 ml of isopropanol at 60°C, followed by filtration,
rinsing and concentrating to about 5 ml, ice-cooling for
about one hour and separating. 466 mg of the expected
product (white crystals) is obtained. M.p. = 146-147°C.



Microanalysis

	C	H	F	N
% calculated	50.15	3.65	21.15	11.70
% found	50.1	3.50	20.9	11.7

5 IR CHCl₃

OH	3612 cm ⁻¹
>=O	1782 (m) - 1727 (f) cm ⁻¹
C≡N	2235 cm ⁻¹

UV EtOH

10 Max	260 nm	ε = 15500
Infl	278 nm	ε = 6700
Infl	286 nm	ε = 3300

EXAMPLE 4: 4-(3,4-dimethyl) 4-(hydroxymethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

15 Stage A: (±) 2-methyl 2-(methylamino) 3-[(tetrahydro 2-H pyran 2-yl) oxy] propanenitrile

1.54 g of methylamine hydrochloride in solution in 10 cm³ of water and 3.35 g of the ketone obtained in Stage A of Example 1 are introduced together and the suspension obtained
20 is agitated for about 10 minutes.

1.06 g of NaCN in solution in 5 cm³ of water is poured into the mixture and agitation is carried out overnight at ambient temperature.

Extraction is carried out with methylene chloride, the
25 extracts are washed with a saturated solution of sodium chloride, dried and the solvent is evaporated off under reduced pressure. 3.72 g of expected product (yellow oil) is obtained, used as it is for the following stage.

IR CHCl₃

30 NH	approx. 3345 cm ⁻¹
C≡N	approx. 2230 cm ⁻¹ .

Stage B: 2-(trifluoromethyl) 4-[5-imino 3,4-dimethyl 4-[[[tetrahydro 2-H-pyran 2-yl) oxy] methyl] 2-thioxo 1-imidazolidinyl] benzonitrile

35 2.38 g of aminonitrile in solution in 8 cm³ of 1,2-dichloroethane is introduced and 0.5 cm³ of triethylamine is added, the mixture is cooled down to a temperature of -5° to 0°C and 2.75 g of the isothiocyanate obtained in the



preparation of Example 11 of the European Patent Application EP 0,494,819 in solution in 17 cm³ of 1,2-dichloroethane is poured in over 20 minutes at a temperature below 0°C. The reaction medium is left to return to ambient temperature and agitation is maintained for about 2 hours, followed by drying and evaporating the solvent under reduced pressure.

After purification on silica (eluant: CH₂Cl₂ - acetone (92-8)), 3.31 g of expected product is obtained.

IR CHCl₃

10	>C=NH	3308 cm ⁻¹
	-C≡N	2236 cm ⁻¹
	>C=N	1679 cm ⁻¹
	>C=S	1614 cm ⁻¹
	Aromatic	1575 cm ⁻¹
15		1505 cm ⁻¹
		1496 cm ⁻¹

Stage C: 4-(3,4-dimethyl) 4-(hydroxymethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

19 cm³ of 2N hydrochloric acid is added drop by drop to 3.25 g of the product obtained in Stage B above, in solution in 35 cm³ of methanol, and the whole is taken to reflux for 35 minutes.

Neutralization is carried out with a solution of sodium bicarbonate, followed by extraction with chloroform, the organic phase is washed with a saturated solution of sodium chloride, dried and the solvent is evaporated off under pressure. After purification on silica (eluant: CH₂Cl₂-ACOEt (85-15), then recrystallization from 10 cm³ of isopropanol, 1.90 g of expected product (white crystals) is obtained.

M.p. = 167°-168°C.

Microanalysis

	C	H	N	F	S
% calculated	48.98	3.52	12.24	16.60	9.34
% found	48.9	3.6	12.1	16.7	9.1

IR CHCl₃

Absence of C=NH

-OH	3620 cm ⁻¹
>C=O	1759 cm ⁻¹



>C≡N	2238 cm ⁻¹
Aromatics	1610 cm ⁻¹
+	1576 cm ⁻¹
conjugated	1505 cm ⁻¹
5 system	1494 cm ⁻¹

EXAMPLE 5: 1,5-dimethyl 5-(hydroxymethyl) 3-(4-nitro 3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione

Stage A: Formation of tetrahydropyranic ether

The operation is carried out as in 1) of Example 2 above, replacing in this preparation the product of Example 1 by 870 mg of the product obtained as in Example 2 of the European Patent Application EP 0,305,270 in 13 ml of tetrahydrofuran, 40 mg of paratoluene sulphonic acid, H₂O, 2.6 ml of dihydropyran. After about 15 minutes, the reaction mixture is poured into 10 ml of a saturated solution of sodium bicarbonate and 1 ml of triethylamine and extracted with chloroform. The organic phase is washed with salt water, dried, the solvent is evaporated off under reduced pressure and purification is carried out on silica (eluant: CH₂Cl₂-MeOH (95-5)) and the expected product is obtained.

Stage B: Methylation of the nitrogen

The operation is carried out as in 2) of Example 2 above, starting from the product obtained in 1) above, and the expected product is obtained.

25 Stage C: Hydrolysis of the tetrahydropyranic ether.

The operation is carried out as in 3) of Example 2 above, starting from 955 mg of the product obtained in 2) above and 698 mg of expected product (white crystals) is obtained. M.p. = 153-154°C.

30 Microanalysis

	C	H	F	N
% calculated	44.96	3.48	16.41	12.10
% found	45.0	3.50	16.3	12.1

IR CHCl₃

35 OH	3620 cm ⁻¹
>C=O	1782 - 1727 cm ⁻¹
Aromatic	1618 - 1596 - 1545 - 1498 cm ⁻¹
and NO ₂ band	



UV EtOH

Infl 214 nm $\epsilon = 13000$

Max 271 nm $\epsilon = 6100$

Infl 320 nm

5 **EXAMPLE 6:** 4-(4-(fluoromethyl) 3,4-dimethyl) 2,5-dioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

0.2 ml of diethylaminosulphide trifluoride, then drop by drop the solution cooled down to -60°C of 0.2 g of the product of Example 2 and 6.5 ml of tetrahydrofuran, are added
10 to 1 ml of tetrahydrofuran, cooled down to about -60°C .

The resultant mixture is left to return to ambient temperature, then heated at 30°C . After one hour, the reaction medium is poured into 18 ml of sodium bicarbonate and extracted with ether. The organic phase is washed with
15 salt water, dried and the solvents are evaporated off under reduced pressure. Purification is carried out on silica (eluant: CH_2Cl_2 -cyclohexane (9-1)) then the crystals obtained are dissolved in 30 ml of isopropanol at 60°C , followed by filtration, rinsing with 2 ml of isopropanol, concentration
20 to about 5 ml and ice-cooling overnight. After separation and drying, 136 mg of expected product (white crystals) is obtained. M.p. = $153-154^{\circ}\text{C}$.

Microanalysis

		C	H	F	N
25	% calculated	51.07	3.37	23.08	12.76
	% found	50.8	3.2	25.0	12.7

IR CHCl_3

$\text{C}\equiv\text{N}$ 2240 cm^{-1}

$>\text{C}=\text{O}$ 1785 - 1733 cm^{-1}

30 Aromatic 1616 - 1575 - 1505 cm^{-1}

UV EtOH

Max 259 nm $\epsilon = 15200$

Infl 278 nm $\epsilon = 5800$

Infl 286 nm $\epsilon = 2900$

35 **EXAMPLE 7:** 4-(3,4-dimethyl) 4-(fluoromethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

2 cm^3 of anhydrous tetrahydrofuran is cooled down to -60°C and drop by drop over about 15 minutes at a temperature



comprised between -60°C and -53°C , 0.88 cm^3 of diethylamino-sulphide trifluoride then 0.930 g of the product of Example 4 in solution in 7 cm^3 of anhydrous tetrahydrofuran are poured in drop by drop. After the reaction medium has returned to ambient temperature, it is maintained for about 30 minutes at about 30°C . It is then poured into 25 cm^3 of a solution of sodium bicarbonate and ice. Extraction is carried out with ether, the ethereal phase is washed with a saturated solution of sodium chloride, dried and the solvents are evaporated off under reduced pressure. After purification on silica (eluant: CH_2Cl_2 -cyclohexane (9-1)) and recrystallization from isopropanol, 1.010 g of expected product (white crystals) is obtained after drying. M.p. = 163°C .

Microanalysis

	C	H	F	N	S
% calculated	48.69	3.21	22.01	12.17	9.28
% found	48.6	3.10	22.2	12.1	9.5

IR CHCl_3

Absence of OH

N $\equiv$ C	approx. 2238 cm^{-1}
>C=O	1762 cm^{-1}
Conjugated syst. +	$1615 - 1580\text{ cm}^{-1}$
Aromatic	$1505 - 1491\text{ cm}^{-1}$

UV EtOH

Max 235 nm	$\epsilon = 19200$
Max 253 nm	$\epsilon = 23000$
Infl 265 nm	$\epsilon = 18300$

EXAMPLE 8: 4-(2,5-dioxo 3-(2-fluoroethyl) 4-(fluoromethyl) 4-methyl 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

1 ml of tetrahydrofuran is cooled down to -50°C and 0.33 ml of diethylaminosulphide trifluoride is added then a solution cooled down beforehand to about -50°C of 360 mg of the product of Example 3 and 4 ml of tetrahydrofuran is added drop by drop. Rinsing is carried out with 0.5 ml of tetrahydrofuran and the medium is left to return to ambient temperature then taken to about 30°C . It is then poured into 30 ml of sodium bicarbonate and 10 g of ice and extracted with chloroform then the organic phase is washed with salt



water and dried. Purification is carried out on silica (eluant: CH_2Cl_2 - ethyl acetate (99-1)) then the crystals obtained are dissolved in 30 ml of isopropanol under reflux, followed by filtration, rinsing with 1 ml of isopropanol, concentration to about 7 ml and leaving at rest for 16 hours at 0°C . After separation and drying, 307 mg of expected product (white crystals) is obtained. M.p. = $137-138^\circ\text{C}$.

Microanalysis

		C	H	F	N
10	% calculated	49.87	3.35	26.29	11.63
	% found	49.8	3.4	26.2	11.6

IR CHCl_3

$\text{C}\equiv\text{N}$ 2235 cm^{-1}

$>=\text{O}$ 1786 - 1730 cm^{-1}

15 Aromatic 1616 - 1575 - 1505 cm^{-1}

UV EtOH

Max 258 nm $\epsilon = 16000$

Infl 277 nm $\epsilon = 5300$

Infl 285 nm $\epsilon = 2700$

20 EXAMPLE 9: 4-(2,4-dioxo 1,3-diazaspiro(4,4)nonan 3-yl) 2-(trifluoromethyl) benzonitrile

Stage A: 1-amino cyclopentanecarbonitrile

40 ml of ammonium hydroxide, 7.9 g of ammonium chloride and 6.14 g of sodium cyanide are introduced together then agitation is carried out until total dissolution in an ice bath at a temperature of -8°C . Then 8.8 ml of cyclopentanone is added drop by drop at a temperature of about -9°C , the reaction medium is left to return to ambient temperature and agitated overnight.

30 The organic phase is then decanted, the aqueous phase is extracted with methylene chloride, then the organic phases are washed with salt water and dried. After distillation at $55^\circ\text{C} \pm 2^\circ\text{C}$, 1.2 g of expected product is obtained.

IR CHCl_3

35 NH_2 3381-3330 cm^{-1}

$\text{C}\equiv\text{N}$ 2226 cm^{-1}

Absence $\text{C}=\text{O}$

Stage B: 2-(trifluoromethyl) 4-[4-imino 2-oxo 1,3-



diazaspiro[4.4]nonan 3-yl] benzonitrile

550 ml of the product obtained in Stage A above, 4 ml of 1,2-dichloroethane and 0.2 ml of triethylamine are introduced together then the mixture is brought to 0°C and 3.1 ml of the product obtained in the preparation of Example 7 of the European Patent Application EP 0,494,819 is added over 5 minutes at a temperature of -4°C and the whole is left to return to ambient temperature.

After about 40 minutes of reaction the medium is concentrated to dryness, the residue is dissolved in 40 ml of acetone, the solvent is evaporated off and purification is carried out on silica (eluant: CH₂Cl₂-Me₂CO (90-10)). 1.24 g of expected product (white crystals) is obtained. M.p. = 212-213°C.

IR nujol

OH/NH	3350-3280 cm ⁻¹
C≡N	2240 cm ⁻¹
C=O	1744 cm ⁻¹
>=N	1670 cm ⁻¹
Aromatic	1610-1574-1510 cm ⁻¹

Stage C: 4-(2,4-dioxo 1,3-diazaspiro(4,4)nonan 3-yl) 2-(trifluoromethyl) benzonitrile

1.17 g of the product obtained in Stage B above in 20 ml of methanol, 3 ml of chloroform and 5 ml of 2N hydrochloric acid are introduced together then taken to about 50°C for about 2 hours.

The mixture is taken to ambient temperature, poured into 40 ml of water and extracted 3 times with methylene chloride. The organic phase is washed with salt water, dried and the solvent is evaporated off under reduced pressure, then purification is carried out on silica (eluant: CH₂Cl₂-Me₂CO (9-1)). 1.108 g of expected product (white crystals) is obtained. M.p. = 184-185°C.

Microanalysis

	C	H	F	N
% calculated	55.73	3.74	17.63	13.00
% found	55.6	3.7	17.4	12.8



IR CHCl₃

=C-NH 3444 cm⁻¹
 C≡N 2236 cm⁻¹
 >=O 1786 - 1731 cm⁻¹

5 Aromatic 1616 - 1505 cm⁻¹

UV EtOH

Max 258 nm ε = 15600
 Infl 286 nm ε = 3500

EXAMPLE 10: 4-(2,4-dioxo 1-(2-fluoroethyl) 1,3-diaza-

10 spiro(4.4)nonan-3-yl) 2-(trifluoromethyl) benzonitrile

0.323 g of the product of Example 9 in solution in 2.5 cm³ of dimethylsulphoxide is poured drop by drop over about 20 minutes into 0.050 g of sodium hydride at 50% in oil. Agitation is carried out for about one hour 20 minutes

15 then 0.09 cm³ of 1-bromo 2-fluoroethane in solution in 0.2 cm³ of dimethylsulphoxide is poured in drop by drop. After about 2 hours at ambient temperature, the reaction medium is heated for 10 minutes at between 30° and 35°C, then poured into 12 cm³ of water containing 0.2 g of monosodium
 20 phosphate and extracted with ether. The ethereal phase is washed with a saturated solution of sodium chloride, dried and evaporated to dryness. Purification is carried out on silica (eluant: CH₂Cl₂ - ethyl acetate (99-1)) and 0.249 g of expected product is obtained. M.p. = 115°C.

25 Microanalysis

	C	H	F	N
% calculated	55.29	4.09	20.58	11.38
% found	55.3	4.1	20.25	11.3

IR CHCl₃

30 -C≡N 2238 cm⁻¹
 -C=O 1776 - 1723 cm⁻¹
 Aromatic 1616 - 1575 - 1505 cm⁻¹

UV EtOH

Max 260 nm ε = 15600
 35 Infl 287 nm

EXAMPLE 11: 1,5-dimethyl 5-(fluoromethyl) 3-(4-nitro 3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione

0.09 ml of diethylaminosulphide trifluoride is added to



1 ml of tetrahydrofuran, cooled down to about -60°C , and drop by drop a solution cooled down to about -60°C of 210 mg of the product of Example 5 and 2.5 ml of tetrahydrofuran is added. The mixture is rinsed with 0.5 ml of tetrahydrofuran, left to return to ambient temperature, taken to a temperature of about -60°C and 0.1 ml of diethylaminosulphide trifluoride is added.

After one hour 20 minutes, the reaction medium is poured into 8 ml of sodium bicarbonate and extracted with ether. The organic phase is washed with salt water, dried, the solvent is evaporated off under reduced pressure and purification is carried out on silica with $\text{CH}_2\text{Cl}_2\text{-Me}_2\text{CO}$ (99-1) as eluant. 152 mg of expected product (white crystals) is obtained. M.p. = $118\text{-}119^{\circ}\text{C}$.

15 Microanalysis

	C	H	F	N
% calculated	44.71	3.17	21.76	12.03
% found	44.9	3.1	21.42	11.9

IR CHCl_3

20 -C=O 1786 - 1732 cm^{-1}
Aromatic and 1618 - 1597 - 1546 - 1498 cm^{-1}

UV EtOH

Inf1 214 nm $\epsilon = 13400$

Max 267 nm $\epsilon = 6200$

25 Inf1 320 nm

EXAMPLE 12: 4-(4,4-dimethyl-2,5-dioxo-3-(2-(2-hydroxyethoxy)ethyl)-1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile

Stage 1: 4-(4,4-dimethyl-2,5-dioxo-3-(2-(2-(((1,1-dimethylethyl) dimethylsilyl) oxy) ethoxy) ethyl)-1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile

The solution of 0.594 g of the product of Example 8 of EP 0,494,819 and 4.5 ml of dimethylsulphoxide are poured drop by drop over 15 minutes into 0.101 g of sodium hydride at 50% in oil and agitation is carried out for 30 minutes after cessation of the release of hydrogen.

0.594 g of (2-(2-bromoethoxy) ethoxy)-dimethyl-(1,1-dimethylethyl) silane in solution in 1 ml of dimethylsulphoxide is poured in drop by drop over 5 minutes.



Agitation is carried out for one hour at ambient temperature then 0.056 g of (2-(2-bromoethoxy) ethoxy)-dimethyl-(1,1-dimethyl-ethyl) silane is added and the whole is maintained for 2 hours 30 minutes between 30° and 40°C.

5 The mixture is poured into 0.6 g of monosodium phosphate and 30 ml of ice-cooled water and extracted with ether.

The ethereal phase is washed with a solution of NaCl, dried and the solvent is evaporated off.

10 After chromatography on silica (eluant: methylene chloride/ethyl acetate 99/1), 0.776 g of expected product (oil) is isolated.

IR CHCl₃ cm⁻¹

Absence of =C-NH

-CN approx. 2235

15

>C=O 1778-1724

$\begin{array}{c} | \\ \text{-O-Si-} \\ | \end{array}$ 838

20 Aromatic 1616-1577-1505

Stage 2: 4-(4,4-dimethyl-2,5-dioxo-3-(2-(2-hydroxyethoxy) ethyl)-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile

0.759 g of the product obtained in Stage 1 above is introduced into 7.5 ml of methanol and 2 ml of 2N

25 hydrochloric acid is added drop by drop.

The mixture is agitated for 40 minutes at ambient temperature, poured into ice-cooled water and extracted with chloroform.

30 The organic phase is washed with a saturated solution of sodium chloride and dried; the solvent is evaporated off then chromatography is carried out on silica (eluant: methylene chloride/acetone 9/1), and 0.549 g of expected product is isolated. M.p. < 60°.

ANALYSES:

35 IR CHCl₃ (cm⁻¹)

Complex -OH towards 3610-3620

-CN approx. 2235

C=O 1779-1725



Aromatics

1616-1575-1505

EXAMPLE 13: 4-(4,4-dimethyl 2,5-dioxo 3-(2-fluoroethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

The solution of 600 mg of the product of Example 8 of
5 the European Patent Application EP 0,494,819 and 5 ml of
dimethylformamide is added drop by drop over about 20 minutes
to 104 ml of 50% sodium hydride. The mixture is rinsed with
0.5 ml of dimethylformamide and after cessation of the
release of hydrogen, 0.16 ml of 1-bromo 2-fluoroethane is
10 added. A further 98 ml of 50% sodium hydride is then added
and after approximately 10 minutes, 0.1 ml of 1-bromo 2-
fluoroethane is added and the whole is heated to 50°C. It is
returned to ambient temperature, poured into 20 ml of water
containing 200 mg of monopotassium phosphate and extracted
15 with ether. The extracts are washed with water then with
salt water, dried, the solvent is evaporated off under
reduced pressure, followed by dissolution in 20 ml of Me₂CO
and purification on silica (eluant CH₂Cl₂ - ethyl acetate
(99-1)). 200 mg of expected product (white crystals) is
20 obtained.

M.p. = 108-109°C.

Microanalysis

	C	H	F	N
% calculated	52.48	3.82	22.14	12.24
25 % found	52.4	3.7	22.00	12.4

IR CHCl₃

C≡N 2236 cm⁻¹

C=O 1780 - 1728 cm⁻¹

Aromatic 1618 - 1580 - 1504 cm⁻¹

30 **EXAMPLE 14:** 4-(4,4-dimethyl 2,5-dioxo 3-(2,2,2-trifluoro-
ethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

0.742 g of the product of Example 8 of the European
Patent Application EP 0,494,819 in solution in 7.5 cm³ of
dimethylsulphoxide is poured over 20 minutes into 0.125 g of
35 sodium hydride at 50% in oil and the resultant mixture is
rinsed with 1 cm³ of dimethylsulphoxide. After the release
of hydrogen is complete, agitation is maintained for about 20
minutes and 0.5 cm³ of iodotrifluoromethane is poured in and



0.5 cm³ of 15-crown-5 ether is added. The mixture is maintained at 60°C for 16 hours. After addition of 0.25 cm³ of iodotrifluoromethane, heating is continued for about 19 hours at 80°C. The reaction medium is then poured into
5 30 cm³ of water + 0.5 g of monosodium phosphate and extracted with ether.

The ethereal phase is washed with a saturated solution of sodium chloride, dried and evaporated to dryness. Purification is carried out on silica (eluant: CH₂Cl₂ - ethyl
10 acetate (99-1)), followed by recrystallization from 10 cm³ of isopropanol and 0.262 g of expected product (white crystals) is obtained. M.p. = 110°C.

Microanalysis

		C	H	F	N
15	% calculated	47.5	2.92	30.05	11.08
	% found	47.3	2.8	30.0	11.0

IR CHCl₃

Absence of N-H

	>C=O	1790 - 1732 cm ⁻¹
20	Aromatic	1616 - 1578 - 1505 cm ⁻¹
	C≡N	2235 cm ⁻¹

UV EtOH

	Max	255 nm	ε = 16400
	Infl	276 nm	ε = 4400
25	Infl	285 nm	ε = 2400

EXAMPLE 15: 4-(4,4-dimethyl 3-(2-fluoroethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Stage A: 4-[3-(2-fluoroethyl) 5-imino 4,4-dimethyl 2-thioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrile

30 1.86 g of 2-[(2-fluoroethyl) amino] 2-methyl propane-nitrile and 0.55 cm³ of triethylamine are introduced into 12 cm³ of 1,2-dichloroethane. The mixture is cooled down to 0°C and 2.97 g of the isothiocyanate obtained as in the preparation of Example 11 of the European Patent Application
35 EP 0,494,819 in solution in 22 cm³ of 1,2-dichloroethane is poured in over about 25 minutes at a temperature of about 0°C. Agitation is continued for 7 hours at ambient temperature then the solvent is evaporated off under reduced



pressure. Purification is carried out on silica (eluant: CH_2Cl_2 - acetone (95-5) then (97-3)), the residue is taken up in a few cm^3 of ether, followed by separating, drying, and 1.84 g of expected product is obtained. M.p. = 160°C .

5 IR CHCl_3

C=NH 3308 cm^{-1}
C≡N 2236 cm^{-1}
Conjugated system 1677 cm^{-1}
+ 1604 cm^{-1}

10 aromatics 1576 - 1504 cm^{-1}

Stage B: 4-(4,4-dimethyl 3-(2-fluoroethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

6.9 cm^3 of 2N hydrochloric acid is added drop by drop to 1.65 g of the product obtained in Stage A above, in solution
15 in 60 cm^3 of methanol. After about one hour 30 minutes at 50°C , the mixture is neutralized with sodium bicarbonate and the methanol is distilled off. The residue is taken up in water, followed by extraction with ether, the ethereal phase is washed with a solution of sodium chloride and dried.

20 After purification on silica with CH_2Cl_2 as eluant and recrystallization from 15 cm^3 of isopropanol, 2.99 g of expected product (white crystals) is obtained. M.p. = 135°C

Microanalysis

		C	H	F	N	S
25	% calculated	50.14	3.65	21.15	11.69	8.92
	% found	50.1	3.60	21.0	11.7	9.2

IR CHCl_3

Absence of =C-NH

>C=O 1758 cm^{-1}
30 N≡C 2236 cm^{-1}
Conjugated syst. 1610 cm^{-1}
+ 1576 cm^{-1}
Aromatic 1504 cm^{-1}

UV EtOH

35 Max 233 nm $\epsilon = 17700$
Max 253 nm $\epsilon = 21600$

EXAMPLE 16: 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 5-(hydroxymethyl) 5-methyl 1-imidazolidinacetonitrile



The operation is carried out as in Example 2, starting with the product of Example 1, replacing the iodomethyl in 2) of Example 2 with bromocyanomethyl and in this way the expected product is obtained. M.p. = 171°C.

5 EXAMPLE 17: 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 5-(fluoromethyl) 5-methyl 1-imidazolidinacetonitrile

The operation is carried out as for the preparation of Example 6, replacing the product of Example 2 with the product of Example 16 and in this way the expected product is
10 obtained. M.p. = 175°C.

EXAMPLE 18: (+) 4-[2-oxo 5-imino [[[4-fluorophenyl) thio] methyl] 4-methyl 1-imidazolidinyl 2-trifluoromethyl benzonitrile

Stage A: (+) 3-[(4-fluorophenyl) thio] 2-amino 2-methyl
15 propane nitrile

A solution of 4.81 g of ammonium chloride in 12 ml of water and 24.6 ml of 25°Be ammonium hydroxide then a solution of 8.32 g of 1-[4-fluorophenylthio] 2-propanone prepared as indicated in the Patent 82 46399 E, in 21 ml of ethanol at
20 96.2%, are added successively to 2.21 g of sodium cyanide in 45 ml of water. The resultant mixture is maintained at 60°C and agitated for about 22 hours. It is cooled down to 0°C/+4°C, rinsed with ethanol, distilled, decanted, the aqueous phase is extracted with CH₂Cl₂, washed with a
25 saturated solution of sodium chloride, dried and the solvent is evaporated off under reduced pressure. Purification is carried out by chromatography on silica with cyclohexane - ethyl acetate (50-50) as eluant and 14.50 g of expected product is obtained.

30 IR CHCl₃

Absorption NM 3382 - 3327 cm⁻¹

Aromatic 1591 - 1491 cm⁻¹

-C≡N 2228 cm⁻¹

Stage B: (+) 4-[2-oxo 5-imino [[[4-fluorophenyl) thio] methyl] 4-methyl 1-imidazolidinyl 2-trifluoromethyl
35 benzonitrile

9.8 g of the product obtained in Stage A above and 35 ml of 1,2-dichloroethane are mixed together, and 0.2 ml of



triethylamine is added. The mixture is cooled down to 5°C and the solution of 7.7 g of the product obtained in the preparation of Example 7 of the European Patent Application EP 0,494,819 and 40 ml of 1,2-dichloroethane is introduced
5 over 12 minutes at a temperature between 5°C and 10°C.

The reaction medium is rinsed with 5 ml of dichloroethane and left for 16 hours at ambient temperature. The solvent is evaporated off under reduced pressure, the residue is purified on silica (eluant: CH₂Cl₂-Me₂CO (93-7)),
10 then dissolved in 100 ml of isopropanol at about 60°C, followed by filtration, rinsing with 20 ml of hot isopropanol, concentration, ice-cooling for about 3 hours, separation, rinsing with ice-cooled isopropanol and drying. 2.815 g of expected product (white crystals) is obtained,
15 M.p. = 150°C.

Microanalysis

	C	H	F	N	S
% calculated	54.03	3.34	17.99	13.26	7.59
% found	54.1	3.30	17.9	13.1	7.7
20 <u>IR</u> CHCl ₃					
C=O	1756 cm ⁻¹				
C=N	1669 cm ⁻¹				
NH	3444 cm ⁻¹				
Aromatic	1614 - 1591 - 1505 - 1491 cm ⁻¹				
25 C≡N exists					

EXAMPLE 19: 4-[2,5-dioxo 4-[[(4-fluorophenyl) thio] methyl] 4-methyl 1-imidazolidinyl] 2-trifluoromethyl benzonitrile

3.95 g of the product obtained in Example 18, 14 ml of 22°Be hydrochloric acid and 14 ml of water are introduced
30 together and the suspension is heated under reflux.

After about one hour 30 minutes, the suspension is returned to ambient temperature, poured over ice + water 100 g (1-1) and extracted with ethyl acetate. The organic phase is washed with water, then with a saturated solution of
35 sodium bicarbonate, and finally with a saturated solution of sodium chloride and the solvent is evaporated off.

Purification is carried out by chromatography on silica (eluant: CH₂Cl₂ - Me₂CO (95-5)). The residue is taken up in



50 ml of ethanol 100 at 50°C, followed by filtration, rinsing with 5 ml of hot ethanol, concentration and leaving for 16 hours in a refrigerator at about 0° to +4°C.

After separation, the product is rinsed with ice-cooled ethanol and dried. 3.55 g of expected product (white crystals) is obtained. M.p. = 153°C.

Microanalysis

	C	H	F	N	S
% calculated	53.9	3.09	17.95	9.92	7.57
10 % found	53.9	3.1	18.3	9.8	7.8

IR CHCl₃

C=O	1791 - 1734 cm ⁻¹
NH	3439 cm ⁻¹
C=N	2236 cm ⁻¹
15 Aromatics	1615 - 1591 - 1505 - 1492 cm ⁻¹

EXAMPLE 20: 4-(2,5-dioxo 3-(2-fluoroethyl) 4-((4-fluorophenyl) thiomethyl) 4-methyl 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile

The solution of 0.254 g of the product obtained as in Example 19 in 2.2 cm³ of dimethylsulphoxide is poured drop by drop over about 10 minutes onto 0.031 g of sodium hydride at 50% in oil. Agitation is maintained for about 40 minutes. Then the solution of 0.54 cm³ of 1-bromo 2-fluoroethane in 0.7 cm³ of dimethyl-sulphoxide is added drop by drop over about 5 minutes.

After agitation for 30 minutes, the reaction medium is poured onto 0.4 g of monosodium phosphate, water + ice. Extraction is carried out with ether, the organic phase is washed with a saturated solution of sodium chloride, dried and the solvent is evaporated off under reduced pressure. After purification on silica (eluant: CH₂Cl₂ - ethyl acetate (100- 0.5)) then recrystallization from 15 cm³ of isopropanol, 0.175 g of expected product (white crystals) is obtained.

M.p. = 155°C.

Microanalysis

	C	H	F	N	S
% calculated	53.73	3.43	20.23	8.95	6.83



% found 53.5 3.2 20.5 9.0 7.1

IR CHCl₃

Absence of =C-NH

C≡N approx. 2235 cm⁻¹

5 >C=O 1780 - 1727 cm⁻¹

Aromatics 1616 - 1591 - 1505 - 1492 cm⁻¹

UV EtOH

Max 255 nm ε = 18600

Infl 278 nm ε = 8000

10 Infl 287 nm ε = 4400

EXAMPLE 21: 4-(4,4-bis(hydroxymethyl) 3-methyl 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Stage A: 2-(methylamino) 2-[[[(tetrahydro 2-H-pyranl 2-yl) oxy] methyl] 3-(tetrahydro 2H-pyran 2-yl) oxy propanenitrile

15 2.7 g of 1,3-bis[(tetrahydro 2H-pyran-2-yl) oxy] 2-propanone obtained as below, 5 ml of water and 0.77 g of methylamine hydrochloride are introduced together then 503 mg of sodium cyanide and 3 ml of water are added over 5 minutes. After 2 hours 30 minutes of reaction, extraction is carried
20 out with methylene chloride, the organic phase is washed with salt water, the solvent is evaporated off under reduced pressure. 3.3 g of expected product is obtained, used as it is for the following stage.

IR CHCl₃

25 NH 3346 cm⁻¹

C≡N 2230 cm⁻¹

C=O 1732 cm⁻¹

Preparation of 1,3-bis-[(tetrahydro 2H-pyran 2-yl) oxy] 2-propanone used at the start of Example 21

30 9 g of 1,3-dihydroxyacetone dimer in suspension in 60 ml of dioxane is heated to 70°C and returned to ambient temperature. 20 ml of 3,4-dihydro 2,4-pyran then 300 mg of paratoluene sulphonic acid and H₂O are added, while maintaining the temperature below 40°C. The reaction medium
35 is maintained for 16 hours under agitation, poured into 300 ml of a saturated solution of sodium bicarbonate, the organic phase is washed with salt water, dried and the solvent is evaporated off under reduced pressure. After chromato-



graphing the residue on silica (eluant: cyclohexane - ethyl acetate - triethylamine (8-2-0.5), 17 g of expected product is obtained. RF = 0.2.

5 Stage B: 2-(trifluoromethyl) 4-[4,4-bis-[[tetrahydro 2-H-pyran 2-yl) oxy] methyl] 5-imino 3-methyl 2-thioxo 1-imidazolidinyl] benzonitrile

2.39 g of the isothiocyanate obtained in the preparation of Example 11 of the European Patent Application EP 0,494,819 and 10 ml of 1,2-dichloroethane are mixed together. Then
10 3.2 g of the product obtained in Stage A above, 0.4 ml of triethylamine and 10 ml of 1,2-dichloroethane are added drop by drop to the solution cooled down to +5°C. After heating for about one hour 20 minutes, the solvent is evaporated off and purification is carried out on silica (eluant: ethyl
15 acetate 7 cyclohexane 3). 3.82 g of the expected product is obtained.

IR CHCl₃

>C=NH	3314 cm ⁻¹
C≡N	2230 cm ⁻¹
20 C=N	1678 - 1670 - 1876
C=S	1505 - 1495 cm ⁻¹

Aromatics

Stage C: 4-(4,4-bis(hydroxymethyl) 3-methyl 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

25 3.8 g of the product obtained in Stage B above is introduced into 38 ml of methanol and 19 ml of 2N hydrochloric acid, then the mixture is heated under reflux. After about 2 hours, it is poured into 200 ml of water and extracted with ether then with ethyl acetate. The organic
30 phases are united and washed with salt water then the solvent is evaporated off. Purification is carried out on silica (eluant: CH₂Cl₂-MeOH (95-5)) then the product is dissolved in 30 ml of isopropyl ether under reflux, followed by filtration and partial concentration. After ice-cooling for about one
35 hour and separating, 282 mg of expected product (yellow crystals) is obtained. M.p. = 169-170°C.



Microanalysis

	C	H	F	N	S
% calculated	46.80	3.37	15.86	11.69	8.92
% found	46.8	3.3	15.9	11.5	9.0

5 IR Nujol

OH/NH	3410 - 3385 cm^{-1}
C $\equiv$ N	2240 cm^{-1}
C=O	1720 cm^{-1}
Aromatics	1608 - 1580 - 1568 cm^{-1}

10 UV EtOH

Max 234 nm $\epsilon = 17600$

Max 256 nm $\epsilon = 23200$

EXAMPLE 22: 4-(4,4-bis(1-oxopropoxy) methyl) 3-methyl 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

- 15 200 mg of the product of Example 21 is introduced into 2 ml of pyridine and 25 mg of 4-dimethylamino pyridine then 16 ml of propionic anhydride is added. After reaction for 25 minutes, the mixture is poured into 20 ml of sodium bicarbonate and extracted with methylene chloride, the
- 20 organic phase is washed with salt water, dried, the solvent is evaporated off and distillation is carried out 3 times with 30 ml of toluene. Purification is carried out on silica (eluant: CH_2Cl_2), then crystallization from ether and 239 mg of expected product (white crystals) is obtained. M.p. =
- 25 117-118°C.

Microanalysis

	C	H	F	N	S
% calculated	50.95	4.27	12.09	8.91	6.80
% found	51.2	4.5	12.1	8.8	6.9

30 IR CHCl_3

>C=O	1755 - 1762 cm^{-1}
C $\equiv$ N	2235 cm^{-1}
Aromatics and C=S	1615 - 1580 - 1504 - 1488 cm^{-1}

UV EtOH

- 35 Infl 236 nm $\epsilon = 18800$
- Max 253 nm $\epsilon = 22600$
- Infl 265 nm $\epsilon = 18200$

EXAMPLE 23: 4-(4,4-bis(fluoromethyl) 3-methyl 5-oxo 2-thioxo



1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

1 ml of tetrahydrofuran is cooled down to -50°C and 0.66 ml of diethylaminosulphide trifluoride is added then the solution, cooled down to a temperature of about -50°C , of 5 360 mg of the product of Example 21 in 4 ml of tetrahydrofuran is added drop by drop. The resultant mixture is heated to a temperature of about 30°C .

After about 30 minutes, the resultant mixture is poured drop by drop into 50 ml of a saturated aqueous solution of 10 sodium bicarbonate, extraction is carried out with chloroform, the organic phase is washed with salt water and the solvent is evaporated off. Purification is carried out on silica with CH_2Cl_2 -cyclohexane (9-1) as eluant then the product is dissolved in 20 ml of isopropanol at a temperature 15 of about 60°C . Filtration is carried out, followed by rinsing with 1 ml of isopropanol and concentration, ice-cooling for one hour and separating. 314 mg of expected product (white crystals) is obtained. M.p. = $122-123^{\circ}\text{C}$.

Microanalysis

20		C	H	F	N	S
	% calculated	46.28	2.77	26.15	11.56	8.82
	% found	46.3	2.7	25.7	11.25	8.8

IR CHCl_3

	$\text{C}\equiv\text{N}$	2236 cm^{-1}
25	$\text{C}=\text{O}$	1763 cm^{-1}
	Aromatics	$1615 - 1580 - 1504 - 1487\text{ cm}^{-1}$

UV EtOH

	Inf1	237 nm	$\epsilon = 20300$
	Max	250 nm	$\epsilon = 22000$
30	Inf1	266 nm	$\epsilon = 17100$

EXAMPLE 24: 4-(4,4-bis(hydroxymethyl) 3-methyl 2,5-dioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

1) Formation of the tetrahydropyranic ethers

360 mg of the product of Example 21 is introduced into 35 5 ml of tetrahydrofuran, 1 ml of 3,4-dihydro 2H pyran, and 15 mg of paratoluene sulphonic acid, H_2O .

After about 40 minutes, 10 ml of a saturated aqueous solution of sodium bicarbonate and 1 ml of triethylamine are



poured into the mixture, extraction is carried out with chloroform, the extracts are washed with salt water, dried and the solvent is evaporated off.

Purification is carried out on silica (eluant: CH_2Cl_2 -
5 MeOH (93-7)) and 600 mg of expected product is obtained, used as it is for the following stage.

2) Transition to hydantoin

600 mg of the diether obtained in 1) is introduced into 4 ml of dimethylformamide and 55 mg of 50% sodium hydride is
10 added, then after cessation of the release of hydrogen, 0.09 ml of methyl iodide is added. About 40 minutes afterwards, 110 mg of 50% sodium hydride, then 10 minutes afterwards 0.18 ml of methyl iodide are successively added. The reaction mixture is poured into 10 ml of ice-cooled water
15 containing 1.3 g of monopotassium phosphate and extraction is carried out with ether. The organic phase is washed with salt water, dried and the solvent is evaporated off.

Purification is carried out on silica (eluant: CH_2Cl_2 - ethyl acetate (92.5-7.5)) and 370 mg of expected product is
20 obtained, used as it is for the following stage.

3) Deprotection of the pyranic ethers

370 mg of the product obtained above in 2) is introduced into 4 ml of methanol and 2 ml of 2N hydrochloric acid then the solution is taken to 60°C for about 2 hours.

25 The solution is then poured into 15 ml of salt water, drying is carried out, the solvent is evaporated off then the residue is dissolved in 20 ml of acetone and evaporated to dryness. Purification is carried out on silica (eluant: CH_2Cl_2 -MeOH (92.5-7.5)) followed by recrystallization from
30 acetone and 197 mg of expected product (white crystals) is obtained, M.p. = 217-218°C.

UV EtOH

Max 263 nm ϵ = 14600

Infl 237, 278, 287 nm

35 EXAMPLE 25: 4-(4,4-bis(hydroxymethyl) 3-methyl 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

The operation is carried out as in Example 21 and at Stage C of the preparation of Example 21, 421 mg of expected



product is obtained.

IR

C≡N 2230 cm⁻¹

C=N, C=S 1680 - 1614 - 1580 - 1510 cm⁻¹

5 Aromatics

EXAMPLE 26: 4-(4,4-bis(hydroxymethyl)-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile

Stage 1: 1,3 bis [(tetrahydro 2H pyran-2 yl) oxy] 2 propanone

9 g of 2,5-dihydroxy 1,4-dioxane 2,5-dimethanol is
10 introduced into 60 ml of dioxane and the suspension is taken
to about 70°C for 15 minutes then returned to ambient
temperature. 20 ml of 3,4-dihydro 2H-pyran and 300 mg of
monohydrated paratoluene sulphonic acid are then added and
the temperature is maintained at about 40°C then the medium
15 is left for 16 hours at ambient temperature.

The medium is then poured into a mixture of 300 ml of a
saturated solution of sodium bicarbonate + 10 ml of
triethylamine and extraction is carried out with methylene
chloride. The organic phase is washed with salt water, dried
20 and the solvent is evaporated off.

After chromatography on silica (eluant: ethyl
cycloacetate/triethylamine 8/2), 17 g of expected product is
obtained (pale yellow syrup).

ANALYSES:

25 IR CHCl₃ (cm⁻¹)

Absence of OH

O=C 1736

Stage 2: 2-amino 3-(((tetrahydro-2H-pyran-2-yl) oxy) 2-
(((tetrahydro-2H-pyran-2-yl) oxy) methyl) propanenitrile

30 5.6 g of the product obtained in Stage 1 above is
introduced into 8 ml of ammonium hydroxide, the mixture is
taken to about -5°C and 1.58 g of ammonium chloride and
1.23 g of sodium cyanide are added successively and the
resultant mixture is left to rise to ambient temperature over
35 about 40 minutes then heated at 40°C ± 5°C under agitation
for 16 hours. It is returned to ambient temperature and
extracted with chloroform, the organic phase is washed with
salt water, dried and the solvent is evaporated off.



After chromatography on silica (eluant: ethyl cycloacetate/triethylamine 3/7), 4.41 g of expected product (pale yellow syrup) is obtained.

ANALYSES:

5 IR CHCl₃ (cm⁻¹)

-CN 2235

NH₂ 3390-3317

Stage 3: 4-(5-imino-2-oxo-4,4-bis(((tetrahydro-2H-pyran-2-yl) oxy) methyl) 1-imidazolidinyl) 2-(trifluoromethyl)

10 benzonitrile

570 mg of the product obtained in Stage 2 above is introduced into 5 ml of isopropyl ether and 0.28 ml of triethylamine and the mixture is taken to -30°C then 2.32 g of a solution of the product obtained in the preparation of
15 Example 7 of the European Patent Application EP 0,494,819 at 18.4% in 1,2-dichloroethane is added over one hour.

4 ml of methylene chloride is added then the reaction medium is left to return to ambient temperature, left for about 2 hours and the solvent is evaporated off. After
20 purification on silica (eluant: methylene chloride/acetone 9/1), 700 mg of expected product is obtained.

ANALYSES:

IR CHCl₃ (cm⁻¹)

NH 3442-3317

25 -CN 2235

C=O 1757

C=N 1670

Aromatic 1614-1575-1505

Stage 4: 4-(4,4-bis(hydroxymethyl)-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile
30

300 mg of the product obtained in Stage 3 above is introduced into 3 ml of methanol and 0.5 ml of 2N hydrochloric acid and the mixture is taken to reflux for one hour 30 minutes.

35 It is returned to ambient temperature, poured into 5 ml of an aqueous solution of sodium bicarbonate, extracted with ethyl acetate then the extracts are washed with a saturated aqueous solution of sodium chloride, dried and the solvent is



evaporated off.

5 ml of methanol is added and purification is carried out on silica (eluant: methylene chloride - methanol 9/1).

The product is taken up in 20 ml of isopropanol under reflux then concentration is carried out and 225 mg of expected product (white crystals) is obtained, M.p. = 207-208°C.

ANALYSES:

IR NUJOL

10 OH/NH 3525-3365-3250 cm^{-1}
CN 2240 cm^{-1}
C=O 1778-1738 cm^{-1}
Aromatic 1618-1578-1506 cm^{-1}

EXAMPLE 27: 4-(4,4-bis(fluoromethyl) 2,5-dioxo 3-methyl 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

The operation is carried out as indicated in Example 23 using 120 mg of the product obtained in Example 24. After chromatography on silica (eluant: CH_2Cl_2 - ethyl acetate 99-1), 111 mg of expected product is obtained. M.p. = 137-138°C.

ANALYSES:

IR CHCl_3

C $\equiv$ N 2235 cm^{-1}
C=O 1790-1735 cm^{-1}
25 Aromatic 1617-1580-1505 cm^{-1}

EXAMPLE 28: 4-(2,5-dioxo 3-ethyl 4-(hydroxymethyl 4-methyl 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

The operation is carried out as indicated in Example 2, Stages 2 and 3, using 1.033 g of the tetrahydropyranic ether prepared in Stage 1 and 0.24 ml of ethyl iodide. After chromatography on silica (eluant: methylene chloride - ethyl acetate), 0.796 g of expected product is obtained which is recrystallized from isopropanol. M.p. = 138°C.

ANALYSES:

35 IR CHCl_3

OH 3616 cm^{-1}
C $\equiv$ N 2236 cm^{-1}
C=O 1779 (m) -1725 (F) cm^{-1}



Aromatic 1617-1506 cm^{-1}

EXAMPLE 29: 3-(2,5-dioxo 3-ethyl 4-methyl 4-(2-methyl 1-oxopropoxy) methyl 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

5 The operation is carried out as in Example 22 using 280 mg of product obtained in Example 28, 2.5 ml of pyridine, 23 mg of dimethylaminopyridine and 0.16 ml of isobutyric anhydride. After extraction with ether, elimination of the solvents and chromatography on silica (eluant: methylene
10 chloride - ethyl acetate 100-1), 321 mg of expected product is obtained.

M.p. = 85°C.

ANALYSES:

IR CHCl_3

15 $\text{C}\equiv\text{N}$ 2235 cm^{-1}
 $\text{C}=\text{O}$ 1781 (m)-1728 (F) cm^{-1}
Aromatic 1615 - 1575-1505 cm^{-1}

EXAMPLE 30: Carbonate of (1-(4-cyano 3-(trifluoromethyl) phenyl) 2,5-dioxo 3-ethyl 4-methyl 4-imidazolidinyl) methyl
20 and of 1-methylethyl

The operation is carried out as in Example 22 using 376 mg of the product obtained in Example 28, 3.8 ml of pyridine, 25 mg of dimethylaminopyridine, and 2.2 ml of a toluene solution of isopropyl chloroformate (1M/l) is added
25 at 0°C. After agitation for 30 minutes at 0°C then for 3 hours at ambient temperature, 0.4 ml of the isopropyl chloroformate solution is added and agitation is continued at ambient temperature for 2 hours 30 minutes. The reaction medium is poured into 20 g of ice-cooled water, extracted
30 with ether, the organic solution is washed with salt water, dried and the solvents are eliminated under reduced pressure. The residue is taken up in toluene, concentrated to dryness, the oil formed is left to crystallize and 422 mg of crude product is obtained which is chromatographed on silica
35 (eluant: methylene chloride - ethyl acetate 100-2). 270 mg of expected product is obtained. M.p. = 123°C.



ANALYSES:

IR CHCl₃

C≡N 2235 cm⁻¹

C=O 1782-1744-1729 cm⁻¹

5 Aromatic 1616-1578-1505 cm⁻¹

EXAMPLE 31: 4-(4,4-bis(hydroxymethyl) 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-trifluoromethyl) benzonitrile.

1) Formation of the tetrahydropyranic ethers.

10 The operation is carried out as in Example 24 Stage 1, using 331 mg of the product obtained in Example 26.

Extraction is carried out with methylene chloride, the extracts are washed with salt water, dried, the solvent is evaporated off and, after chromatography on silica (eluant:

15 CH₂Cl₂-MeOH 9-1), 500 mg of expected product is obtained, used as it is for the following stage.

2) Hydroxyalkylation.

456 mg of the diether obtained above in 3 ml of dimethylsulphoxide is added drop by drop over 20 minutes to
20 52 mg of sodium hydride then 20 minutes after cessation of the release of hydrogen, 374 mg of trimethylsilyl-4-iodo-butanol is added. After 40 minutes of reaction, the medium is poured into 20 ml of water, extracted with ether, the organic phase is washed with salt water, dried and the
25 solvent is evaporated off. 650 mg of crude product is obtained which is used as it is for the following stage.

3) Hydrolysis of the protective groups.

650 mg of the product obtained above is introduced into 7 ml of methanol and 3 ml of 2N hydrochloric acid then the
30 solution is taken to 40°C for about 40 minutes. It is poured into 20 ml of an aqueous solution of sodium bicarbonate, extracted with ethyl acetate, the extracts are washed with salt water, dried, the solvent is evaporated off. Purification is carried out on silica (eluant: CH₂Cl₂-MeOH 9-
35 1) and 950 mg of expected product is obtained.

ANALYSES:

UV EtOH

Max. 237 nm ϵ = 8600



Max. 263 nm ϵ = 14000

Infl. 278 nm ϵ = 8400

Infl. 287 nm ϵ = 4200

EXAMPLE 32: 4-(4,4-bis(hydroxymethyl) 2,5-dioxo 3-(2-fluoroethyl) 1-imidazolidinyl) 2-trifluoromethyl) benzonitrile.

1) Fluoroalkylation.

The operation is carried out as in Example 3 Stage a, starting with 5 g of the tetrahydropyranic diether prepared as indicated in Example 31 Stage 1, and 1.1 ml of 2-bromo 1-fluoroethane. 5.31 g of expected product is obtained.

2) Hydrolysis of the tetrahydropyranic ether.

The operation is carried out as in Example 3 Stage b starting with 550 mg of the product obtained above, 6 ml of methanol and 2 ml of 2N hydrochloric acid. After chromatography on silica (eluant: CH_2Cl_2 - Me_2CO 8-2), 351 mg of expected product is obtained. M.p. = 138-139°C.

ANALYSES:

IR NUJOL

OH/NH 3580-3505 cm^{-1}
C $\equiv$ N 2245 cm^{-1}
C=O 1778-1716 cm^{-1}
Aromatic 1616-1580-1512 cm^{-1}

UV EtOH

Max. 260 nm ϵ = 15300
Infl. 280 nm ϵ = 3400

EXAMPLE 33: 4-(4,4-bis(fluoromethyl) 2,5-dioxo 3-(2-fluoroethyl) 1-imidazolidinyl) 2-trifluoromethyl) benzonitrile.

1 ml of tetrahydrofuran is cooled down to -50°C under an inert atmosphere and 0.66 ml of diethylamino sulphide trifluoride is added drop by drop, then 375 mg of the product obtained in Example 32 in 4 ml of tetrahydrofuran is added over 5 minutes. The reaction medium is left to return to ambient temperature, maintained under agitation for one hour, poured into an ice-cooled aqueous solution of sodium bicarbonate, extraction is carried out with chloroform, the organic phase is washed with salt water, dried, the solvent



is evaporated off, the residue is chromatographed on silica (eluant: CH_2Cl_2 - cyclohexane 9-1) and 337 mg of expected product is obtained. M.p. = $136-137^\circ\text{C}$.

ANALYSES:

5 IR CHCl_3

$\text{C}\equiv\text{N}$ 2235 cm^{-1}
 $\text{C}=\text{O}$ 1787-1736 cm^{-1}
Aromatic 1617-1577-1505 cm^{-1}

EXAMPLE 34: 4-(4,4-bis(2-methyl 1-oxopropoxy) methyl) 2,5-dioxo 3-(2-fluoroethyl) 1-imidazolidinyl) 2-trifluoromethyl) benzonitrile.

0.5 ml of isobutyric anhydride is added under an inert atmosphere to a solution containing 375 mg of the product obtained in Example 32, 4 ml of pyridine and 122 mg of dimethylamino-pyridine. Agitation is carried out for 30 minutes, the reaction medium is poured into 20 ml of a 50% aqueous solution of sodium bicarbonate, followed by drying and evaporating the solvent under reduced pressure. The residue is chromatographed on silica (eluant: CH_2Cl_2 -AcOEt 95-5) and 457 mg of expected product is obtained. M.p. = $71-72^\circ\text{C}$.

ANALYSES:

IR CHCl_3

$\text{C}\equiv\text{N}$ 2236 cm^{-1}
25 $\text{C}=\text{O}$ 1789-1733 cm^{-1}
Aromatic 1616-150 cm^{-1}

UV EtOH

Max. 257 nm $\epsilon = 17000$
Infl. 285 nm $\epsilon = 2600$

30 EXAMPLE 35: Carbonate of bis (1-methylethyl) and (3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 1-(2-fluoroethyl) 5-imidazolidinyl) bis (methylene) and $\pm$ racemic of carbonate of (3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 1-(2-fluoroethyl) 5-(hydroxymethyl) 5-imidazolidinyl) methyl and
35 of 1-methylethyl

375 mg of the product obtained in Example 32 in 4 ml of pyridine and 122 mg of 4-dimethylaminopyridine is cooled down to -4°C under an argon atmosphere. 550 mg of isopropyl



chloroformate is added drop by drop at -4°C . The reaction medium is left to return to ambient temperature, agitation is continued for 2 hours. The reaction being incomplete, 122 mg of dimethylaminopyridine and 2 ml of isopropyl

5 chloroformate are added and the mixture is heated for 18 hours at 50°C . It is returned to ambient temperature, poured into salt water, extraction is carried out with ethyl acetate, the extracts are dried, the solvents are eliminated, and 570 mg of crude product is obtained which is purified by

10 chromatography on silica (eluant: CH_2Cl_2 -AcOEt 95-5), in order to obtain 275 mg of dicarbonate (M.p. = $122-123^{\circ}\text{C}$) then (eluant: CH_2Cl_2 - Me_2CO 9-1), in order to obtain 156 mg of monocarbonate (M.p. = $154-155^{\circ}\text{C}$).

ANALYSES:

15 . Dicarbonate

IR CHCl_3

$\text{C}\equiv\text{N}$ 2238 cm^{-1}
 $\text{C}=\text{O}$ 1789-1749-1734 cm^{-1}
Aromatic 1615-1578-1505 cm^{-1}

20 UV EtOH

Max. 256 nm $\epsilon = 15400$
Infl. 285 nm $\epsilon = 2500$

. Monocarbonate

IR (Nujol)

25 OH/NH 3450 cm^{-1}
 $\text{C}\equiv\text{N}$ 2250 cm^{-1}
 $\text{C}=\text{O}$ 1789-1736 cm^{-1}
Aromatic 1616-1576-1506 cm^{-1}

EXAMPLE 36: Carbonate of bis (2-methylpropyl) and of (3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 1-(2-fluoroethyl) 5-imidazolidinyl) bis (methylene)

30

375 mg of the product obtained in Example 32 in 4 ml of pyridine and 122 mg of 4-dimethylaminopyridine is cooled down to -4°C under an argon atmosphere. 550 mg of isobutyl

35 chloroformate is added drop by drop at -4°C . The medium is left to return to ambient temperature. After 40 minutes, the reaction medium is poured into water, washed with salt water, dried and the solvents are eliminated, the residue is



chromatographed on silica (eluant: CH₂Cl₂-AcOEt 92.5-7.5) and 476 mg of expected product is obtained. M.p. = 109-110°C.

ANALYSES:

IR CHCl₃

5 C≡N 2236 cm⁻¹
C=O 1790-1754-1734 cm⁻¹
Aromatic 1615-1578-1505 cm⁻¹

UV EtOH

Max. 256 nm ε = 15500
10 Infl. 285 nm ε = 2700

EXAMPLE 37:

Tablets were prepared having the following composition:

- Product of Example 3 100 mg
- Excipient s.q. for a tablet made up to 300 mg
- 15 (Detail of the excipient: lactose, starch, talc, magnesium stearate).

EXAMPLE 38:

Tablets were prepared having the following composition:

- Product of Example 26 100 mg
- 20 - Excipient s.q. for a tablet made up to 300 mg
- (Detail of the excipient: lactose, starch, talc, magnesium stearate).

PHARMACOLOGICAL STUDY OF THE PRODUCTS OF THE INVENTION

25

1) Study of the affinity of the products of the invention for the androgen receptor

Male Sprague Dawley EOPS rats weighing 180-200 g, castrated 24 hours previously, are sacrificed, the prostates
30 are removed, weighed and homogenized at 0°C using a Potter glass, in a buffered solution (10mM Tris, 0.25M saccharose, 0.1mM PMSF (phenylmethanesulphonylfluoride), 20mM sodium molybdate, HCl pH 7.4) to which is added extemporaneously 2mM of DTT (DL dithiothreitol), at the rate of 1 g of tissue per
35 8 ml of buffer.

The homogenate is then ultracentrifuged at 0°C, for 30 minutes at 209,000 g. Aliquots of the supernatant obtained (=cytosol), are incubated for 30 minutes and 24 hours at 0°C,



with a constant concentration (T) of tritiated testosterone and in the presence of increasing concentrations (0 to $2500 \cdot 10^{-9}M$), either of unlabelled testosterone, or of the products under test. The concentration of bound tritiated testosterone (B) is then measured in each incubate by the method of adsorption with carbon-dextran.

Calculation of the relative bond affinity (RBA).

The following 2 curves are drawn: the percentage of the bound tritiated hormone B/T as a function of the logarithm of the concentration of the unlabelled reference hormone and B/T as a function of the logarithm of the concentration of the unlabelled product tested. The straight line of the equation $I_{50} = (B/T_{max} + B/T_{min})/2$ is determined.

B/T_{max} = % of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T).

B/T_{min} = % of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T) in the presence of a large excess of unlabelled hormone ($2500 \cdot 10^{-9}M$).

The intersections of the straight line I_{50} and the curves enable the concentrations of the unlabelled reference hormone (CH) and of the unlabelled tested product (CX) which inhibit by 50% the binding of the tritiated hormone on the receptor to be evaluated. The relative bond affinity (RBA) of the tested product is determined by the equation $RBA = 100 (CH)/(CX)$.

The following results, expressed in RBA, are obtained.
Reference product (Testosterone): 100

Product of Examples	Incubation : 24 hours
3	6
6	16
26	4



2) Determination of the androgen or anti-androgen activity of the products of the invention using dosage of ornithine decarboxylase (ODC).

- Treatment protocol

5 6-week old male SWISS mice, castrated 24 hours previously, receive, by oral or percutaneous route, the products being studied (suspension in methyl cellulose at 0.5% or in solution in ethanol), simultaneously with a sub-cutaneous injection of testosterone propionate 3 mg/kg
10 (solution in corn oil) in order to determine the anti-androgen activity. The agonistic activity is determined in the absence of testosterone propionate.

Testosterone propionate is administered in a volume of 10 ml/kg.

15 20 hours after the treatments, the animals are sacrificed, the kidneys are removed, then homogenized at 0°C, using a teflon glass grinder in 10 volumes of Tris-HCl 50 mM (pH 7.4) buffer containing 250 µM of pyridoxal phosphate, 0.1 mM EDTA, and 5 mM of dithiothreitol. The homogenate is
20 then centrifuged at 209,000 g for 30 minutes.

- Dosage principle

 At 37°C, renal ornithine decarboxylase converts an isotopic mixture of unlabelled ornithine and tritiated ornithine into unlabelled putrescine and tritiated
25 putrescine.

 The putrescine is then collected on selective ion-exchange papers. After drying, the excess unconverted tritiated and unlabelled ornithine is eliminated by washing 3 times with 0.1 M of ammonium hydroxide. The papers are
30 dried, then the radioactivity is counted after addition of scintillating Aqualite.

 The results are expressed as fmoles (10^{-15} M) of tritiated putrescine formed/hour/mg of proteins.

 The results are expressed as % of inhibition of the ODC
35 of the controls receiving only testosterone propionate.

Test: the products are administered by percutaneous route at 1.5 mg/kg in a volume of 10 µl.



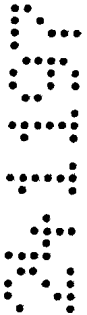
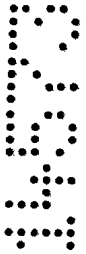
5

Products of Examples	Test
3	47
6	84

- 10 **Conclusion:** The tests indicated above show that the tested products of the invention possess a strong anti-androgen activity.

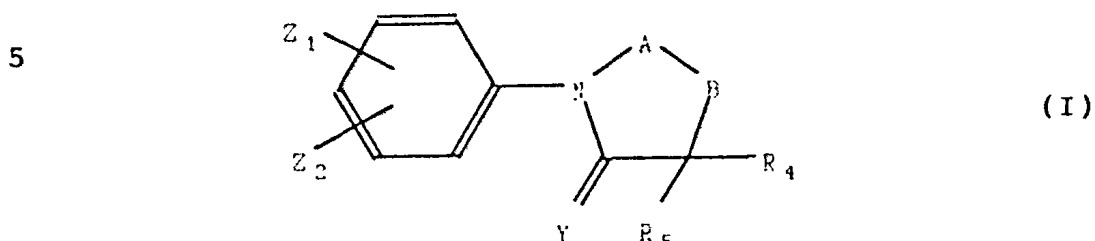


Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification, they are to be interpreted as specifying the presence of the stated features, integers, steps or components referred to, but not to preclude the presence or addition of one or more other feature, integer, step,
5 component or group thereof.



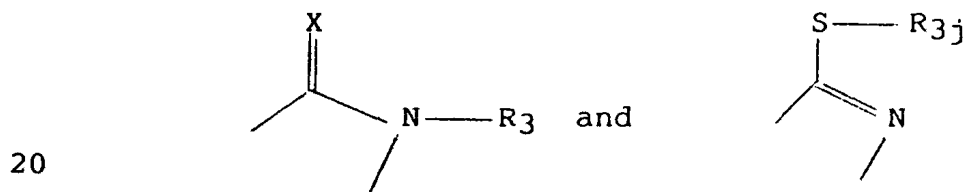
CLAIMS

1) The products of general formula (I):



in which:

Z_1 and Z_2 , identical or different, represent a cyano, nitro radical, a halogen atom, a trifluoromethyl radical or an esterified, amidified or salified free carboxy radical,
 15 the group -A-B- is chosen from the radicals



- 25 - a hydrogen atom,
 - alkyl, alkenyl, alkynyl, aryl or arylalkyl radicals having at most 12 carbon atoms, these radicals being optionally substituted by one or more substituents chosen from halogen atoms and the following radicals: optionally esterified,
 30 etherified or protected hydroxy, alkoxy, hydroxyalkyl, alkenyloxy, alkynyloxy, trifluoromethyl, mercapto, cyano, acyl, acyloxy, aryl, optionally substituted S-alkyl, S-aryl, in which the sulphur atom is optionally oxidized in the form of the sulfoxide or sulphone, free, esterified, amidified or
 35 salified carboxy, amino, mono- or dialkylamino, a cyclic radical containing 3 to 6 members and optionally containing one or more heteroatoms chosen from sulphur, oxygen or



nitrogen atoms and the -O-C-R_7 radical in which R_7 represents

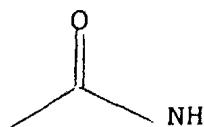
an alkyl, hydroxy, alkoxy, aryl or aryloxy radical,
the alkyl, alkenyl or alkynyl radicals moreover being

5 optionally interrupted by one or more atoms of oxygen,
nitrogen or sulphur optionally oxidized in the form of the
sulphoxide or sulphone, the nitrogen atoms being optionally
oxidized,

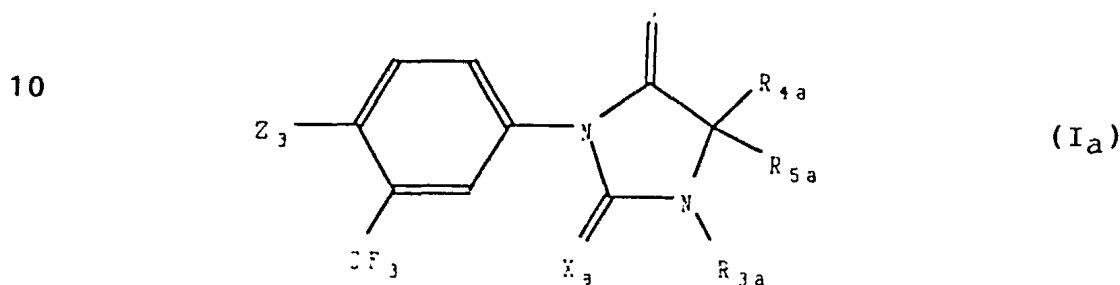
the aryl and aralkyl radicals moreover being optionally
10 substituted by an alkyl, alkenyl or alkynyl, alkoxy,
alkenyloxy, alkynyloxy or trifluoromethyl radical,
Y represents an oxygen or sulphur atom or an NH radical,
 R_4 and R_5 , identical or different, represent a hydrogen atom
or an alkyl radical having 1 to 12 carbon atoms optionally
15 substituted by one or more substituents chosen from halogen
atoms, the -O-C-R_7 radical as defined above, the optionally

esterified, etherified or protected hydroxyl radical, linear
or branched phenylthio and alkylthio radicals containing at
20 most 8 carbon atoms, phenylthio and alkylthio radicals, in
which the sulphur atom can be oxidized in the form of the
sulphoxide or sulphone, themselves being optionally
substituted by one or more radicals chosen from halogen
atoms, the optionally esterified, etherified or protected
25 hydroxyl radical, the free, esterified, amidified or salified
carboxy radical, amino, mono- or dialkylamino radicals, with
the exception of the products in which R_4 and R_5 , identical
or different, represent a hydrogen atom or an alkyl radical
having 1 to 12 carbon atoms non-substituted or substituted by
30 one or more halogen atoms, those in which one of R_4 or R_5
represents a methyl radical and the other represents a
hydroxymethyl radical, Y represents an oxygen atom or an NH
radical, the group -AB- represents the radical

35



Z_1 in position 4 represents a nitro radical and Z_2 in position 3 represents a trifluoromethyl radical, those in which Z_1 and Z_2 both represent a halogen atom and those in which one of Z_1 and Z_2 represents a halogen atom, one of R_4 and R_5 represents an alkyl radical substituted by the group -S-CH₃ and R_3 represents a hydrogen atom or an alkyl radical, b) the products of formula (I_a):



15 in which Z_3 represents a cyano or nitro radical, R_{3a} represents a hydrogen atom or a linear or branched alkyl radical, containing at most 4 carbon atoms, optionally substituted by a fluorine atom, a cyano radical,

20 R_{4a} and R_{5a} are such that one represents a methyl radical and the other represents a methyl radical substituted by a fluorine atom or R_{4a} and R_{5a} are identical and represent a methyl radical substituted by a fluorine atom, or R_{4a} and R_{5a} form with the carbon atom to which they are linked a

25 cyclopentyl radical, X_a represents a sulphur or oxygen atom, with the exception of the product in which Z_3 represents a cyano radical, X_a represents a sulphur atom, R_{3a} represents a methyl radical and R_{4a} and R_{5a} form with the carbon atom to which they are

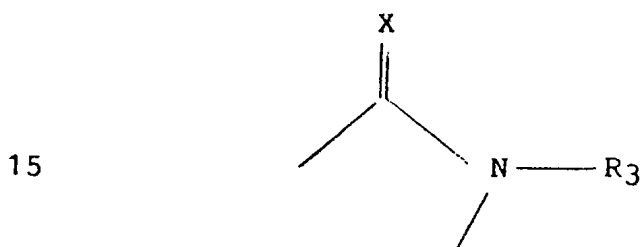
30 linked a cyclopentyl radical, and c) the following products:

- 4-(4,4-dimethyl 2,5-dioxo 3-(2-fluoroethyl) 1-imidazol-
idiny1) 2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl 2,5-dioxo 3-(2,2,2-trifluoroethyl) 1-
35 imidazolidiny1) 2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl 3-(2-fluoroethyl) 5-oxo 2-thioxo 1-
imidazolidiny1) 2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl 2,5-dioxo 3-(2-(2-hydroxyethoxy) ethyl) 1-



imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
the said products of formula (I), (I_a) and the products
mentioned being in all the possible racemic, enantiomeric and
diastereoisomeric isomer forms, as well as the addition salts
5 with mineral and organic acids or with mineral and organic
bases of the said products.

2) The products of formula (I) as defined in claim 1, in
which Z₁ and Z₂ represent a trifluoromethyl, nitro or cyano
radical, Y represents an oxygen atom or an NH radical, the
10 group -A-B- represents the radical:



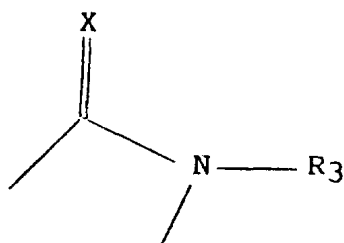
in which X represents an oxygen or sulphur atom,
R₃ represents a hydrogen atom, a linear or branched alkyl
20 radical containing at most 6 carbon atoms, optionally
interrupted by one or more oxygen or sulphur atoms, a phenyl
or pyridyl radical, these radicals being optionally
substituted by one or more radicals chosen from halogen
atoms, the following radicals: phenyl, optionally esterified,
25 etherified or protected hydroxyl, alkoxy, cyano,
trifluoromethyl, hydroxyalkyl, free, esterified, amidified or
salified carboxy, amino, mono- or dialkylamino, the nitrogen
atom of the pyridyl radical being optionally oxidized,
R₄ and R₅ represent a linear or branched alkyl radical
30 containing at most 6 carbon atoms, optionally substituted by
one or more radicals chosen from optionally esterified,
etherified or protected hydroxyl radicals, halogen atoms, the
-O-C-R₇ radical in which R₇ represents a linear or branched

35 alkyl or alkoxy radical and alkylthio and phenylthio
radicals, themselves optionally substituted by one or more
radicals chosen from halogen atoms and the free, esterified,
etherified or protected hydroxyl radical,



the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of
5 formula (I).

3) The products of formula (I) as defined in claim 1, in which Z_1 and Z_2 represent a trifluoromethyl, nitro or cyano radical, Y represents an oxygen atom or an NH radical, the group -A-B- represents the group:



in which X represents an oxygen or sulphur atom, R_3 represents a hydrogen atom or an alkyl radical having 1 to 6 carbon atoms optionally substituted by one or more radicals
20 chosen from halogen atoms and the optionally esterified, etherified or protected hydroxyl radical, the free, esterified, amidified or salified carboxy radical and the cyano radical, the alkyl radical being optionally interrupted by one or more oxygen or sulphur atoms,

25 R_4 and R_5 represent an alkyl radical containing at most 6 carbon atoms optionally substituted by one or more radicals chosen from the optionally esterified, etherified or protected hydroxyl radical, halogen atoms and alkylthio and phenylthio radicals themselves optionally substituted by one
30 or more radicals chosen from halogen atoms and the hydroxyl radical, the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products
35 of formula (I).

4) The products of formula (I) as defined in claim 3, in which Y represents an oxygen atom or an NH radical, Z_2 in position 3 represents a trifluoromethyl radical and Z_1 in



position 4 represents a cyano or nitro radical,
X represents an oxygen or sulphur atom,
R₃ represents a hydrogen atom or an alkyl radical having at
most 4 carbon atoms, optionally substituted by one or more
5 radicals chosen from halogen atoms or the cyano radical,
R₄ and R₅, identical or different, represent a linear or
branched alkyl radical containing at most 4 carbon atoms
optionally substituted by an optionally esterified,
etherified or protected hydroxyl radical, a halogen atom, or
10 a phenylthio radical optionally substituted by a halogen atom
or a hydroxyl radical,
the said products of formula (I) being in all the possible
racemic, enantiomeric and diastereoisomeric isomer forms, as
well as the addition salts with mineral and organic acids or
15 with mineral and organic bases of the said products of
formula (I).

5) The products of formula (I) as defined in any one of
claims 1 to 4, the names of which follow:

- 2-(trifluoromethyl) 4-(4-(hydroxymethyl) 4-methyl 2,5-dioxo
20 1-imidazolidinyl) benzonitrile,
- 4-(3,4-dimethyl) 4-(hydroxymethyl) 5-oxo 2-thioxo 1-
imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 2-(trifluoromethyl) 4-(4-(hydroxymethyl) 3,4-dimethyl 2,5-
dioxo 1-imidazolidinyl) benzonitrile,
- 25 - 4-(2,5-dioxo 3-(2-fluoroethyl) 4-(hydroxymethyl) 4-methyl
1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
- 1,5-dimethyl 5-(hydroxymethyl) 3-(4-nitro 3-(trifluoro-
methyl) phenyl) 2,4-imidazolidinedione,
- 4-(4,4-bis(hydroxymethyl)-2,5-dioxo-1-imidazolidinyl)-2-
30 (trifluoromethyl)-benzonitrile

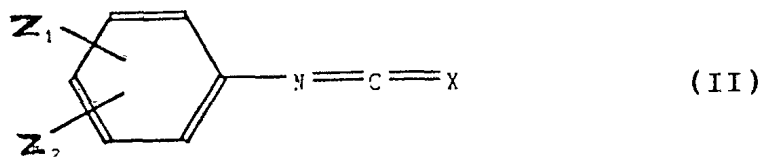
the said products of formula (I) being in all their racemic,
enantiomeric and diastereoisomeric isomer forms, as well as
the addition salts with mineral and organic acids or with
mineral and organic bases of the said products of formula
35 (I).

6) The products of formula (I_a) as defined in claim 1, the
names of which follow:

- 4-(4-(fluoromethyl) 3,4-dimethyl) 2,5-dioxo 1-



- imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
 - 4-(3,4-dimethyl) 4-(fluoromethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
 - 4-(2,5-dioxo 3-(2-fluoroethyl) 4-(fluoromethyl) 4-methyl 1-imidazolidinyl) 2-trifluoromethyl) benzonitrile,
 5 - 4-(2,4-dioxo 1,3-diazaspiro(4.4)nonan-3-yl) 2-(trifluoromethyl) benzonitrile,
 - 4-(2,4-dioxo 1-(2-fluoroethyl) 1,3-diazaspiro(4.4)nonan-3-yl) 2-(trifluoromethyl) benzonitrile,
 10 - 1,5-dimethyl 5-(fluoromethyl) 3-(4-nitro 3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione,
 - 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 5-(fluoromethyl) 5-methyl 1-imidazolidinacetonitrile,
 - 4-(4,4-bis-(fluoromethyl) 3-methyl 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,
 15 the said products of formula (I_a) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of
 20 formula (I_a).
 7) Preparation process for the products of formulae (I), (I_a) and the cited products as defined in claim 1, characterized in that:
either a product of formula (II):



30 in which Z₁, Z₂ and X have the meaning indicated above, is reacted in the presence of a tertiary base with a product of formula (III):

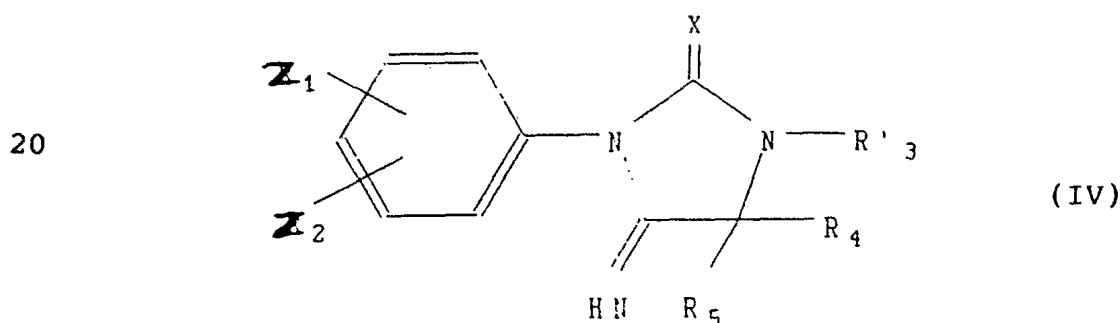
35





5

in which R_4 and R_5 have the meaning indicated above and R'_3 has the values indicated above for R_3 in which the optional reactive functions are optionally protected and it being understood that R_4 and R_5 do not represent simultaneously a methyl radical and that if Z_1 represents an NO_2 radical in position 4, Z_2 represents a CF_3 radical in position 3, X represents an oxygen atom and R'_3 represents a hydrogen atom, then one of R_4 or R_5 does not represent a CH_3 radical and the other a CH_2OH radical, in order to obtain a product of formula (IV):



20

25

in which Z_1 , Z_2 , X , R'_3 , R_4 and R_5 have the previous meaning, or the product of formula (II), as defined above, is reacted in the presence of a tertiary base with a product of formula (VII):

30



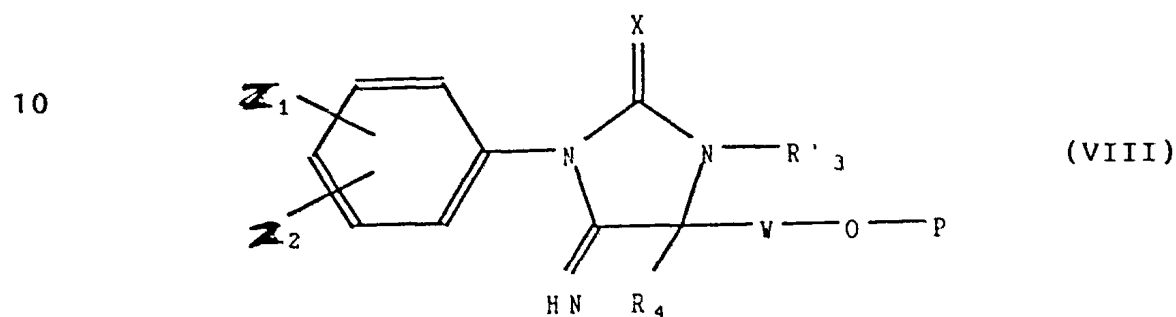
35

in which W has the meaning indicated above for R_5 with the exception of the hydrogen atom, the alkyl radical substituted



by a free, esterified, etherified or protected hydroxyl

radical and the value $-O-\overset{\overset{O}{\parallel}}{C}-R_7$ as defined in claim 1 and P represents a protective group of OH or a radical such that -
 5 O-P represents an etherified hydroxyl radical and R'_3 and R_4 have the meaning indicated above, in order to obtain a product of formula (VIII):



in which X, Z_1 , Z_2 , R'_3 , R_4 , W and P have the meaning indicated above,

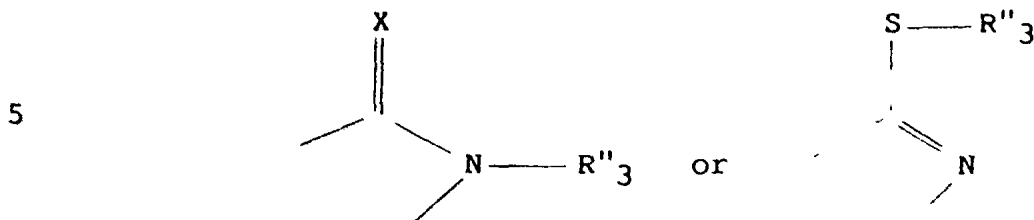
of which product of formula (VIII) if necessary and if desired, the OH radical can be released from OP which can

20 then if necessary and if desired, be esterified or converted into a halogen radical, which products of formulae (IV) and (VIII), if necessary or if desired, are subjected to any one or more of the following reactions, in any order:

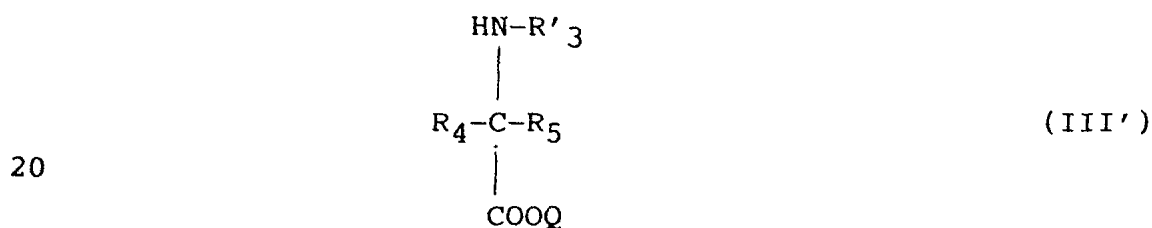
- 25 a) elimination reaction of the optional protective groups that can be carried by R'_3 ;
 b) hydrolysis reaction of the $>C=NH$ group into a carbonyl function and if appropriate conversion of the $>C=S$ group into the $>C=O$ group;
 30 c) conversion reaction of the $>C=O$ group or groups into the $>C=S$ group;
 d) action on the products of formula (IV) or (VIII) in which R'_3 represents a hydrogen atom, and after hydrolysis of the $>C=NH$ group into a carbonyl function, of a reagent of formula
 35 $Hal-R''_3$ in which R''_3 has values of R'_3 with the exception of the hydrogen value and Hal represents a halogen atom, in order to obtain products of formulae (I), (I_a) and cited products as defined in claim 1, in which the -A-B- group



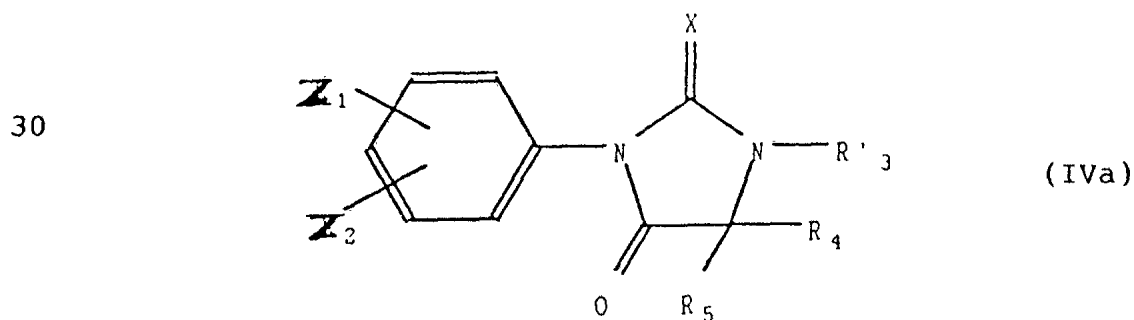
represents the group



in which R''_3 has the meaning indicated previously then, if desired, action on these products, of an elimination agent of the optional protective groups that can be carried by R''_3 or if appropriate, action of an esterification, amidification or salification agent,
or a product of formula (II) as defined above is reacted in the presence of a tertiary base with a product of formula
 15 (III'):



in which R'_3 , R_4 and R_5 have the meaning indicated above and Q represents either an alkali metal atom or an alkyl radical containing 1 to 6 carbon atoms, in order to obtain a product of formula (IVa):

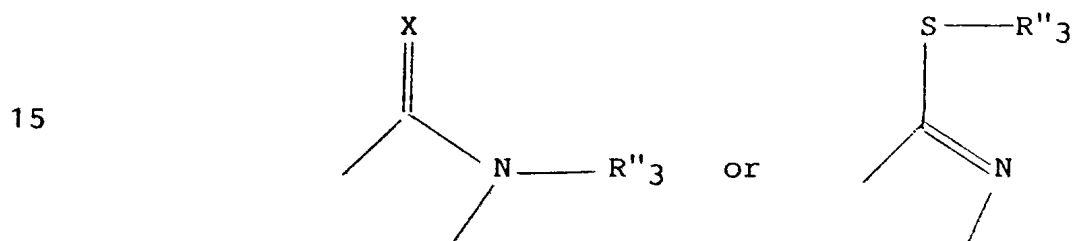


35

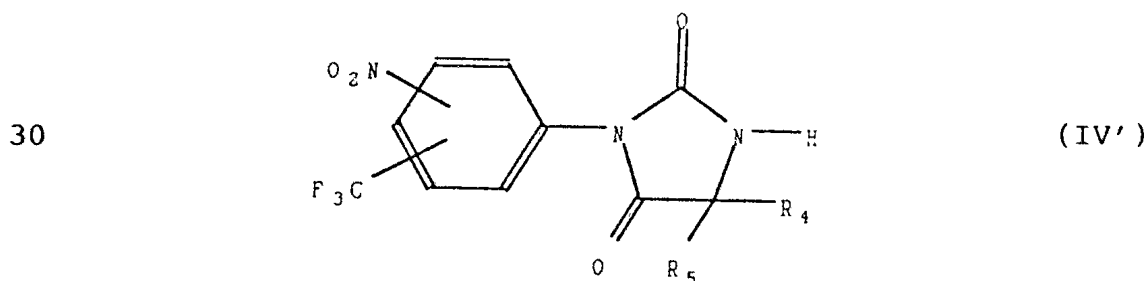
in which X, Z_1 , Z_2 , R'_3 , R_4 and R_5 have the meaning indicated above, which if desired is subjected to any one or more of the following reactions, in any order:



- a) elimination reaction of the optional protective groups that can be carried by R'_3 ;
 b) conversion reaction of the $>C=O$ group or groups into the $>C=S$ group or if appropriate of the $>C=S$ group into the $>C=O$ group;
 5 c) action on the products of formula (IVa) in which R'_3 represents a hydrogen atom of a reagent of formula $Hal-R''_3$ in which R''_3 has the values of R'_3 with the exception of the hydrogen value and Hal represents a halogen atom, in order to
 10 obtain products of formulae (I), (Ia) and cited products as defined above, in which the A-B- group represents the group

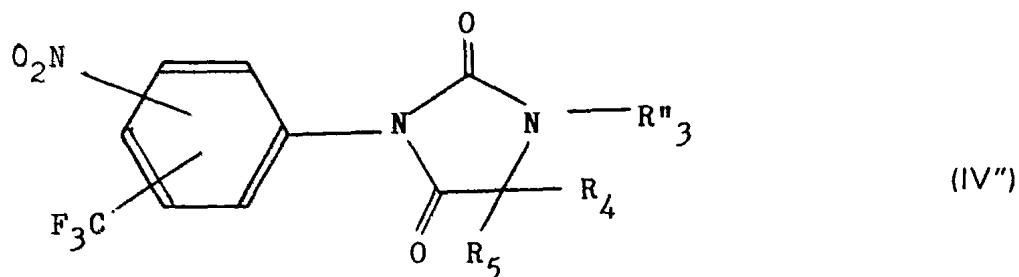


- in which R''_3 has the meaning indicated previously then, if
 20 desired, action on these products of an elimination agent of the optional protective groups that can be carried by R''_3 or if appropriate, action of an esterification, amidification or salification agent,
or a reagent of formula $Hal-R''_3$ in which Hal and
 25 R''_3 have the values indicated previously is reacted on a product of formula (IV'):



- 35 in order to obtain a product of formula (IV''):





10 which product of formula (IV), (IVa), (IV'), (IV'') or (VIII) represents or does not represent a product of formula (I) and which, in order to obtain if necessary or if desired a product of formula (I), is subjected to any one or more of the following reactions in any order:

15 a) elimination reaction of the optional protective groups that can be carried by R''3 then if appropriate action of an esterification, amidification or salification agent;

b) conversion reaction of the >C=O group or groups into >C=S groups, the said products of formula (I) thus obtained being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms.

20 8. A pharmaceutical composition comprising the pharmaceutically acceptable products of formulae (I) and (Ia) as defined in any one of claims 1 to 6 together with a suitable adjuvant, diluent, excipient and/or carrier.

9. A pharmaceutical composition comprising any one of the following products:

25 -4-(4,4-dimethyl 2,5-dioxo 3-(2-fluoroethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,

-4-(4,4-dimethyl 2,5-dioxo 3-(2,2,2-trifluoroethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,

30 -4-(4,4-dimethyl 3-(2-fluoroethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,



-4-(4,4-dimethyl 2,5-dioxo 3-(2-(2-hydroxyethoxy)ethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile together with a suitable adjuvant, diluent, excipient and/or carrier.

10. A pharmaceutical composition as defined in claim 8, wherein the products of formula (I) are selected from the group consisting of:

-2-(trifluoromethyl) 4-(4-hydroxymethyl) 4-methyl 2,5-dioxo 1-imidazolidinyl) benzonitrile,

-4-(3,4-dimethyl) 4-(hydroxymethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,

-2-(trifluoromethyl) 4-(4-(hydroxymethyl) 3,4-dimethyl 2,5-dioxo 1-imidazolidinyl) benzonitrile,

-4-(2,5-dioxo 3-(2-fluoroethyl) 4-(hydroxymethyl) 4-methyl 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,

-1,5-dimethyl 5-(hydroxymethyl) 3-(4-nitro 3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione, or

-4-(4,4-bis(hydroxymethyl) -2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile.

11. A pharmaceutical composition as defined in claim 8 wherein the products of formula (I_a) are selected from the group consisting of:

-4-(4-(fluoromethyl) 3,4-dimethyl 2,5-dioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,

-4-(3,4-dimethyl) 4-(fluoromethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,

-4-(2,5-dioxo 3-(2-fluoroethyl) 4-(fluoromethyl) 4-methyl 1-imidazolidinyl) 2-trifluoromethyl) benzonitrile,

-4-(2,4-dioxo 1,3-diazaspiro(4.4)nonan-3-yl) 2-(trifluoromethyl) benzonitrile,

-4-(2,4-dioxo 1-(2-fluoroethyl) 1,3-diazaspiro(4.4)nonan-3-yl) 2-(trifluoromethyl) benzonitrile,

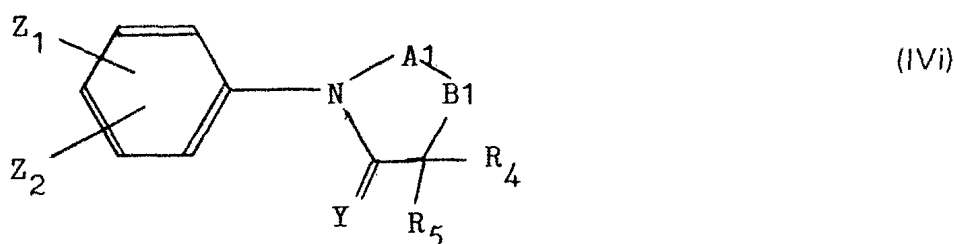
-1,5-dimethyl 5-(fluoromethyl) 3-(4-nitro 3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione,



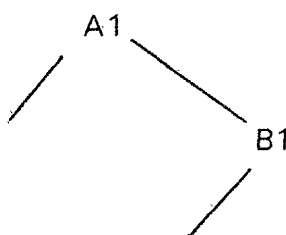
-3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 5-(fluoromethyl) 5-methyl
1-imidazolidinacetonitrile, or

-4-(4,4-bis-(fluoromethyl) 3-methyl 5-oxo 2-thioxo 1-imidazolidinyl 2-
(trifluoromethyl) benzonitrile.

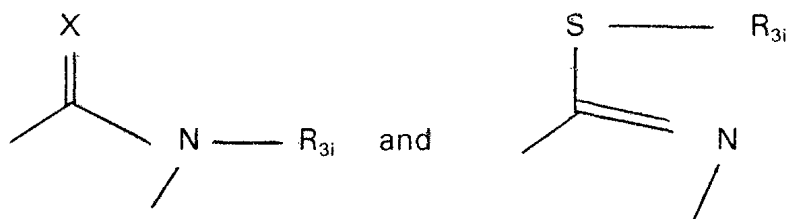
5 12. As new industrial products, the products of formula (IVi):



in which Z_1 , Z_2 , R_4 , R_5 and Y have the meanings indicated above and the
group:



is chosen from the radicals:



in which X represents an oxygen or sulphur atom and R_{3i} is chosen from
the values of R_3 containing a protected reactive function.

13. The products of formula (I) or formula (1_a) as defined in claim 1,
substantially as herein described with reference to any one of the
Examples.



14. -4-(4,4-dimethyl 2,5-dioxo 3-(2-fluoroethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,

-4-(4,4-dimethyl 2,5-dioxo 3-(2,2,2-trifluoroethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,

5 -4-(4,4-dimethyl 3-(2-fluoroethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile,

-4-(4,4-dimethyl 2,5-dioxo 3-(2-(2-hydroxyethoxy)ethyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile, substantially as herein described with reference to any one of Examples 12 to 15.

10 15. Preparation process for the products of formula (I), (Ia) and the cited products as defined in claim 1, which process is substantially as herein described with reference to any one of the Examples.

16. The products of formula (I), (I_a) and the cited products whenever prepared by the process of claim 7 or claim 15.

15 17. A pharmaceutical composition as defined in any one of claims 8 to 11, substantially as herein described with reference to any one of the Examples.

18. A method for the treatment of adenomas and neoplasias of the prostate or benign hypertrophy of the prostate in a patient requiring said treatment which method comprises administering to said patient an effective amount of the products of formula (I) according to any one of claims 1 to 6, 13 or 16 either alone or in combination with analogues of LHRH or of a pharmaceutical composition according to any one of claims 8, 10, or 17.

20 19. A method for the treatment of benign or malignant tumours possessing androgen receptors in the breast, skin, ovaries, bladder, lymphatic system, kidney or liver in a patient requiring said treatment, which method comprises administering to said patient an effective amount of the products of formula (I) according to any one of claims 1 to 6, 13 or 16 or of a pharmaceutical composition according to any one of claims 8, 10 or 17.

25

30



20. A method for the treatment of cutaneous affections in a patient requiring said treatment, which method comprises administering to said patient an effective amount of the products of formula (I) according to any one of claims 1 to 6, 13 or 16 either alone or in combination with antibiotics or of a pharmaceutical composition according to any one of claims 8, 10 or 17.

21. A method according to claim 20, wherein the cutaneous affections are acne, hyperseborrhea, alopecia or hirsutism.

22. A method according to claim 20 or claim 21, wherein the products of formula (I) are used in combination with antibiotics including derivatives of azelaic and fusidic acids, ethythromycin, derivatives of retinoic acid, an inhibitor of 5α -reductase or a product stimulating hair growth.

23. A method according to claim 22, wherein the inhibitor of 5α -reductase is $(5\alpha, 17\beta)$ -1,1-dimethylethyl 3-oxo 4 aza-androst-1-ene 17-carboxamide.

24. A method according to claim 22, wherein the product stimulating hair growth is Minoxidil.

25. A method for the treatment of behavioural disorders, androgen-dependent affections or tumours having androgen receptors in mammals requiring said treatment, which method comprises administering to said mammal an effective amount of the products of formulae (I), (I_a), or the cited products according to any one of claims 1 to 6, 13, 14 or 16 or of a pharmaceutical composition according to any one of claims 8 to 11 or 17.

26. A method according to claim 25, wherein the behavioural disorder is aggressiveness.

27. A method according to claim 25 or claim 26, wherein the androgen-dependent affection is circum anum in dogs.



28. Industrial products as defined in claim 12 substantially as herein described.

DATED this 19th day of November 1997.

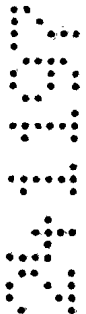
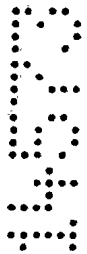
5

ROUSSEL UCLAF

By their Patent Attorneys:

CALLINAN LAWRIE

Michael J. Houlahan.



INTERNATIONAL SEARCH REPORT

Internat 1 Application No

PCT/FR 95/00004

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D233/78 C07D235/02 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 2 no. 15 (C-77) ,31 January 1978 & JP,A,52 113965 (NIPPON SODA K.K.) 24 September 1977, see abstract ---	1
X	PATENT ABSTRACTS OF JAPAN vol. 2 no. 148 (C-78) ,9 December 1978 & JP,A,53 112875 (SUMITOMO KAGAKU KOGYO K.K.) 2 October 1978, see abstract ---	1
X	PATENT ABSTRACTS OF JAPAN vol. 3 no. 3 (C-33) ,16 January 1979 & JP,A,53 124267 (SUMITOMO KAGAKU KOGYO K.K.) 30 October 1978, see abstract ---	1
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 April 1995

Date of mailing of the international search report

27. 04. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Voyiazoglou, D

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/FR 95/00004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 3 no. 50 (C-44) ,27 April 1979 & JP,A,54 027564 (SUMITOMO KAGAKU KOGYO K.K.) 1 March 1979, see abstract ---	1
X	GB,A,997 037 (I.C. LTD) 30 June 1965 see page 1, line 51 - line 54; claim 4 ---	1
X	US,A,4 093 444 (C. CLAPOT ET AL) 6 June 1978 see examples 31-36 ---	1
X	US,A,4 753 957 (HAK-FOON CHAN) 28 June 1988 see column 3 ---	1
X	DE,B,10 32 258 (KALIE-CHEMIE A.G.) 19 June 1958 see example 6 ---	1
X	DE,A,25 40 872 (BASF A.G.) 24 March 1977 see examples 1,2 ---	1
X	FR,A,2 024 141 (SUMITOMO CHEM. CO., LTD) 28 August 1970 see examples ---	1
X	FR,A,2 117 527 (SUMITOMO CHEM. CO., LTD) 21 July 1972 see examples 9,21,26,34 ---	1
X	EP,A,0 091 596 (CELAMERCK GMBH & CO. K.G.) 19 October 1983 cited in the application see page 15; example 5; table I ---	1
X	BE,A,884 897 (F. HOFFMANN-LA ROCHE & CIE) 23 February 1981 see page 2 - page 3 ---	1,8,12
X	EP,A,0 001 813 (F. HOFFMANN-LA ROCHE & CO.) 16 May 1979 see examples 1-5 ---	1,8,12
X	EP,A,0 017 976 (F. HOFFMANN-LA ROCHE & CO.) 29 October 1980 see examples 1-5,7 ---	1,8,12
X	EP,A,0 494 819 (ROUSSEL-UCLAF) 15 July 1992 cited in the application see page 15 - page 29 ---	1,8,12
	-/--	

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/FR 95/00004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR,A,2 329 276 (ROUSSEL-UCLAF) 27 May 1977 cited in the application see the whole document ---	1,8,12
A	EP,A,0 305 270 (ROUSSEL-UCLAF) 1 March 1989 cited in the application see the whole document ---	1,8,12
P,X	EP,A,0 578 516 (ROUSSEL-UCLAF) 12 January 1994 see the whole document ---	1,8,12
P,X	EP,A,0 580 459 (ROUSSEL-UCLAF) 26 January 1994 see the whole document -----	1,8,12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FR 95/00004

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims subject to a complete search : 5,6, 9-11
 Claims subject to an incomplete search : 1-4, 7-8, 12-13

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No

PCT /FR 95/00004

For want of clear and concise formulation (PCT Article 6), the claims encompass such an inordinate number of compositions that a meaningfully complete search could not be carried out (PCT Article 17(2)(a)(ii)). Consequently, the search was limited to areas directly illustrated by the examples and clearly defined in the claim.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/FR 95/00004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-997037		NONE	
US-A-4093444	06-06-78	FR-A- 2230629	20-12-74
		BE-A- 815441	16-09-74
		CH-A- 601987	14-07-78
		DE-A- 2423273	19-12-74
		GB-A- 1476333	10-06-77
		JP-A- 50018634	27-02-75
		OA-A- 4707	31-08-80
		US-A- 3990883	09-11-76
		US-A- 4099955	11-07-78
US-A-4753957	28-06-88	NONE	
DE-B-1032258		NONE	
DE-A-2540872	24-03-77	NONE	
FR-A-2024141	28-08-70	BE-A- 742115	04-05-70
		CH-A- 520471	31-03-72
		DE-A- 1958183	04-06-70
		GB-A- 1251907	03-11-71
		NL-A- 6917658	27-05-70
		US-A- 3668217	06-06-72
FR-A-2117527	21-07-72	AU-A- 3647771	07-06-73
		CA-A- 971969	29-07-75
		CH-A- 565770	29-08-75
		DE-A- 2160912	22-06-72
		GB-A- 1353179	15-05-74
		NL-A- 7116872	13-06-72
		US-A- 3846441	05-11-74
EP-A-0091596	19-10-83	DE-A- 3213140	20-10-83
		DE-A- 3238447	19-04-84
		DE-A- 3301008	19-07-84
		CA-A- 1264750	23-01-90
		DE-A- 3382406	17-10-91
		JP-A- 58188864	04-11-83
		US-A- 4944791	31-07-90

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/FR 95/00004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
BE-A-884897	23-02-81	NONE	
EP-A-0001813	16-05-79	CH-A- 642944	15-05-84
		AT-B- 366671	26-04-82
		AT-B- 366374	13-04-82
		AU-B- 522536	10-06-82
		AU-A- 4096178	01-05-80
		AU-B- 522796	24-06-82
		AU-A- 4096278	01-05-80
		AU-B- 551161	17-04-86
		AU-A- 8105182	08-07-82
		BE-A- 871584	27-04-79
		CA-A- 1107744	25-08-81
		CA-A- 1138334	28-12-82
		CA-A- 1137091	07-12-82
		DE-A- 2846945	03-05-79
		DE-A- 2846946	03-05-79
		FR-A, B 2407205	25-05-79
		FR-A, B 2422643	09-11-79
		GB-A, B 2008101	31-05-79
		GB-A, B 2008102	31-05-79
		GB-A, B 2087870	03-06-82
		JP-A- 54070271	05-06-79
		JP-B- 62005145	03-02-87
		JP-A- 54073754	13-06-79
		LU-A- 80422	07-05-80
		NL-A- 7810562	02-05-79
		NL-A- 7810563	02-05-79
		SE-B- 433304	21-05-84
		SE-A- 7811193	29-04-79
		SE-A- 7811194	29-04-79
		SE-A- 8202106	01-04-82
		SE-A- 8202318	13-04-82
		SE-A- 8202500	21-04-82
		SE-A- 8202501	21-04-82
		SE-A- 8202502	21-04-82
		US-A- 4407814	04-10-83
		US-A- 4482739	13-11-84
		US-A- 4234736	18-11-80
		CH-A- 644850	31-08-84

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/FR 95/00004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0017976	29-10-80	AT-T- 3860	15-07-83
		CA-A- 1135706	16-11-82
		JP-A- 55143974	10-11-80
EP-A-0494819	15-07-92	FR-A- 2671348	10-07-92
		AU-B- 648376	21-04-94
		AU-A- 1010692	16-07-92
		CA-A- 2059052	10-07-92
		CN-A- 1063102	29-07-92
		JP-A- 4308579	30-10-92
FR-A-2329276	27-05-77	AU-B- 500542	24-05-79
		AU-A- 1909576	04-05-78
		BE-A- 847742	28-04-77
		CA-A- 1086751	30-09-80
		CH-A- 599164	12-05-78
		DE-A- 2649925	12-05-77
		GB-A- 1518444	19-07-78
		JP-C- 1289956	14-11-85
		JP-A- 52057176	11-05-77
		JP-B- 60011701	27-03-85
		LU-A- 76085	31-05-77
		LU-A- 88282	04-05-94
		NL-A- 7611576	03-05-77
		SE-B- 430502	21-11-83
		SE-A- 7610859	30-04-77
		US-A- 4097578	27-06-78
EP-A-0305270	01-03-89	FR-A- 2619381	17-02-89
		AU-B- 618018	12-12-91
		AU-A- 2091588	16-02-89
		CA-A- 1304093	23-06-92
		JP-A- 1070473	15-03-89
		US-A- 4873256	10-10-89
EP-A-0578516	12-01-94	FR-A- 2694290	04-02-94
		CA-A- 2097247	09-01-94
EP-A-0580459	26-01-94	FR-A- 2693461	14-01-94
		AU-B- 3987693	13-01-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/FR 95/00004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0580459		CA-A- 2097248	09-01-94
		CN-A- 1081182	26-01-94
		HU-A- 64527	28-01-94
		JP-A- 6073017	15-03-94

RAPPORT DE RECHERCHE INTERNATIONALE

Demande internationale PCT

PCT/IR 95/00004

A. CLASSEMENT DE L'OBJET DE LA DEMANDE

CIB 6 C07D233/78 C07D235/02 A61K31/415

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)

CIB 6 C07D A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si cela est réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	PATENT ABSTRACTS OF JAPAN vol. 2 no. 15 (C-77), 31 Janvier 1978 & JP,A,52 113965 (NIPPON SODA K.K.) 24 Septembre 1977, voir abrégé ---	1
X	PATENT ABSTRACTS OF JAPAN vol. 2 no. 148 (C-78), 9 Décembre 1978 & JP,A,53 112875 (SUMITOMO KAGAKU KOGYO K.K.) 2 Octobre 1978, voir abrégé ---	1
X	PATENT ABSTRACTS OF JAPAN vol. 3 no. 3 (C-33), 16 Janvier 1979 & JP,A,53 124267 (SUMITOMO KAGAKU KOGYO K.K.) 30 Octobre 1978, voir abrégé ---	1
	--- -/-	

☒ Voir la suite du cadre C pour la fin de la liste des documents☒ Les documents de familles de brevets sont indiqués en annexe

* Catégories spéciales de documents cités:

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié après la date de dépôt international ou la date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

"&" document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée

10 Avril 1995

Date d'expédition du présent rapport de recherche internationale

27.04.95

Nom et adresse postale de l'administration chargée de la recherche internationale

Office Européen des Brevets, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Fonctionnaire autorisé

Voyiazoglou, D

C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	PATENT ABSTRACTS OF JAPAN vol. 3 no. 50 (C-44) ,27 Avril 1979 & JP,A,54 027564 (SUMITOMO KAGAKU KOGYO K.K.) 1 Mars 1979, voir abrégé ---	1
X	GB,A,997 037 (I.C. LTD) 30 Juin 1965 voir page 1, ligne 51 - ligne 54; revendication 4 ---	1
X	US,A,4 093 444 (C. CLAPOT ET AL) 6 Juin 1978 voir exemples 31-36 ---	1
X	US,A,4 753 957 (HAK-FOON CHAN) 28 Juin 1988 voir colonne 3 ---	1
X	DE,B,10 32 258 (KALIE-CHEMIE A.G.) 19 Juin 1958 voir exemple 6 ---	1
X	DE,A,25 40 872 (BASF A.G.) 24 Mars 1977 voir exemples 1,2 ---	1
X	FR,A,2 024 141 (SUMITOMO CHEM. CO., LTD) 28 Août 1970 voir exemples ---	1
X	FR,A,2 117 527 (SUMITOMO CHEM. CO., LTD) 21 Juillet 1972 voir exemples 9,21,26,34 ---	1
X	EP,A,0 091 596 (CELAMERCK GMBH & CO. K.G.) 19 Octobre 1983 cité dans la demande voir page 15; exemple 5; tableau I ---	1
X	BE,A,884 897 (F. HOFFMANN-LA ROCHE & CIE) 23 Février 1981 voir page 2 - page 3 ---	1,8,12
X	EP,A,0 001 813 (F. HOFFMANN-LA ROCHE & CO.) 16 Mai 1979 voir exemples 1-5 ---	1,8,12
X	EP,A,0 017 976 (F. HOFFMANN-LA ROCHE & CO.) 29 Octobre 1980 voir exemples 1-5,7 ---	1,8,12
3 X	EP,A,0 494 819 (ROUSSEL-UCLAF) 15 Juillet 1992 cité dans la demande voir page 15 - page 29 ---	1,8,12
	--- -/--	

C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	FR,A,2 329 276 (ROUSSEL-UCLAF) 27 Mai 1977 cité dans la demande voir le document en entier ---	1,8,12
A	EP,A,0 305 270 (ROUSSEL-UCLAF) 1 Mars 1989 cité dans la demande voir le document en entier ---	1,8,12
P,X	EP,A,0 578 516 (ROUSSEL-UCLAF) 12 Janvier 1994 voir le document en entier ---	1,8,12
P,X	EP,A,0 580 459 (ROUSSEL-UCLAF) 26 Janvier 1994 voir le document en entier -----	1,8,12

Cadre I Observations - lorsqu'il a été estimé que certaines revendications ne pouvaient pas faire l'objet d'une recherche (suite du point 1 de la première feuille)

Conformément à l'article 17.2)a), certaines revendications n'ont pas fait l'objet d'une recherche pour les motifs suivants:

1. ☐ Les revendications n°s
se rapportent à un objet à l'égard duquel l'administration n'est pas tenue de procéder à la recherche, à savoir:
2. ☒ Les revendications n°s
se rapportent à des parties de la demande internationale qui ne remplissent pas suffisamment les conditions prescrites pour qu'une recherche significative puisse être effectuée, en particulier:
REVENDEICATIONS AYANT FAIT L'OBJET DE RECHERCHES COMPLETES : 5,6,9-11
REVENDEICATIONS AYANT FAIT L'OBJET DE RECHERCHES INCOMPLETES : 1-4, 7-8,
12-13.
3. ☐ Les revendications n°s
sont des revendications dépendantes et ne sont pas rédigées conformément aux dispositions de la deuxième et de la troisième phrases de la règle 6.4.a).

Cadre II Observations - lorsqu'il y a absence d'unité de l'invention (suite du point 2 de la première feuille)

L'administration chargée de la recherche internationale a trouvé plusieurs inventions dans la demande internationale, à savoir:

1. ☐ Comme toutes les taxes additionnelles ont été payées dans les délais par le déposant, le présent rapport de recherche internationale porte sur toutes les revendications pouvant faire l'objet d'une recherche.
2. ☐ Comme toutes les recherches portant sur les revendications qui s'y prêtaient ont pu être effectuées sans effort particulier justifiant une taxe additionnelle, l'administration n'a sollicité le paiement d'aucune taxe de cette nature.
3. ☐ Comme une partie seulement des taxes additionnelles demandées a été payée dans les délais par le déposant, le présent rapport de recherche internationale ne porte que sur les revendications pour lesquelles les taxes ont été payées, à savoir les revendications n°s:
4. ☐ Aucune taxe additionnelle demandée n'a été payée dans les délais par le déposant. En conséquence, le présent rapport de recherche internationale ne porte que sur l'invention mentionnée en premier lieu dans les revendications; elle est couverte par les revendications n°s:

Remarque quant à la réserve

- ☐ Les taxes additionnelles étaient accompagnées d'une réserve de la part du déposant.
- ☐ Le paiement des taxes additionnelles n'était assorti d'aucune réserve.

SUITE DES RENSEIGNEMENTS INDIQUÉS SUR PCT/ISA/

DU FAIT DE SON MANQUE DE CLARTE ET DE CONCISION (ART.6, PCT), LE TEXTE DES REVENDICATIONS ENGLOBE UN NOMBRE INCOMMENSURABLE DE POSSIBILITES DE COMPOSES SI BIEN QU'UNE RECHERCHE SIGNIFICATIVEMENT COMPLETE S'AVERE IMPOSSIBLE (ART.17(2)(a) (ii),PCT).

EN CONSEQUENCE, LA RECHERCHE DOCUMENTAIRE A ETE LIMITE AUX DOMAINES ILLUSTRÉS DIRECTEMENT PAR LES EXEMPLES QUI SONT CLAIREMENT DEFINIS DANS LA DEMANDE.

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demande internationale No

PCT/FR 95/00004

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
GB-A-997037		AUCUN	
US-A-4093444	06-06-78	FR-A- 2230629	20-12-74
		BE-A- 815441	16-09-74
		CH-A- 601987	14-07-78
		DE-A- 2423273	19-12-74
		GB-A- 1476333	10-06-77
		JP-A- 50018634	27-02-75
		OA-A- 4707	31-08-80
		US-A- 3990883	09-11-76
		US-A- 4099955	11-07-78
US-A-4753957	28-06-88	AUCUN	
DE-B-1032258		AUCUN	
DE-A-2540872	24-03-77	AUCUN	
FR-A-2024141	28-08-70	BE-A- 742115	04-05-70
		CH-A- 520471	31-03-72
		DE-A- 1958183	04-06-70
		GB-A- 1251907	03-11-71
		NL-A- 6917658	27-05-70
		US-A- 3668217	06-06-72
FR-A-2117527	21-07-72	AU-A- 3647771	07-06-73
		CA-A- 971969	29-07-75
		CH-A- 565770	29-08-75
		DE-A- 2160912	22-06-72
		GB-A- 1353179	15-05-74
		NL-A- 7116872	13-06-72
		US-A- 3846441	05-11-74
EP-A-0091596	19-10-83	DE-A- 3213140	20-10-83
		DE-A- 3238447	19-04-84
		DE-A- 3301008	19-07-84
		CA-A- 1264750	23-01-90
		DE-A- 3382406	17-10-91
		JP-A- 58188864	04-11-83
		US-A- 4944791	31-07-90

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demande internationale No

PCT/FR 95/00004

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
BE-A-884897	23-02-81	AUCUN	
EP-A-0001813	16-05-79	CH-A- 642944	15-05-84
		AT-B- 366671	26-04-82
		AT-B- 366374	13-04-82
		AU-B- 522536	10-06-82
		AU-A- 4096178	01-05-80
		AU-B- 522796	24-06-82
		AU-A- 4096278	01-05-80
		AU-B- 551161	17-04-86
		AU-A- 8105182	08-07-82
		BE-A- 871584	27-04-79
		CA-A- 1107744	25-08-81
		CA-A- 1138334	28-12-82
		CA-A- 1137091	07-12-82
		DE-A- 2846945	03-05-79
		DE-A- 2846946	03-05-79
		FR-A, B 2407205	25-05-79
		FR-A, B 2422643	09-11-79
		GB-A, B 2008101	31-05-79
		GB-A, B 2008102	31-05-79
		GB-A, B 2087870	03-06-82
		JP-A- 54070271	05-06-79
		JP-B- 62005145	03-02-87
		JP-A- 54073754	13-06-79
		LU-A- 80422	07-05-80
		NL-A- 7810562	02-05-79
		NL-A- 7810563	02-05-79
		SE-B- 433304	21-05-84
		SE-A- 7811193	29-04-79
		SE-A- 7811194	29-04-79
		SE-A- 8202106	01-04-82
		SE-A- 8202318	13-04-82
		SE-A- 8202500	21-04-82
		SE-A- 8202501	21-04-82
		SE-A- 8202502	21-04-82
		US-A- 4407814	04-10-83
		US-A- 4482739	13-11-84
		US-A- 4234736	18-11-80
		CH-A- 644850	31-08-84

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demande internationale No
PCT/FR 95/00004

Document brevet cite au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
EP-A-0017976	29-10-80	AT-T- 3860	15-07-83
		CA-A- 1135706	16-11-82
		JP-A- 55143974	10-11-80

EP-A-0494819	15-07-92	FR-A- 2671348	10-07-92
		AU-B- 648376	21-04-94
		AU-A- 1010692	16-07-92
		CA-A- 2059052	10-07-92
		CN-A- 1063102	29-07-92
		JP-A- 4308579	30-10-92

FR-A-2329276	27-05-77	AU-B- 500542	24-05-79
		AU-A- 1909576	04-05-78
		BE-A- 847742	28-04-77
		CA-A- 1086751	30-09-80
		CH-A- 599164	12-05-78
		DE-A- 2649925	12-05-77
		GB-A- 1518444	19-07-78
		JP-C- 1289956	14-11-85
		JP-A- 52057176	11-05-77
		JP-B- 60011701	27-03-85
		LU-A- 76085	31-05-77
		LU-A- 88282	04-05-94
		NL-A- 7611576	03-05-77
		SE-B- 430502	21-11-83
		SE-A- 7610859	30-04-77
		US-A- 4097578	27-06-78

EP-A-0305270	01-03-89	FR-A- 2619381	17-02-89
		AU-B- 618018	12-12-91
		AU-A- 2091588	16-02-89
		CA-A- 1304093	23-06-92
		JP-A- 1070473	15-03-89
		US-A- 4873256	10-10-89

EP-A-0578516	12-01-94	FR-A- 2694290	04-02-94
		CA-A- 2097247	09-01-94

EP-A-0580459	26-01-94	FR-A- 2693461	14-01-94
		AU-B- 3987693	13-01-94

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demar internationale No

PCT/FR 95/00004

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
EP-A-0580459		CA-A- 2097248	09-01-94
		CN-A- 1081182	26-01-94
		HU-A- 64527	28-01-94
		JP-A- 6073017	15-03-94
