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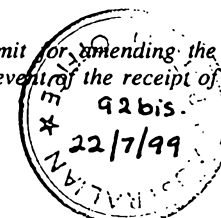
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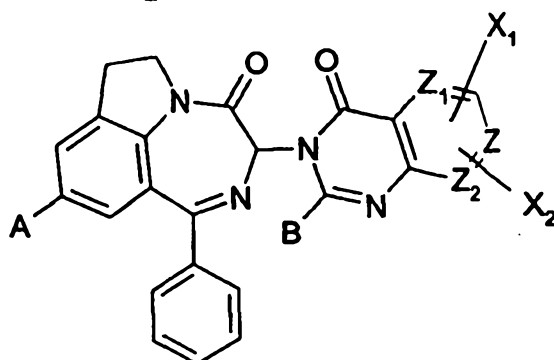
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(I)

(57) Abstract

The present invention presents compounds that inhibit phosphodiesterase 4 having Formula (I). The present invention also provides methods of using the compounds of Formula (I) to prevent or treat asthma, atopic dermatitis, rheumatoid arthritis, inflammatory bowel disorders, pulmonary hypertension, liver injury, bone loss, septic shock, or multiple sclerosis, and to pharmaceutical compositions that contain the compounds of Formula (I).

PHOSPHODIESTERASE 4-INHIBITING DIAZEPINOINDOLONES

FIELD OF THE INVENTION

The present invention relates to new [1,4]diazepino[6,7,1-*hi*]indol-4-ones which are useful for the preparation of medicaments that enable complaints which are amenable to therapy by a phosphodiesterase 4 inhibitor to be treated. In certain preferred embodiments, these medicaments are useful, in particular, as anti-inflammatories, anti-allergics, bronchodilators or anti-asthmatics and are bereft of digestive or cardiac side-effects. Conditions also amenable to treatment with preferred compounds according to the invention include inflammatory bowel diseases like ulcerative colitis and Crohn's disease, disorders characterized by a significant increase of TNF- α , such as pulmonary hypertension (primary or secondary), liver failure in particular following immunologic or inflammatory hepatic injury, bone loss (osteoporosis or osteomalacia), septic shock, and multiple sclerosis.

TECHNOLOGICAL BACKGROUND OF THE INVENTION

Cyclic adenosine 3',5'-monophosphate (cAMP) is a ubiquitous intracellular second messenger, intermediate between a first messenger (hormone, neurotransmitter or autacoid) and the cellular functional responses: the first messenger stimulates the enzyme responsible for cAMP synthesis; cAMP then participates, depending on the cells in question, in a very large number of functions: metabolic, contractile or secretory.

The effects of cAMP come to an end when it is degraded by the cyclic nucleotide phosphodiesterases, intracellular enzymes which catalyze its hydrolysis to inactive adenosine 5'-monophosphate.



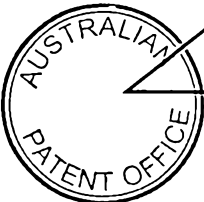
In mammals, at least seven types of cyclic nucleotide phosphodiesterases (PDE) are distinguished, numbered from 1 to 7 according to their structure, their kinetic behaviour, their substrate specificity or their sensitivity to effectors (Beavo J.A. *et al.* (1990) Trends Pharmacol. Sci. 11, 150-155. Beavo J.A. *et al.* (1994) Molecular
5 Pharmacol. 46, 399-405). The distribution of these different types varies according to the tissues.

Accordingly, a specific inhibitor of one type of PDE isoenzyme should bring about an increase in the cAMP only in the cells in which this type of enzyme is to be found.

An increase in the cAMP in the leukocytes involved in inflammation inhibits their
10 activation: inhibition of the synthesis and release of mediators in the mast cells, monocytes, _____

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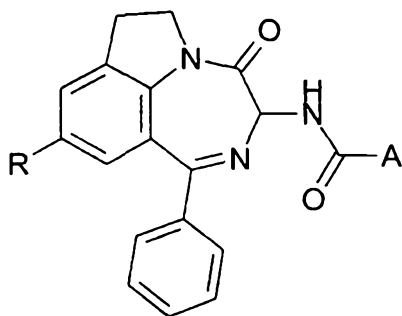


eosinophilic and basophilic polynuclear leukocytes, inhibition of neutrophilic and eosinophilic polynuclear leukocyte chemotaxis and degranulation, inhibition of lymphocyte division and differentiation. Among these mediators, the cytokines, in particular (tumor necrosis factor)TNF- α and interleukins, produced by the T lymphocytes and eosinophilic polynuclear leukocytes play an important part in the triggering of inflammatory manifestations, especially in response to stimulation by an allergen in the airways. Furthermore, cAMP decreases the tonus of the smooth muscle fibers of the airways.

In these cells and these tissues, the PDE4 enzymes play an important part in the hydrolysis of cAMP. Selective PDE4 inhibitors can hence be expected to possess therapeutic activity as anti-inflammatory, antiallergic and bronchodilatory medicaments, and in the treatment of asthma where an infiltration of the airways by inflammatory cells and bronchoconstriction are observed. Asthma is a frequent and often severe condition. While mortality trends for other medical conditions amenable to treatment have declined in recent decades, asthma has become more prevalent, more severe and more deadly, despite the availability of improved pharmacotherapy to treat it (Lang D.M., Ann. Allergy Asthma Immunol ,1997; 78 : 333-7.) Prevalence is especially high in children, which makes the availability of an oral treatment highly desirable.

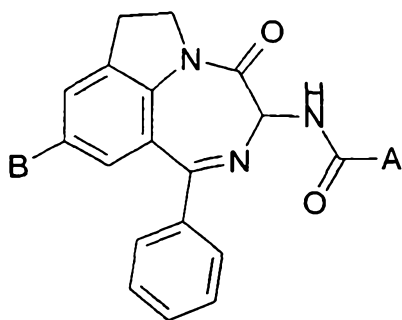
For some years, extensive research has been carried out in order to obtain and develop potent PDE4 inhibitors. This proves difficult on account of the fact that many potential PDE4 inhibitors are not without activity with respect to the phosphodiesterases of the other families.

The level of activity and of selectivity of PDE4 inhibitors represents a considerable problem in view of the range of functions which are regulated by cAMP. There hence exists a need for potent and selective PDE4 inhibitors, that is to say ones that have no action with respect to the PDEs belonging to other families. The international Patent Application published under No. WO 96 11690 describes the application of diazepinoindolone derivatives of formula



in which R is hydrogen, lower alkyl or lower alkoxy and A is an optionally substituted aromatic ring system, for the preparation of medicaments intended for the treatment of complaints which are amenable to a phosphodiesterase 4 inhibitor. International

Application WO 97/36905 describes diazepinoindoles of formula

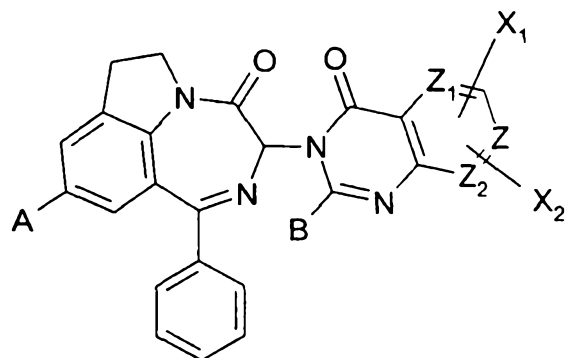


in which A is aryl or nitrogenous heteroaryl, optionally substituted; B is a hydroxyl or amino radical which is itself optionally substituted. These products are useful for treating complaints which are amenable to therapy by the inhibition of PDE4.

The search for potent and selective PDE4 inhibitors remains a major objective for the treatment of pathologies in which the PDE4 enzymes are involved.

SUMMARY OF THE INVENTION

The present invention provides new [1,4]diazepino[6,7,1-*hi*]indol-4-one derivatives, which are very potent PDE4 inhibitors, at concentrations at which they have no action on the other PDE families. The invention relates to the diazepinoindolones (I) of formula



in which:

-A is hydrogen, C₁-C₄alkyl, OR¹, hydroxy, nitro, cyano, -NH₂, -NHR¹, or -NR¹R²;

R¹ and R² independently are C₁-C₄alkyl, cyclopropyl, cyclopropylmethyl, or NR¹R² taken together with the nitrogen to which they are bound complete a ring having 4 or 5 carbon atoms;

-B is hydrogen, C₁-C₄alkyl, -CH₂OM, -CH₂OC(=O)(CH₂)_a(CO)_bY¹-Y², or

-(CH₂)_cC(=O)OM;

- 4 -

Y^1 is $-(VCH_2CH_2)_c-$, with $V = -NH-$ or $-O-$; or Y^1 is $-NHCHR^A-C(=O)-$;

Y^2 is hydrogen, hydroxy, $-OCH_3$, or 4-morpholinyl;

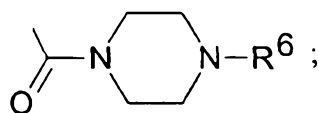
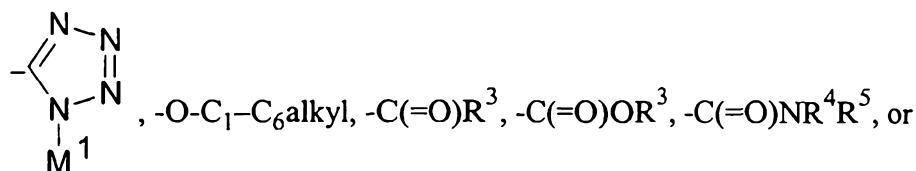
M is hydrogen or C_1-C_4 alkyl;

$a = 1$ or 2 ; $b = 0$ or 1 ; $c = 0, 1$, or 2 ;

5 $-Z$ is CH , then Z_1 and Z_2 both are CH or N ; or

Z is N , then Z_1 and Z_2 are CH ;

$-X_1$ and X_2 independently are hydrogen, C_1-C_4 alkyl, $-(CH_2)_n-OR^3$, halogen, cyano,



10 R^3 is hydrogen, C_1-C_6 alkyl, benzyl, phenethyl, or $-Q^1-Q^2$;

R^4 is hydrogen, or C_1-C_4 alkyl;

R^5 is hydrogen, C_1-C_4 alkyl, $-\text{CHR}^A-\text{C}(=\text{O})\text{OM}^1$, or $-Q^3-Q^4$;

R^6 is hydrogen, C_1-C_4 alkyl, or $-Q^3-Q^5$;

15 R^A is a residue of a natural α -amino-acid, the carbon atom to which it is linked having either a S configuration, or a R configuration;

Q^1 is $-(CH_2)_n-(CHOH)_m-(CH_2)_p-$;

Q^2 is hydroxy, $-\text{O}-\text{C}_1-\text{C}_6$ alkyl, $-\text{OC}(=\text{O})-\text{C}_1-\text{C}_6$ alkyl, or 4-morpholinyl;

Q^3 is $-(CH_2)_n-$;

Q^4 is $-\text{NHM}^1$, $-\text{NM}^1\text{M}^2$, or 4-morpholinyl;

20 Q^5 is $-\text{M}^1$ or $-\text{OM}^1$;

M^1 and M^2 are independently hydrogen or C_1-C_4 alkyl;

n is 1, 2, or 3; m is 0, 1, 2, 3, or 4; p is 0, 1, 2, or 3, provided that if m is not 0, then p is not 0;

-their racemic forms and each of their isomers, in particular those whose configuration is

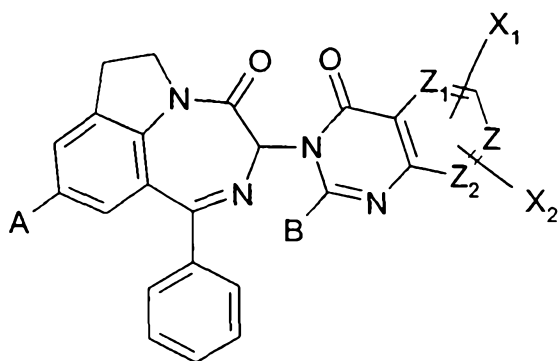
- 5 -

determined by carbon 3 of the [1,4]diazepino[6,7,1-*hi*]-indol-4-one ring system,
-and the pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof.

The invention also relates to a process for preparing them and to their application for
obtaining medicaments intended for treating complaints which are amenable to therapy by the
5 inhibition of PDE4.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to the diazepinoindolones (I) of formula



10

in which:

-A is hydrogen, C₁-C₄alkyl, OR¹, hydroxy, nitro, cyano, -NH₂, -NHR¹, or -NR¹R²;

R¹ and R² independently are C₁-C₄alkyl, cyclopropyl, cyclopropylmethyl, or NR¹R²

taken together with the nitrogen to which they are bound complete a ring having 4 or

15

5 carbon atoms;

-B is hydrogen, C₁-C₄alkyl, -CH₂OM, -CH₂OC(=O)(CH₂)_a(CO)_bY¹-Y², or

-(CH₂)_cC(=O)OM;

Y¹ is -(VCH₂CH₂)_c-, with V = -NH- or -O-; or Y¹ is -NHCHR^A-C(=O)-;

Y² is hydrogen, hydroxy, -OCH₃, or 4-morpholinyl;

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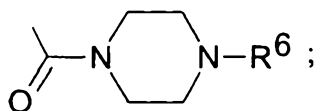
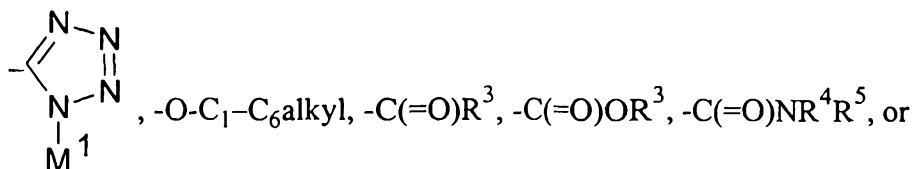
M is hydrogen or C₁-C₄alkyl;

a = 1 or 2; b = 0 or 1; c = 0, 1, or 2;

-Z is CH, then Z₁ and Z₂ both are CH or N; or

Z is N, then Z₁ and Z₂ are CH;

-X₁ and X₂ independently are hydrogen, C₁-C₄alkyl, -(CH₂)_n-OR³, halogen, cyano,



R³ is hydrogen, C₁-C₆alkyl, benzyl, phenethyl, or -Q¹-Q²;

R⁴ is hydrogen, or C₁-C₄alkyl;

5 R⁵ is hydrogen, C₁-C₄alkyl, -CHR^A-C(=O)OM¹, or -Q³-Q⁴;

R⁶ is hydrogen, C₁-C₄alkyl, or -Q³-Q⁵;

R^A is a residue of a natural α -amino-acid, the carbon atom to which it is linked having either a S configuration, or a R configuration;

Q¹ is -(CH₂)_n-(CHOH)_m-(CH₂)_p-;

10 Q² is hydroxy, -O-C₁-C₆alkyl, -OC(=O)-C₁-C₆alkyl, or 4-morpholinyl;

Q³ is -(CH₂)_n-;

Q⁴ is -NHM¹, -NM¹M², or 4-morpholinyl;

Q⁵ is -M¹ or -OM¹;

M¹ and M² are independently hydrogen or C₁-C₄alkyl;

15 n is 1, 2, or 3; m is 0, 1, 2, 3, or 4; p is 0, 1, 2, or 3, provided that if m is not 0, then p is not 0;

their racemic forms and their isomers, in particular those whose configuration is determined by carbon 3 of the [1,4]diazepino[6,7,1-*hi*]indol-4-one ring system, as well as their pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs.

20 In a preferred embodiment of the compounds of Formula I, the carbon 3 of the [1,4]diazepino[6,7,1-*hi*]-indol-4-one ring system has the S configuration according to the rule of Cahn, Ingold and Prelog.

In another preferred embodiment of the compounds of Formula I,

A is hydrogen, methyl, hydroxy, -OCH₃, -NH₂, -NHCH₃; -N(CH₃)₂ or 1-pyrrolidinyl;

25 B is C₁-C₄alkyl, -CH₂OH, -CH₂OCH₃, -CO₂-CH₂-CH₃; and

X_1 et X_2 are independently hydrogen, methyl, methoxy, $-\text{CH}_2\text{OH}$, F, Cl, Br, $-\text{C}(=\text{O})\text{OR}^3$, or $\text{C}(=\text{O})\text{NR}^4\text{R}^5$;

R^3 , R^4 , and R^5 being as defined above.

In another preferred embodiment of the compounds of Formula I,

5 A is $-\text{CH}_3$ or $-\text{NH}_2$; and

B is $-\text{CH}_3$ or $-\text{CH}_2\text{OCH}_3$.

In another preferred embodiment of the compounds of Formula I,

Z, Z_1 , Z_2 are CH; and

X_1 or X_2 is methyl, F, Cl, or Br at position 5 of the quinazoline ring system.

10 In another especially preferred embodiment of the compounds of Formula I,

Z, Z_1 , Z_2 are CH;

A is $-\text{NH}_2$; and

X_1 or X_2 is $-\text{C}(\text{O})\text{OR}^3$ or $-\text{C}(=\text{O})\text{NR}^4\text{R}^5$ at position 7 of the quinazoline ring system;

R^3 , R^4 , and R^5 being as defined above.

15 In a most preferred embodiment of the present invention, the compounds are

(3S)-3-(2-Methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-

3H[1,4]diazepino[6,7,1-*hi*]indol-4-one;

9-Methoxy-3-(2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-

[1,4]diazepino[6,7,1-*hi*]indol-4-one;

20 2-Methyl-3-(9-methoxy-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-

hi]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid methyl ester;

2-Methyl-3-(9-methoxy-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-

hi]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid.

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-

25 3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-

3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid methyl ester;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-

3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid;

30 D-Glucamine 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-

[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylate salt;

(3R) 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid;

(3S) 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid;

5 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 2-morpholin-4-yl-ethyl ester;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 2-acetoxy-ethyl ester;

10 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 2-methoxy-ethyl ester;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 2-hydroxy-ethyl ester;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 1-(2S)-glycerol ester;

15 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 2-hydroxy-3-morpholin-4-yl-propyl ester.

9-Methyl-3-(2-methyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

20 (3S)9-Methyl-3-(2,5-dimethyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

(3S)9-Methyl-3-(2,6-dimethyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

25 (3S)9-Methyl-3-(2,6-dimethyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.;

(3S)9-Methyl-3-(2,8-dimethyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(5-Methoxy-2-methyl-4-oxo-4H-quinazolin-3yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

30 3-(7-Methoxy-2-methyl-4-oxo-4H-quinazolin-3yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(6-Methoxy-2-methyl-4-oxo-4H-quinazolin-3yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(6-Bromo-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(5-Hydroxymethyl-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

5 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-5-carboxylic acid tertibutyl ester ;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-5-carboxylic acid;

10 3-(7-Hydroxymethyl-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

(3S)3-(5-Fluoro-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(5-Chloro-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

15 (9-Methyl-3-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino [6,7,1-*hi*]indol-4-one.

3-(9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid ethyl ester;

20 5-Chloro-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid ethyl ester;

[3-(9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-acetic acid ethyl ester;

Acetic acid 3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl ester;

25 9-Methyl-3-(2-methyloxymethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

9-Methyl-3-(2-hydroxymethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

30 Succinic acid mono-[3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl] ester;

[2-(2-Methoxy-ethoxy)-ethoxy]-acetic acid mono-[3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl] ester;

N-(2-Morpholin-4-yl-ethyl)-succinamic acid 3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl-methyl ester;

Succinic acid 3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl ester 2-morpholin-4-yl-ethyl ester;

6-*t*-Butoxycarbonylamino-2-{3-[3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxycarbonyl]-propionylamino}-hexanoic acid methyl ester;

3-[3-(9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-propanoic acid ethyl ester.

(3S) 3-(2-Methyl-4-oxo-4H-pyrido[3,4-*d*]pyrimidin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-1-one;

3-(2-Methyl-4-oxo-4H-pteridin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

9-Amino-3-(2-methyl-4-oxo-4H-pyrido[3,4-*d*]pyrimidin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

3-(2-Methyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(2,5-Dimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(2,6-Dimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(2,7-Dimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(2,8-Dimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(2,6,8-Trimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(8-Bromo-2,6-dimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

(3S)3-(2-Methyl-4-oxo-4H-pyrido[3,4-*d*]pyrimidin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

5-Chloro-2-methyl-3-(9-nitro-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline.

(3S)9-Amino-3-(2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(9-Amino-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-2-methyl-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid methyl ester, and its enantiomers;

3-(9-Amino-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-2-methyl-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid;

5 9-Amino-3-(2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

9-Amino-3-(2,5-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

10 9-Amino-3-(2,6-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

9-Amino-3-(2,8-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

9-Amino-3-(2,6,8-trimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

15 9-Amino-3-(5-chloro-2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxamide;

20 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carbonitrile;

9-Methyl-3-[2-methyl-4-oxo-7-(1H-tetrazol-5-yl)-4H-quinazolin-3-yl]-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-N-methylcarboxamide;

25 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-N-dimethylcarboxamide;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;

30 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid (3-(morpholin-4-yl-propyl)-amide;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-(2-amino)-ethylcarboxamide, and the hydrochloride salt thereof;

3- {7-[4-(2-Hydroxy-ethyl)-piperazine-1-carbonyl]-2-methyl-4-oxo-4*H*-quinazolin-3-yl}-9-methyl-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-4-one, and the hydrochloride salt thereof;

(2*S*) 6-*t*-Butoxycarbonylamino-2- {[2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carbonyl]-amino}-hexanoic acid methyl ester;

(2*S*) 6-Amino-2- {[2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carbonyl]-amino}-hexanoic acid methyl ester.

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carboxylic acid pentafluorophenyl ester;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carboxyl-)-tyrosine;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carboxyl-)-alanine;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carboxyl-)-phenylalanine;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carboxyl-)-glycine;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carboxyl-)-leucine;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carboxyl-)-aspartic acid;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carboxyl-)-glutamic acid;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carboxyl-)-lysine;

2{[2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carbonyl]-amino}-3-phenyl-(*L*)-propionic acid ethyl ester;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carboxyl-)-proline.

In the foregoing as well as hereinafter:

the terms "C₁-C₄ alkyl" and "C₁-C₆ alkyl" mean straight and branched aliphatic groups

having from 1 to 4, respectively from 1 to 6, carbon atoms, examples of which include methyl, ethyl, isopropyl, tert.-butyl, *n*-hexyl, and isohexyl;

the terms "O-C₁-C₄ alkyl" and "O-C₁-C₆ alkyl" mean above-mentioned alkyl groups having from 1 to 4, respectively from 1 to 6, carbon atoms, attached to an oxygen atom,

5 examples of which include methoxy, ethoxy, isopropoxy, tertibutoxy, and the like;

the term "natural α amino-acid" refers to one of the naturally occurring amino acids which are constituents of proteins: typical amino acids thus include glycine, alanine, valine, leucine, isoleucine, phenylalanine, serine, cysteine, threonine, lysine, arginine, aspartic acid, asparagine, glutamic acid, glutamine, tyrosine, methionine, tryptophan,

10 histidine and proline; aromatic is understood to mean a compound containing a phenyl, pyridyl or pyrazinyl ring;

halogen is understood to mean fluorine, chlorine, bromine or iodine;

the symbol "-" means a bond;

Unless the context clearly requires otherwise, throughout the description and the claims,

15 the words 'comprise', 'comprising', and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

The term "patient" means all animals including humans: examples of patients include humans, cows, dogs, cats, goats, sheep, and pigs;

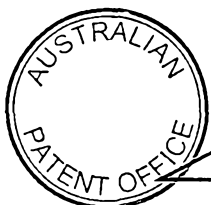
20 those skilled in the art are easily able to identify patients at risk of having, having, or having had asthma, rheumatoid arthritis, atopic dermatitis, bone loss, pulmonary hypertension, liver injury, septic shock, multiple sclerosis, or inflammatory bowel disorders such as ulcerative colitis and Crohn's disease;



a therapeutically effective amount is an amount of a compound (I) that, when administered to a patient, prevents or ameliorates a symptom of the disease.

The compounds of the present invention can be administered to a patient either alone or a part of a pharmaceutical composition. The compositions can be administered to
5 patients either orally, rectally, parenterally (intravenously, intramuscularly, or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray.

A review of salts which are acceptable in pharmacy will be found in J. Pharm. Sci., 1977, 66, 1-19. However, pharmacologically acceptable salt of a compound of formula
10 (I) possessing a basic portion is understood to mean the addition salts of the compounds of formula (I) which are formed from nontoxic inorganic or organic acids such as, for example, the salts of hydrobromic, hydrochloric, sulfuric, phosphoric, nitric, acetic, succinic, tartaric, citric, maleic, hydroxymaleic, benzoic, fumaric, toluenesulfonic, isethionic, and the like, acids. The various quaternary ammonium salts of the derivatives
15 (I) are also included in this category of the compounds of the invention. And pharmacologically acceptable salt of a compound of formula (I) possessing an acidic portion is understood to mean the commonplace salts of the compounds of formula (I)

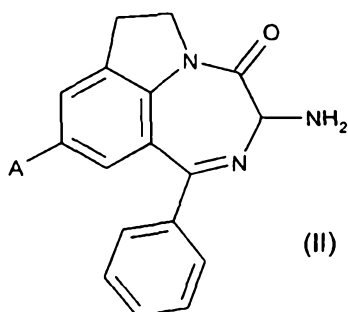


which are formed from nontoxic inorganic or organic bases such as, for example, alkali metal and alkaline-earth metal hydroxides (sodium, potassium, magnesium and calcium hydroxides), amines (dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or alternatively quaternary ammonium hydroxides such as tetramethylammonium

5 hydroxide.

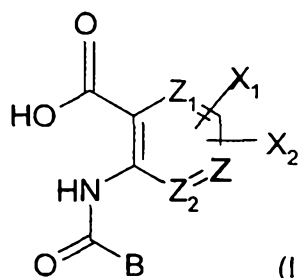
Another aspect of the invention relates to a process for preparing the diazepinoindolones (I), which consists:

- 10 *i*) - for preparing compounds (I) in which A and Z have the designations of (I), B the designations of (I) except for those comprising a carboxylic acid function, and X₁ and X₂ the meanings of (I) except for those comprising a reactive hydroxyl function, in reacting an intermediate aminodiazepinoindolone (II) of formula



in which A has the designations of (I),

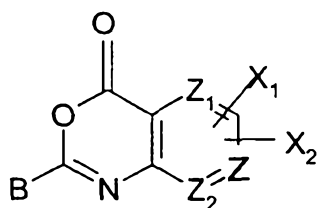
- with an aromatic 2-amido acid (IIIa) of formula



in which B, Z, Z₁, Z₂, X₁ and X₂ have the designations defined

15 above, or

- with a 4-oxo-4H-oxazine (IIIb) of formula

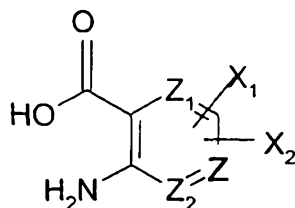


in which B, Z, X₁ and X₂ have the designations defined above,

or

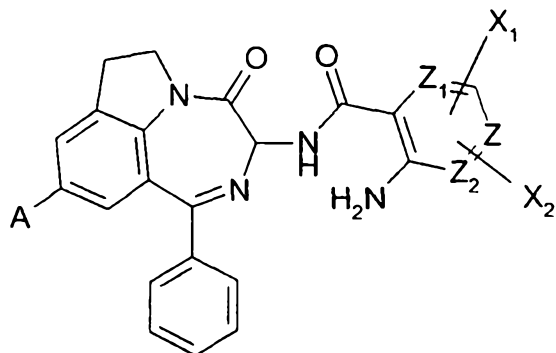
- with a mixture comprising from 95 to 5% by weight of an intermediate (IIIa) with from 5 to

95% of an intermediate (IIIb), in which B, Z, X₁ and X₂, which are identical for both intermediates, have the designations defined above, the intermediates (IIIa) and (IIIb) being isolated or otherwise after their preparation by N-acylation and then, where appropriate, cyclization of an aromatic 2-amino acid (III) of formula

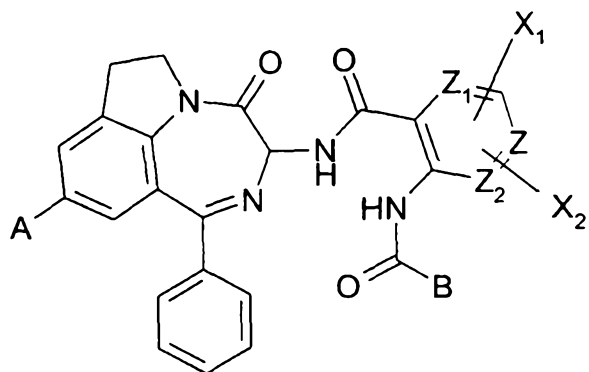


5 (III) with 1,1,1-trimethoxyethane, or with a reactant (B-CO)_nW in which B has the designations of (I) except for those comprising a carboxylic acid function, and W is halogen, in particular chlorine or bromine, when n has the value 1, or alternatively is oxygen when n has the value 2;

10 *ii*) - for preparing compounds (I) in which B and Z have the designations of (I), A the designations of (I) except for amino and X₁ or X₂ the meanings of (I) except for those comprising a reactive hydroxyl function, in N-acylating an intermediate diazepinoindolone (IV) of formula



in which A, Z, X₁ and X₂ have the designations defined above, with a reactant (B-CO)_nW defined above in which B has the meanings designated above, to obtain an intermediate (V) of formula



15

which is cyclized to a diazepinoindolone (I);

iii) - for preparing a compound (I) in which A is amino and where B, Z, X₁ and X₂ have the meanings of (I), in reducing with sodium sulfide or a metal chloride, in particular tin chloride, a compound (I) in which A is nitro; or

iv) - for preparing a compound (I) in which A and Z have the meanings of (I), and

5 B and/or X₁ and/or X₂ are functionalized:

- in hydrolyzing in an acid or alkaline medium a compound (I) comprising an amide (-CO-N<) or ester (-CO-O- or -O-CO-) function, to obtain a corresponding acid or alcohol compound (I);

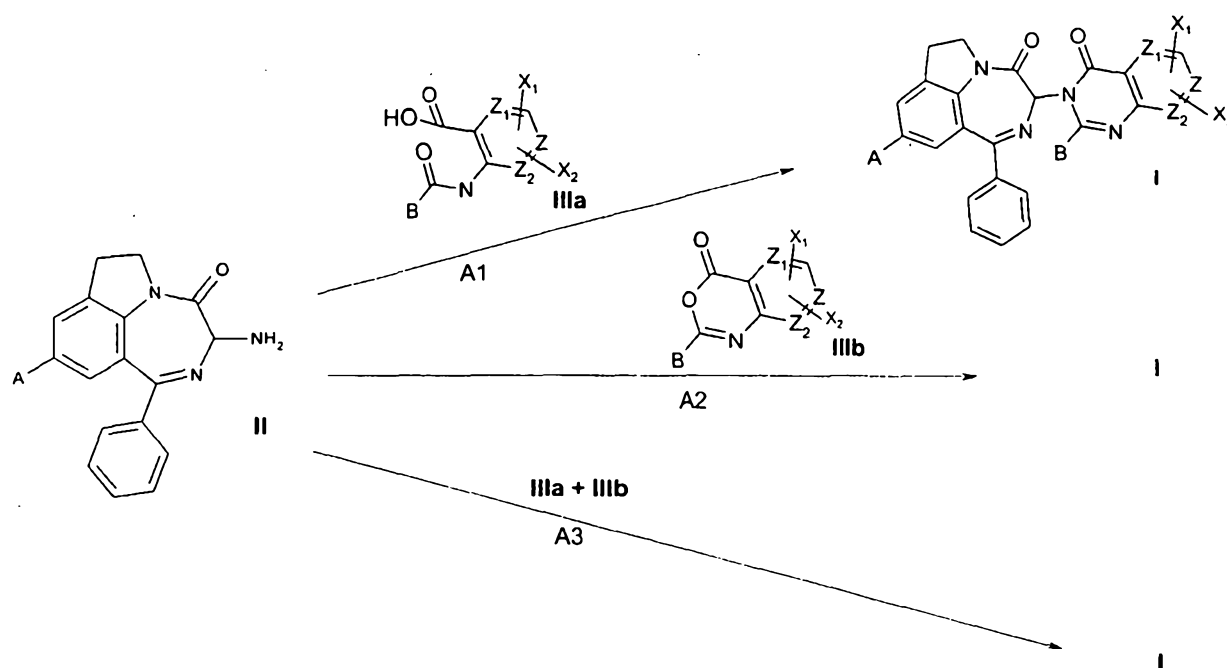
10 - in reducing with a complex metal hydride or organometallic hydride a compound (I) comprising an acid (-CO-OH) or ester (-CO-O-) function, to obtain a corresponding alcohol compound (I);

- in carrying out the hydrogenolysis in the presence of a metal catalyst of a compound (I) comprising an ether, in particular a benzyl ether (-O-CH₂-C₆H₅), function, to obtain a corresponding alcohol compound (I);

15 - in esterifying or transesterifying with an alcohol a compound (I) having an acid (-CO₂H) or ester (-CO-O-) function, to obtain a compound (I) ester of said alcohol; or

- in amidating with ammonia or a primary or secondary amine a compound (I) comprising an acid (-CO-OH) or ester (-CO-O) function, to obtain a corresponding primary, secondary or tertiary amide compound (I).

20 **Scheme 1**



More specifically, the process A for preparing the compounds (I), by reacting an amino

intermediate (II) with an intermediate prepared from a 2-amino acid (III), as presented in Scheme 1, consists:

1) - in a process A1 wherein a 2-acetamido acid (IIIa) is employed, in carrying out the N-acylation of the amine (II) and cyclizing the intermediate obtained to obtain the diazepinoindolone (I). The operation is carried out in an anhydrous organic solvent such as a chlorinated hydrocarbon, for instance CH_2Cl_2 or chloroform, a linear or cyclic ether such as 1,2-dimethoxyethane, tetrahydrofuran or dioxane, an aprotic polar solvent such as pyridine, dimethyl sulfoxide, N,N-dimethylformamide or any other suitable solvent, and mixtures thereof. Advantageously, the reaction is carried out in the presence of a condensing agent and optionally of an organic base. Thus, as condensing agent, phosphorus trichloride is used in a process A1a, an isobutyl chloroformate/ N-methylmorpholine combination in a process A1b and, preferably, an O-[(ethoxycarbonyl)cyanomethylamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate/N,N-diisopropylethylamine (OTUT/DIEA) combination in a process A1c.

To carry out these processes A1, the acetamido acid (IIIa) is employed in isolated form or, according to a preferred alternative method, in the form of an unisolated compound (IIIa) prepared beforehand by reacting an acid (III) with the acylating agent $(\text{B-CO})_n\text{W}$ or 1,1,1-trimethoxyethane described above, according to widely documented techniques.

In the experimental part which illustrates the invention, Example 15 is representative of the process A1a, Example 19 of the process A1b and Examples 1 and 3 of the alternatives of the process A1c;

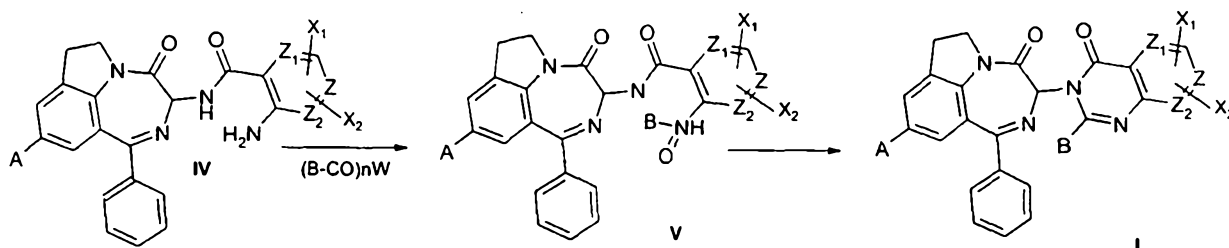
2) - in a process A2 wherein an amine (II) is condensed with a 4-oxo-4H-oxazine (IIIb), in carrying out the operation in an anhydrous medium in a chlorinated hydrocarbon such as CH_2Cl_2 or an aromatic hydrocarbon such as toluene, heating, where appropriate under pressure, above the boiling point of the solvents in order to favor the progress of the reaction.

Just as in the process A1, the intermediate (IIIb) is employed in isolated form or, alternatively, in unisolated form, it being prepared beforehand by conventional processes of acylation of a compound (III) with the agent $(\text{B-CO})_n\text{W}$ described above and in which, preferably, n has the value 2 and W is oxygen, or alternatively being prepared by a cyclization reaction of an intermediate (IIIa) under the action of an anhydride such as acetic anhydride, Example 7 of the experimental part being representative of this process A2; or

3) - in a process A3, in condensing an amine (II) with a mixture in varied proportions of unisolated intermediates (IIIa) and (IIIb) (which mixture is obtained beforehand by reacting an

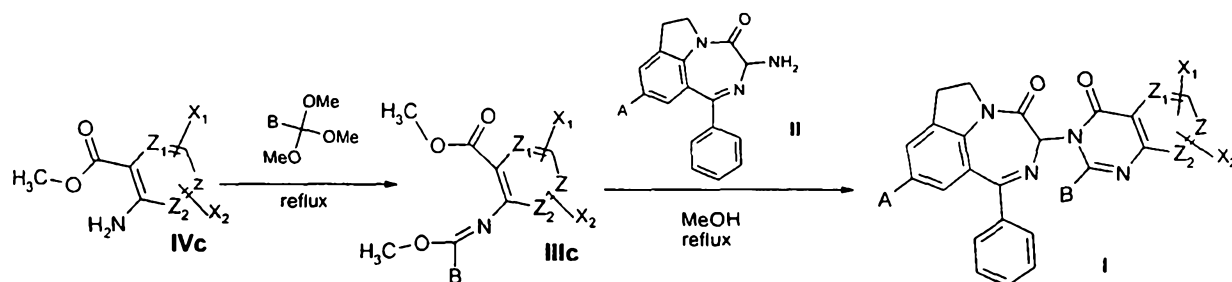
acid (III) in the presence of a strong organic base with an acylating agent $(B-CO)_nW$ described above and in which, preferably, n has the value 1 and W is halogen, and in particular chlorine) in an anhydrous medium in a halogenated hydrocarbon such as CH_2Cl_2 . Example 16 of the experimental part is representative of this process.

5

Scheme 2

The process B as presented in scheme 2 consists, in a first step, in carrying out the N-acylation of an intermediate (IV), which is carried out by conventional methods such as the reaction of (IV) with the acylating agent $(B-CO)_nW$ described above, to obtain an intermediate (V) which, in a second step, is cyclized to a compound (I); this is carried out by heating in an inert solvent having a high boiling point, such as xylene or 1,2-dichlorobenzene, which is preferred. In the experimental part illustrating the invention, Example 27 is representative of this process.

10

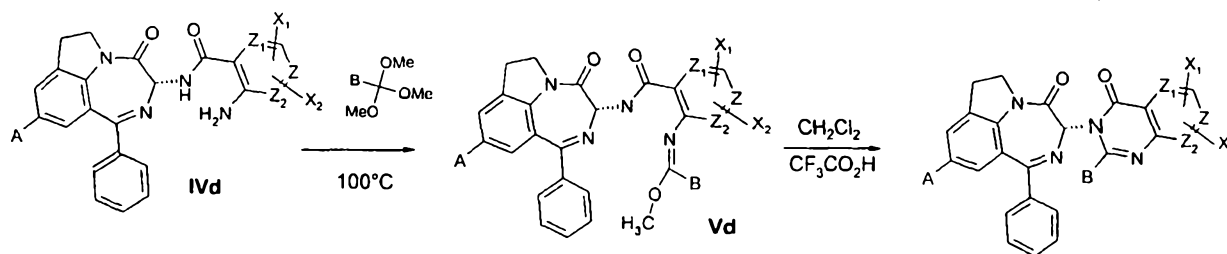
Scheme 3

15

The process A4 as presented in scheme 3 consists in carrying out the N-acylation of the amine (II) with a imine derivative of an aromatic ester (IIIc), and cyclizing the intermediate obtained under conditions similar to those of process A2. The intermediate (IIIc), isolated or, preferably, not isolated is first prepared by conventional condensation of an aromatic amine (IVc) with a 1,1,1-trimethoxy-alkane, 1,1,1-trimethoxy-ethane being preferred ($B = CH_3$). The reaction can be carried out in an organic anhydrous solvent like those indicated for process A1. Example 28A is representative of this process.

20

Scheme 4



The process A5, preferred, as presented in scheme 4 consists in reacting an optically active amine (IVd), prepared according to WO 97/36905, with an ortho-ester, 1,1,1-trimethoxyethane being preferred (B = CH₃), to obtain the imine derivative (Vd), and cyclizing the

5 intermediate obtained in a neutral solvent with an acid catalyst.

The process C consists in reducing specifically a compound (I) in which A is nitro to a compound (I) in which A is amino, which is carried out with suitable reducing systems, namely, inter alia, titanium chloride or zinc in an acid medium, or alternatively and preferably, according to a process C1, sodium sulfide in an ethanolic medium, or, according to the process C2, tin

10 chloride in an ethanolic medium, which processes are represented in the experimental part of the invention by Examples 29 and 32, respectively.

The processes D, which, starting from (I), enable compounds to be prepared in which B and/or X₁ and/or X₂ are functionalized, make use of processes which are known to a person skilled in the art and are widely documented, references to which will be found in a general work such as

15 "Advanced Organic Chemistry" by J. March (3rd Edition - Ed. J. Wiley Intersciences), and which, as may be recalled briefly, consists:

- 1) - for hydrolyzing an amide (-CO-N=) to a corresponding acid by a process D1a, in performing a hydroxy-de-amination in an aqueous medium and in the presence of an acid catalyst or basic catalyst under conditions suited to the nature of the amide and in the presence of water-miscible

20 inert solvents;

- 2) - for hydrolyzing an ester (-CO-O-) or (-O-CO-) and obtaining a corresponding acid or alcohol by a process D1b, in performing a hydroxy-de-alkoxylation in an aqueous medium in the presence of an acid catalyst or, and preferably, basic catalyst. The hydrolysis can take place in a two-phase heterogeneous medium for water-insoluble esters, or alternatively in solution in the

25 presence of water-miscible solvents such as, in particular, C₁ to C₄ alcohols, under time and temperature conditions specific to the product to be treated;

- 3) - for reducing an acid (-CO-OH) or an ester (-CO-O-) and obtaining a corresponding alcohol by a process D2, in reacting a hydride; a general account of the possibilities will be found in "Advanced Organic Chemistry" - J. March. - 3rd Edition - (Ed. J. Wiley Intersciences) p. 1093 et

seq. The process D2a consists of a reduction with metal hydrides or organometallic hydrides: the monometallic hydrides are of general formula $M_1(H)_{Y_1}(R_3)_{Z_1}$ in which M_1 is aluminum or boron, R_3 is linear- or branched-chain C_2 to C_4 lower alkyl, Y_1 is 1, 2 or 3, Z_1 is 0, 1 or 2, the sum $Y_1 + Z_1$ being in any case equal to 3.

5 The dimetallic complex hydrides are of formula $M_2M_1(H)_{Y_2}(R_3)_{Z_2}$ in which M_1 is aluminum or boron, M_2 is an alkali metal, in particular lithium or sodium, R_3 is linear- or branched-chain C_2 to C_4 lower alkyl or alternatively linear- or branched-chain C_2 to C_4 lower alkoxy or alternatively alkoxyalkoxy, Y_2 is 1, 2, 3 or 4, Z_2 is 0, 1, 2 or 3, the sum $Y_2 + Z_2$ being in any case equal to 4.

10 Among these hydrides, the dimetallic ones are preferred and, when Z_2 is equal to 0, those in which M_1 is aluminum and M_2 lithium, or alternatively those in which M_1 is boron and M_2 sodium, namely, in the latter case, sodium borohydride which, favorably, is used in the presence of a Lewis acid such as $AlCl_3$ or in the presence of a sulfuric acid. As regards the hydrides in which Z_2 is 1, 2 or 3, those in which Z_2 has the value 2, M_2 is sodium and M_1 aluminum and R_3 is
15 alkoxyalkoxy such as a methoxyethoxy group are preferred.

An alternative process D2b consists in performing this reduction on an intermediate ester of the acid, produced *in situ* for example with an alkyl chloroformate, and in then reducing this unisolated ester with a hydride; as an illustration, Example 11 is representative of this process;
4) - for the hydrogenolysis of a benzyl ether ($-O-CH_2-C_6H_5$) in the presence of a catalyst and to
20 obtain a corresponding alcohol by a process D3, in performing the reaction in a neutral protic solvent, for instance a water-miscible primary alcohol of boiling point below $100^\circ C$, such as ethanol, which is preferred. A suitable catalyst is, inter alia, palladium absorbed on charcoal in the proportion of 5 to 10% and appropriately activated. The reaction is conducted under a hydrogen pressure of 1 to 10 bar and at a temperature of 20 to $70^\circ C$ depending of the reactivity
25 of the compound to be treated;

5) - for esterifying, according to a process D4a, a compound (I) comprising an acid function ($-CO-OH$), and for transesterifying, according to a process D4b, a compound (I) comprising an ester function ($-CO-O-$):

- according to D4a, in reacting the acid compound (I) with a primary alcohol derivative
30 in an anhydrous neutral solvent such as DMF in the presence of a coupling agent such as a carbodiimide (for instance N,N' -diisopropylcarbodiimide (DIC) or N,N' -dicyclohexylcarbodiimide (DCC)) and a catalyst like 4-dimethylamino-pyridine tosylate, or alternatively in the presence of carbonyldiimidazole, which is preferred, as in Example 10 which is representative of this process, and

- according to D4.b, in reacting an ester compound (I) with an alcohol in the presence of a metal catalyst, optionally in the form of its alkoxide with a C₁ to C₃ primary alcohol, it being possible for the reaction to be carried out in a neutral aromatic solvent such as benzene, toluene or xylene, and the reaction being favored by the removal of the alcohol formed during the trans-
5 esterification, which may be achieved by continuous azeotropic distillation;

6) - for amidating with ammonia or a primary or secondary amine an acid compound (I) according to a process D5a, in reacting the acid compound with the amine in the presence of a coupling agent identical to the ones indicated for D4a, or also, in tetrahydrofuran, in the presence of "PyBrop", which is bromotris(pyrrolidino)phosphonium hexafluorophosphate. An alternative
10 method D5b, which is preferred, consists in preparing "in situ", in a first stage, a halide of the acid (I), which is produced with suitable reagents such as, advantageously, oxalyl chloride, and then, in a second stage, in reacting the acid chloride thereby obtained with the amine, which can be in gaseous or liquid form or in solution in a neutral solvent. By way of illustration, Example 8 represents this process;

7) - for dehydrating an amide -CO-NH₂ into nitrile, according to a process D6, in reacting an amide compound (I) with a dehydrating agent according to processes referred to in particular in *Advanced Organic Chemistry* - J. March, - 3rd Edition - (Ed. J. Wiley Intersciences) or, preferably, using the Burgess reagent, which is the internal salt of
15 (methoxycarbonylsulfamoyl)triethylammonium hydroxide;

8) - for adding an azide and an unsubstituted amide compound (I) in order to obtain the corresponding tetrazole according to a process D7, in reacting the amide with NaN₃ in the presence of ammonium chloride;

9) - to obtain from an acid a ketone of formula (I) with X₁ or X₂ = -C(=O) R³ where R³ is preferably C₁-C₄alkyl, in first preparing a derivative of the acid: acyl chloride, anhydride,
25 ester or amide, which is further reacted according to conventional techniques with an organo-metallic compound, such as R³MgX at a low temperature, or with an alkyl-lithium. In the latter case, one can use directly the acid or, preferably, its lithium salt;

10) - to demethylate a compound (I) wherein A = -OCH₃ and obtain the corresponding phenol, in reacting (I) with BBr₃ according to a process identical to the one described in application
30 WO 97/36905, Example 1;

11) - to obtain a compound (I) wherein A = -CN, in carrying out a cyanation with BrCN or Cl₃C-CN in acidic medium according to processes referred to in particular in *Advanced*

Organic Chemistry - J. March, - 3rd Edition - (Ed. J. Wiley Intersciences) page 497.

The invention also relates to a medicament for preventing or treating inflammatory disorders including, where it is present, an autoimmune component, allergic disorders or
5 bronchoconstriction, and which is useful, in particular, in the treatment of asthma, rheumatoid arthritis, atopic dermatitis or inflammatory intestinal diseases. Treatment of animals, including humans, consist in administering a diazepinoindolone according to the invention, in a pharmaceutical dosage form which is suited to the disease to be treated. Conditions also
10 amenable to treatment with a compound according to the invention include inflammatory intestinal diseases like ulcerative colitis and Crohn's disease, disorders characterized by an important increase of TNF- α , such as pulmonary hypertension (primary or secondary), liver failure in particular following immunologic or inflammatory hepatic injury, bone loss (osteoporosis or osteomalacia), septic shock, and multiple sclerosis.

The examples which follow illustrate, without, however, limiting it, the implementation
15 of the processes and the products of the invention. The purity, identity and physicochemical properties of the products and of the essential intermediates prepared are determined; thus:
- the purity is verified by thin-layer chromatography (TLC) on silica gel (Merck 60 - F254), and the R_f observed is recorded for the elution solvent used which is, more often than not, identical to the one used for the preparative chromatographic purification of the compounds. These solvents
20 are identified by the following designations:

C/A20: cyclohexane/acetone, 80:20 (v/v),

C/A30: cyclohexane/acetone, 70:30 (v/v),

D/A1: CH₂Cl₂/acetone, 99:1 (v/v),

D/A1.5: CH₂Cl₂/acetone, 98.5:1.5 (v/v),

25 D/A2: CH₂Cl₂/acetone, 98:2 (v/v),

D/A3: CH₂Cl₂/acetone, 97:3 (v/v),

D/A4: CH₂Cl₂/acetone, 96:4 (v/v),

D/A5: CH₂Cl₂/acetone, 95:5 (v/v),

D/A6: CH₂Cl₂/acetone, 94:6 (v/v),

30 D/A10: CH₂Cl₂/acetone, 90:10 (v/v),

D/A20: CH₂Cl₂/acetone, 80:20 (v/v),

D/A30: CH₂Cl₂/acetone, 70:30 (v/v),

D/M1: CH₂Cl₂/methanol, 99:1 (v/v),

D/M2: CH₂Cl₂/methanol, 98:2 (v/v),

D/M3: CH₂Cl₂/methanol, 97:3 (v/v),

D/M5: CH₂Cl₂/methanol, 95:5 (v/v),

D/M7: CH₂Cl₂/methanol, 93:7 (v/v),

5 D/M30: CH₂Cl₂/methanol, 70:30 (v/v),

D/MN2: CH₂Cl₂/10% ammoniacal methanol, 98:2 (v/v),

D/MN5: CH₂Cl₂/10% ammoniacal methanol, 95:5 (v/v)

D/MN10: CH₂Cl₂/10% ammoniacal methanol, 90:10 (v/v),

D/MN20: CH₂Cl₂/10% ammoniacal methanol, 80:20 (v/v),

10 Ea: ethyl acetate;

- the identity of the products obtained with the proposed structures is verified by their proton nuclear magnetic resonance spectrum and by their infrared spectrogram.

The ¹H NMR spectra are recorded at 400 MHz on a Brhcker make instrument, the compounds being dissolved in deuteriochloroform with tetramethylsilane as internal reference.

15 The nature of the signals, their chemical shifts in ppm and the number of protons they represent are noted.

The infrared spectra are recorded in a potassium bromide disk on a Shimadzu IR-435 spectrometer.

20 - the physicochemical properties, recorded wherever a sufficient amount of product was available, are their uncorrected melting point, determined by the capillary tube method, and their optical rotation, determined at room temperature in the region of 20°C on a Polartronic instrument in a cell 10 cm long, and the results of which enable the optical purity to be assessed in some cases by calculation of the enantiomeric excess (e.e.). Commonly used abbreviations for some reagents and solvents have been used, such as:

25 - THF, for tetrahydrofuran;

- DMF, for N,N-dimethylformamide;

- OTUT, for O-[(ethoxycarbonyl)cyanomethylamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate;

- DIEA, for N,N-diisopropylethylamine.

30 As regards the experimental description, concentration or removal of the solvents is understood to mean, where appropriate after they are dried over a suitable drying agent such as Na₂SO₄ or MgSO₄, a distillation under a vacuum of 25 to 50 mm of Hg and with moderate heating on a water bath; flash chromatography on a silica column is understood to mean the implementation of a method adapted from that of Still *et al.* (1978) *J. Org. Chem.* **43**: 2923, the

purity of the elution fractions being verified before they are pooled and evaporated under the conditions defined above.

EXAMPLES

5

Intermediate compounds

Intermediate 1: (3RS)-3-Amino-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one [(II); A = H]

10 The preparation of the racemic compound is described in Example 1 stages a) and b) of EP 0 340 064 A1, in which the enantiomers are also disclosed.

Intermediate 2.a: (3RS)-3-amino-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one [(II); A = CH₃].

The compound is synthesized as described in Patent FR 94 12282 (Publication No. 15 2 725 719), in the preparation of the intermediate 2.a.

Intermediate 2.b: (3R)-3-amino-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one [(II); A = CH₃].

The compound is synthesized as described in Patent FR 94 12282 (Publication No. 20 2 725 719), in the preparation of the intermediate 2.b.

Intermediate 3.a: (3RS)-3-amino-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one [(II); A = NO₂] and

Intermediate 3.b: (3R)-3-amino-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one [(II); A = NO₂]. The compound is synthesized as described in International 25 Application WO 97/36905 (intermediate 2, stage 1) from the precursor of the same stereochemistry.

Intermediate 4: (3R)-3,9-diamino-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one [(II); A = -NH₂]. The compound is synthesized as described in International Application WO 97/36905 (intermediate 2, stage 2).

30 **Intermediate 5:** (3S)-3-amino-N-(9-nitro-4-oxo-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)isonicotinamide

Stage 1: 25.4 g (184 mmol) of 3-aminoisonicotinic acid in 600 ml of dioxane are introduced into a reactor, and 184 ml of 1N NaOH solution are then added. The mixture is cooled with stirring to 5°C and 60.24 g (236 mmol) of di-*t*-butyl dicarbonate are then added dropwise. The mixture is

then maintained for 4 h at 20-25°C and thereafter 38.6 g (200 mmol) of citric acid are added portionwise. The solvents are distilled off and the residue is taken up with 500 ml of water. The insoluble matter is filtered off, washed with water and then dried under vacuum at 50°C. 36.5 g of 3-(*t*-butyloxycarbonylamino)isonicotinic acid are obtained. Yld = 81% - TLC (D/M30): Rf = 0.45.

Stage 2: 11.1 g (46.5 mmol) of the compound obtained in the preceding stage in 500 ml of THF dried over molecular sieve are introduced into a reactor protected from moisture. With stirring, 19.5 ml, equivalent to 14.13 g (139.6 mmol), of triethylamine are added and, after solubilization, 15.0 g (46.5 mmol) of the intermediate (R) amine 3.b and then 26.0 g (55.8 mmol) of PyBrop are added. The mixture is stirred for 20 h at 20-25°C and the solvents are then removed by distillation. The residue is purified by flash chromatography on a silica column. Elution with the mixture D/M2 enables 9.0 g of (3*S*)-3-*t*-butyloxycarbonylamino-N-(9-nitro-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)isonicotinamide to be obtained. Yld = 36% - TLC (D/M5): Rf = 0.45.

Stage 3: 9.0 g (16.6 mmol) of the compound obtained in the preceding stage in 90 ml of CH₂Cl₂ are introduced into a reactor protected from moisture. With stirring at 20-25°C, 45 ml of pure trifluoroacetic acid are introduced dropwise. The mixture is then maintained for 1 h under these conditions and thereafter the solvents are removed by distillation. The residue is taken up with 100 ml of ethyl acetate and the mixture is extracted with 3 times 75 ml of saturated NaHCO₃ solution and then with water. The ethyl acetate is removed by distillation and the residual product, intermediate 5 in amorphous form, is found to be pure by TLC. Weight: 5.1 g - Yld = 69.0% - TLC (D/M5): Rf = 0.25.

EXAMPLE 1

(3*S*)-3-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3*H*[1,4]diazepino[6,7,1-*hi*]indol-4-one.

(I); A = H, Z = CH, B = CH₃, X₁ = H, X₂ = H (process A1c)

In a reactor protected from moisture, 2.65 g (5.5 mmol) of the intermediate amine 1 of R configuration are dissolved with stirring in 30 ml of CH₂Cl₂. 1.08 g (6.0 mmol) of 2-acetamidobenzoic acid and then 1.8 g (5.5 mmol) of OTUT are added. The mixture is cooled to 0°C and 1.4 g (11 mmol) of DIEA are then added. After 16 h with stirring at laboratory temperature, the insoluble matter is filtered off and the filtrate extracted successively with 1*N* HCl solution and saturated NaHCO₃ solution and lastly with water. The solvent is evaporated off and the residue purified by flash chromatography on a silica column, eluting with the solvent

- 26 -

D/A3. 0.65 g of a crystallized white solid is obtained. Yld = 28% - M.p. = 210°C - TLC (D/M3): Rf = 0.26 - $[\alpha]_D^{20} = +23.6E$ (c = 1, CH₂Cl₂).

¹H NMR δ (ppm): 1.75 (s, 1H); 2.85 (s, 3H); 3.15 (m, 1H); 3.4 (m, 1H); 4.0 (m, 1H); 4.22 (m, 1H); 7.12 (m, 1H); 7.20 (s, 1H); 7.45 (m, 5H); 7.55 (d, 2H); 7.75 (m, 2H); 8.2 (d, 1H).

5 IR: 1660, 1570, 1460, 1440, 1380, 1340, 1290, 1240, 1170, 770, 690 cm⁻¹.

(3S)-3-(2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H[1,4]diazepino[6,7,1-*hi*]indol-4-one.

(I); A = H, Z = CH, B = CH₃, X₁ = H, X₂ = H (process A4)

1 g of 2-amino-N-((3R) 9-amino-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]-
10 indol-3-yl)-benzamide is dissolved in 10 ml of 1,1,1-trimethoxyethane in a reactor. The medium is stirred and refluxed for 5 h, and then concentrated to dryness at 50°C under vacuum. The residue is dissolved in 10 ml CH₂Cl₂; a few drops of trifluoroacetic acid are added. After 10 h, the solvent is evaporated off and the residue purified by chromatography on a silica column, eluting with CH₂Cl₂ containing increasing concentration of MeOH. The title compound is
15 obtained as a white solid, with a yield of 96% and an e.e. >97%.

EXAMPLE 2

9-methyl-3-(2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

20 (I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = H (process A1c)

In a 50-ml reactor protected from moisture and under a nitrogen atmosphere, 2.3 g (7.9 mmol) of the intermediate amine 2.a are introduced into 25 ml of CH₂Cl₂, followed by 1.41 g (7.9 mmol) of 2-acetamidobenzoic acid. The mixture is cooled to 0°C and 2.24 g (17 mmol) of DIEA are added. The mixture is kept stirring for 1 min at 0°C and then for 12 h at room
25 temperature, and 2.56 g (7.9 mmol) of OTUT are then added. The mixture is cooled to 0°C and 2.24 g of DIEA are added. The mixture is maintained for 1 min at 0°C and then 2 h at room temperature. 2.56 g of OTUT and 2.24 g of DIEA are then added under the same conditions; the mixture is then kept stirring for 48 h at room temperature and thereafter washed with 20 ml of
30 water. The solvent is evaporated off and the residue purified by flash chromatography on silica, eluting with the solvent D/A2. The fractions determined pure by TLC are pooled and the solvent is evaporated off. 1.4 g of a light yellow solid are obtained. Yld = 40% - TLC (D/A5): Rf = 0.36.
¹H NMR δ (ppm): 2.2 (s, 3H); 2.8 (s, 3H); 3.05 (m, 1H); 3.3 (m, 1H); 3.4 (m, 1H); 4.65 (m, 1H); 7.0 (s, 1H); 7.1 (s, 1H); 7.35-7.7 (m, 9H); 8.15 (d, 1H).

IR: 3300, 2850, 1660, 1580, 1570, 1460, 1380, 1290, 1230, 1170, 870, 770, 690 cm^{-1} .

EXAMPLE 2A

9-methoxy-3-(2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

(I); A = OCH₃, Z = CH, B = CH₃, X₁ = H, X₂ = H (process A12c).

0.834 g (4.65 mmol) of acetylanthranilic acid and 1.3 g (4.23 mmol) of 3-amino-9-methoxy-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one are dissolved in 13 ml of CH₂Cl₂, the mixture is stirred at room temperature and 0.7 g (5 mmol) of phosphorus trichloride is added. The mixture is stirred for 20 h and 0.35 g of phosphorus trichloride is added, followed by a further 0.35 g 8 h later. The mixture is cooled, 50 ml of saturated NaHCO₃ solution and 100 ml of CH₂Cl₂ are added and the organic phase is separated out after settling has taken place and washed with water. This solution is dried, evaporated and purified by chromatography in the mixture DM1. 0.33 g of yellow powder is obtained. M.p. = 277°C. - Yld = 17%. - TLC (DM3):

R_f = 0.47.

¹H NMR δ (ppm): 2.7 (s, 3H); 3.15 (m, 1H); 3.4 (m, 1H); 3.75 (s, 3H); 3.9 (q, 1H); 4.6 (m, 1H); 6.7 (s, 1H); 7.0 (s, 1H); 7.3 (s, 1H); 7.5 (m, 4H); 7.55 (m, 2H); 7.6 (m, 1H); 7.8 (m, 1H); 8.1 (dd, 1H).

IR: 3300, 2850, 1660, 1580, 1570, 1460, 1380, 1290, 1230, 1170, 870, 770, 690 cm^{-1} .

EXAMPLE 2B

Methyl 2-methyl-3-(9-methoxy-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylate.

(I); A = OCH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CO₂CH₃ at 7. (Process A1c).

The compound is prepared in two steps according to Example 6A below, using dimethyl 2-aminoterephthalate and 3-amino-9-methoxy-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

Yld: 56% - powder - M.p. = 264-265°C - TLC (D/M5): R_f = 0.8.

¹H NMR δ (ppm): 2.7 (s, 3H); 3.15 (m, 1H); 3.35 (m, 1H); 3.7 (s, 1H); 3.95 (s, 3H); 4.0 (m, 1H); 4.6 (t, 1H); 6.65 (s, 1H); 6.9 (s, 1H); 7.45-7.6 (m, 6H); 8 (dd, 1H); 8.2 (m, 2H).

EXAMPLE 2C

2-methyl-3-(9-methoxy-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylic acid.

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(I); A = OCH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CO₂H at 7 (process D1b).

1.3 g of product of Example 2B (2.55 mmol) are dissolved in 55 ml of THF, 18 ml of water containing 0.33 g of potassium hydroxide are added and the mixture is stirred at 20-25°C for 5 h. Ice is added and the mixture is acidified to pH = 5. It is extracted with CH₂Cl₂. The extracts are purified by chromatography. 0.55 g obtained. Yld: 44%. Decomposition starting at 225°C. - TLC (DM5): Rf = 0.1.

¹H NMR δ (ppm): 2.7 (s, 3H); 3.2 (m, 1H); 3.4 (m, 1H); 3.8 (s, 3H); 3.9 (m, 1H); 4.6 (t, 1H); 6.65 (d, 1H); 6.9 (s, 1H); 7.5 (m, 6H); 8.0 (d, 1H); 8.1 (m, 2H).

10

EXAMPLE 3

(3S)-9-methyl-3-(2,5-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]-diazepino[6,7,1-*hi*]indol-4-one.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CH₃ at position 5 (process A1c)

In a 50-ml round-bottomed flask protected from moisture and under a nitrogen atmosphere, 1.2 g (4.12 mmol) of the intermediate amine 2.b of R configuration, 0.88 g (4.53 mmol) of 2-acetamido-6-methylbenzoic acid, prepared by reacting 2-amino-6-methylbenzoic acid with acetic anhydride, and then 1.33 g (4.12 mmol) of OTUT are introduced into 20 ml of CH₂Cl₂. The medium is cooled in an ice bath and 1.44 ml (8.24 mmol) of DIEA are added. The mixture is kept stirring for 1 min at 0°C and then for 16 h at room temperature, and 1.33 g of OTUT are then added. The mixture is cooled to 0°C and 1.44 ml of DIEA are added. The mixture is maintained for 1 min at 0°C and then for 1.5 h at room temperature, and then washed with 1N HCl followed by saturated NaHCO₃. It is dried over Na₂SO₄, the solvent is evaporated off and the residue purified by flash chromatography on silica, eluting with the solvent D/M1. The fractions determined pure by TLC are pooled and the solvent is evaporated off. The product is recrystallized in methanol. Weight = 0.85 g - Yld: 46% - white solid - M.p. = 225°C - [α]_D = +23.6E (c = 1, CH₂Cl₂). -TLC (D/M2): Rf = 0.42.

25

¹H NMR δ (ppm): 2.35 (s, 3H); 2.8 (2s, 6H); 3.1 (m, 1H); 3.4 (m, 1H); 4.0 (q, 1H); 4.7 (t, 1H); 7.05 (s, 1H); 7.4 (m, 10H).

30

EXAMPLE 4

(3S)-9-methyl-3-(2,6-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CH₃ at position 6 (process A1c)

In a first step, 2-acetamido-5-methylbenzoic acid is prepared as described in the preceding example from 2-amino-5-methylbenzoic acid, and the compound is then prepared according to a procedure identical to Example 3.

Yld: 31% - pink solid - M.p. = 152°C - TLC (D/M2): Rf = 0.39

5 ¹H NMR δ (ppm): 2.3 (s, 3H); 2.4 (s, 3H); 2.8 (s, 3H); 3.05 (m, 1H); 3.3 (m, 1H); 3.9 (q, 1H); 4.65 (t, 1H); 7.3 (m, 10H); 7.95 (s, 1H).

EXAMPLE 5

(3S)-9-methyl-3-(2,8-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one. (I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CH₃ at position 8 (process A1.c)

The compound is prepared in two steps according to Example 3, using 2-amino-3-methylbenzoic acid - Yld: 15% - brown solid - M.p. = 158°C - TLC (D/M2): Rf = 0.72

¹H NMR δ (ppm): 2.3 (s, 3H); 2.6 (s, 3H); 2.8 (s, 3H); 3.0 (m, 1H); 3.3 (m, 1H); 3.9 (q, 1H); 4.65 (t, 1H); 7.3 (m, 10H); 8.0 (d, 1H).

EXAMPLE 6

3-(5-methoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one. (I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = OCH₃ at position 5 (process A1.c)

The compound is prepared in two steps according to Example 3, using 2-amino-6-methoxybenzoic acid. Yld: 25% - M.p. = 160-162°C - TLC (C/A30): Rf = 0.22.

¹H NMR δ (ppm): 2.35 (s, 3H); 2.6 (s, 3H); 3.1 (m, 1H); 3.35 (m, 1H); 3.8 (s, 3H); 3.9 (q, 1H); 4.55 (t, 1H); 6.9 (s, 1H); 7.0 (m, 2H); 7.05 (d, 1H); 7.5 (m, 6H); 7.7 (t, 1H).

25 IR: 3400, 2900, 1680, 1590, 1560, 1470, 1380, 1320, 1260, 1080, 700 cm⁻¹

EXAMPLE 6A

3-(7-methoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]-diazepino[6,7,1-*hi*]indol-4-one. (I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = OCH₃ at 7 (process A11.c)

The compound is prepared in two steps using 2.05 g of methyl 2-amino-4-methoxybenzoate, which is refluxed for 6 h in 6 ml of 1,1,1-trimethoxyethane. The volatile products are evaporated and stripped off under high vacuum. The intermediate compound is not purified, and is used directly in the following step. 0.65 g of the amine 2.a is added to 5 ml of

methanol and the solution is refluxed for 16 h under a nitrogen atmosphere. The product is purified by flash chromatography on silica in the mixture D/M1.

Yld: 9% - TLC (D/M2): Rf = 0.3.

¹H NMR δ (ppm): 2.3 (s, 3H); 2.7 (s, 3H); 3.0-3.1 (m, 1H); 3.25-3.35 (m, 1H); 3.85-3.95 (m, 4H); 4.6-4.7 (m, 1H); 6.9-7.05 (m, 3H); 7.15-7.55 (m, 7H); 8.05 (d, 1H).

IR: 3500, 2900, 1685, 1600, 1585, 1565, 1425, 1380, 1280, 1160, 1020, 780, 700 cm⁻¹

EXAMPLE 6B

3-(6-methoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]-diazepino[6,7,1-*hi*]indol-4-one.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = OCH₃, at 6 (process A1c)

The compound is prepared in two steps according to Example 6A, using methyl 2-amino-5-methoxybenzoate. Yld: 28% - TLC (D/M2): Rf = 0.4. White powder - m.p. > 270°C

¹H NMR δ (ppm): 2.4 (s, 3H); 2.6 (s, 3H); 3.15 (m, 1H); 3.35 (m, 1H); 3.85 (s, 3H); 4.0 (q, 1H); 4.55 (t, 1H); 7.0 (s, 1H); 7.05 (m, 2H); 7.4-7.55 (m, 8H); 7.6 (d, 1H).

IR: 1690, 1660, 1590, 1490, 1370, 1270, 1240, 1140, 1100, 1020, 970, 940, 700 cm⁻¹

EXAMPLE 6C

3-(6-bromo-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino-[6,7,1-*hi*]indol-4-one.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = Br at 6 (process A1c)

The compound is prepared in two steps according to Example 6A, using methyl 2-amino-5-bromobenzoate.

Yld: 33% - TLC (D/M2): Rf = 0.75. - White powder - M.p. = 178-181°C.

¹H NMR δ (ppm): 2.35 (s, 3H); 2.65 (s, 3H); 3.1-3.2 (m, 1H); 3.3-3.4 (m, 1H); 4.0 (m, 1H); 4.6 (m, 1H); 6.95 (s, 1H); 7.05 (s, 1H); 7.45-7.55 (m, 6H); 7.65 (d, 1H); 8.0 (d, 1H); 8.15 (s, 1H).

IR: 1660, 1580, 1460, 1380, 1330, 1270, 1230, 1150, 1110, 830, 770, 700 cm⁻¹.

EXAMPLE 6D

3-(5-hydroxymethyl-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]-diazepino[6,7,1-*hi*]indol-4-one.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CH₂OH at 5 (process D2b)

The product is prepared as in Example 11 below, starting with the product of Example 6F. Starting with 0.3 g, 12 mg of white foam are obtained after flash chromatography.

Yld: 4% - TLC (D/M2): Rf = 0.45.

EXAMPLE 6E

***tert*-Butyl 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-**
5 **[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-5-carboxylate.**

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CO₂C(CH₃)₃ at 5 (process A1c)

1.55 g (6.2 mmol) of methyl 2-amino-6-*tert*-butyloxycarbonylbenzoate are refluxed in 5 ml of 1,1,1-trimethoxyethane for 5 h and the solution is evaporated to dryness under a high vacuum. 1.854 g of the intermediate 2a (6 mmol) and 4 ml of methanol are added and the
10 mixture is refluxed for 24 h. After chromatography, 1 g (Yld = 41%) of product which crystallizes from CH₃OH is obtained. White crystals - M.p. = 255°C. - TLC (D/M2.5): Rf = 0.5. ¹H NMR δ (ppm): 1.6 (s, 9H); 2.35 (s, 3H); 2.8 (s, 3H); 3.05 (m, 1H); 3.15 (m, 1H); 3.35 (m, 1H); 3.45 (m, 1H); 4.65-4.75 (m, 1H); 7.05 (s, 1H); 7.15 (s, 1H); 7.25-7.6 (m, 7H); 7.7 (d, 1H). IR: 3300, 12900, 1720, 1640, 1590, 1570, 1440, 1360, 1310, 1280, 1140, 980, 780, 750,
15 705 cm⁻¹.

EXAMPLE 6F

2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-
4-oxo-3,4-dihydroquinazoline-5-carboxylic acid. (I); A = CH₃, Z = CH, B =

20 CH₃, X₁ = H, X₂ = CO₂H at 5 (process D1b)

0.5 g of the ester obtained in the above example is dissolved in 7 ml of CH₂Cl₂. 3 ml of trifluoroacetic acid are added dropwise and the mixture is stirred for 90 min at room temperature. Water, ice and CH₂Cl₂ are added, the organic phase is washed with saturated sodium chloride solution, the phases are separated after settling has taken place and the organic phase is dried.
25 Obtained: 0.42 g - Yld: 95% - White powder - M.p. = 195-200°C. TLC (D/M15): Rf = 0.2. ¹H NMR δ (ppm): 2.35 (s, 3H); 2.7 (s, 3H); 3.1-3.2 (m, 1H); 3.4-3.5 (m, 1H); 3.95-4.05 (m, 1H); 4.55-4.65 (m, 1H); 6.9 (s, 1H); 7.05 (s, 1H); 7.4-7.55 (m, 7H); 7.7 (d, 1H); 7.8-7.9 (t, 1H). IR: 3400, 1670, 1590, 1570, 1540, 1480, 1300, 1250, 1160, 830, 790, 695 cm⁻¹.

30

EXAMPLE 7

2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-
3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylic acid. (I); A = CH₃, Z = CH, B = CH₃, X₁ =
H, X₂ = CO₂H at position 7 (process A2)

In an autoclave, a mixture of 1 g (4.9 mmol) of 2-methyl-4-oxo-4H-benzo[d][1,3]oxazine-7-carboxylic acid (prepared from 2-aminoterephthalic acid and acetic anhydride according to J. Am. Chem. Soc., 29 (1907) p.86) and 1.42 g (4.9 mmol) of the intermediate 2.a in 15 ml of CH₂Cl₂ is brought to 200°C under a pressure of 3 bar for 8 h. The medium is cooled, the solvent is evaporated off and the residue is purified by flash chromatography on a silica column, eluting with the solvents D/M3, D/M5 and D/M7. The fractions of interest are pooled, evaporated and again subjected to flash chromatography on silica, eluting with the solvent D/MN20. 100 mg of an amorphous solid are obtained. Yld: 4% - TLC (D/MN20): R_f = 0.37.

¹H NMR δ (ppm): 2.35 (s, 3H); 2.65 (s, 3H); 3.1 (m, 1H); 3.35 (q, 1H); 3.95 (q, 1H); 4.45 (t, 1H); 6.95 (s, 1H); 7.05 (s, 1H); 7.4-7.55 (m, 6H); 8.0 (d, 1H); 8.1 (d, 2H).

EXAMPLE 7A

Methyl 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylate.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CO₂CH₃ at 7. (Process A1c)

The compound is prepared in two steps according to Example 6A, using dimethyl 2-aminoterephthalate.

Yld: 32% - Powder - M.p. = 246°C - TLC (D/M1): R_f = 0.15.

¹H NMR δ (ppm): 2.3 (s, 3H); 2.8 (s, 3H); 3.0-3.1 (m, 1H); 3.2-3.3 (m, 1H); 3.85-3.95 (m, 4H); 4.6-4.7 (m, 1H); 7.0 (s, 1H); 7.1 (s, 1H); 7.3 (s, 1H); 7.35-7.6 (m, 5H); 8.0 (d, 1H); 8.2 (d, 1H); 8.3 (s, 1H).

IR: 3400, 1730, 1675, 1585, 1435, 1280, 1240, 760, 700 cm⁻¹.

EXAMPLE 7B

2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylic acid. Same product as Ex. 7 : (I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CO₂H at 7 (process D1b).

1.3 g (2.6 mmol) of the product of Example 7A are dissolved in 100 ml of THF; 20 ml of water containing 0.35 g of potassium hydroxide are added and the mixture is stirred at room temperature for 5 h. Ice is added and the mixture is acidified to pH = 2. A yellow precipitate is filtered off, which is purified as in Example 7. 0.75 g (60%) obtained.

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EXAMPLE 7C

Salt of 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylic acid with D-glucamine.

The acid of Example 7B is refluxed in 80 ml of methanol, 0.2 g (0.417 mmol), the suspension almost completely dissolves. 0.076 g of D-glucamine (0.417 mmol) is added. The entire mixture dissolves on refluxing. It is left to cool, the solvent is evaporated off and the product is crystallized from ethanol. HPLC (ODH column thermostatically adjusted to 37°C, 1 ml/min, eluent (%): 94.9 hexane/5 ethanol/0.1 trifluoroacetic acid. 140 mg are obtained (Yld: 51%).

10 TLC (D/MN20): R_f = 0.45.

EXAMPLE 7D

(3R)-2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylic acid (I); A = CH₃, Z =

15 CH, B = CH₃, X₁ = H, X₂ = CO₂H at 7, 3R isomer.

500 mg (1.04 mmol) of the racemic acid of Example 7B in 60 ml of ethanol are stirred at reflux. 349 mg (1.04 mmol) of (-)-strychnine are added portionwise. Everything dissolves. The mixture is left for 48 h at room temperature, and 490 mg of the salt of the 3R acid are separated out with an enantiomeric excess of 70% (ee = 70%). The salt crystals are recrystallized from 20 35 ml of ethanol. 350 mg (ee = 99%) are obtained. In order to obtain the pure acid, the salt is stirred in a mixture of CH₂Cl₂ and 0.1 N hydrochloric acid, the aqueous phase is separated out after settling has taken place and the CH₂Cl₂ is washed three times with 10 ml of 0.1 N hydrochloric acid. The product is chromatographed by HPLC on a *Chiralcel* ODH column, eluting with a 94.9 hexane/5 ethanol/0.1 trifluoroacetic acid (%) mixture.

25

EXAMPLE 7E

(3S)-2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylic acid. (I); A =

CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CO₂H at 7, 3S isomer.

30

3 g (6.26 mmol) of the racemic acid of Example 7B in 600 ml of methanol are stirred at reflux. 2.096 g (6.26 mmol) of (-)-strychnine are added portionwise. Insoluble material remains, which is filtered off. 1.6 g of the (R) salt are obtained with an ee = 77%. The mixture is left for 48 h at room temperature, and 2.25 g of the (S) salt are separated out with an enantiomeric excess of 60% (ee = 60%). 2.25 g of the (S) salt are heated in 100 ml of ethanol. 1.2 g of (S) salt (ee =

97.5%) are obtained. In order to obtain the pure acid, the salt is stirred in a mixture of CH_2Cl_2 and 0.1 N hydrochloric acid, the aqueous phase is separated out after settling of the phases has taken place and the CH_2Cl_2 is washed three times with 10 ml of 0.1 N hydrochloric acid. The product is chromatographed by HPLC on a *Chiralcel* ODH column, eluting with a 94.9 hexane/5 ethanol/0.1 trifluoroacetic acid (%) mixture.

EXAMPLE 8

2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxamide. (I); A = CH_3 , Z = CH, B = CH_3 , $X_1 = \text{H}$, $X_2 = \text{CONH}_2$ at position 7 (process D5.b)

0.5 g (1.04 mmol) of the compound of Example 7 is introduced into a reactor protected from moisture, and 1.14 mmol of oxalyl chloride in 2M solution in CH_2Cl_2 are added. One drop of dimethylformamide is added and the mixture is left stirring for 16 hours at 20-25°C. The solvents are evaporated off, the residue is taken up twice in succession with benzene which is then evaporated off, thereafter 10 ml of 28% aqueous ammonia are added and the mixture is left stirring again for 16 hours. It is extracted with CH_2Cl_2 , the organic phases are evaporated and the residue is purified by flash chromatography, first on a silica column, performing elution with ethyl acetate, and then on a so-called reverse-phase column, eluting with a 60:40 v/v water/acetonitrile mixture. The fractions determined pure are pooled and evaporated, and 0.20 g of purified product is obtained in amorphous form.

Yld = 40% - TLC (Ea): Rf = 0.20.

^1H NMR δ (ppm): 2.3 (s, 3H); 2.85 (s, 3H); 3.1 (m, 1H); 3.35 (m, 1H); 4.0 (q, 1H); 4.7 (t, 1H); 6.0 (s, 1H); 6.1 (s, 1H); 7.0-7.6 (m, 8H); 7.9 (d, 1H); 8.1 (s, 1H); 8.25 (d, 1H)

25

EXAMPLE 8A

2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carbonitrile. (I); A = CH_3 , Z = CH, B = CH_3 , $X_1 = \text{H}$, $X_2 = \text{CN}$, at 7 (process D6).

1.5 g (3.1 mmol) of the product of Example 8 are dissolved in 100 ml of CH_2Cl_2 and 2.24 g (9.4 mmol) of Burgess reagent are added. The mixture is left for 4 h at 20-25°C, washed with 30 ml of water, then with normal hydrochloric acid and finally with water. The resulting solution is dried, the solvent is evaporated off and the residue is chromatographed. 1.1 g of a beige-colored solid are obtained. Yld = 76% - TLC (DM1): Rf = 0.38.

^1H NMR δ (ppm): 2.3 (s, 3H); 2.75 (m, 3H); 3.05 (m, 1H); 3.3 (m, 1H); 3.9 (m, 1H); 4.55 (m,

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1H); 7.95 (m, 1H); 7.0 (m, 1H); 7.3-7.55 (m, 7H); 7.9 (m, 1H); 8.2 (m, 1H).

EXAMPLE 8B

5 **9-methyl-3-[2-methyl-4-oxo-7-(1H-tetrazol-5-yl)-4H-quinazolin-3-yl]-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-hi]indol-4-one.** (I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CN₄H at 7 (process D7).

0.86 g (1.8 mmol) of the product of Example 8 are dissolved in 19 ml of DMF and 0.18 g (2.8 mmol) of sodium azide and 0.15 g (2.8 mmol) of ammonium chloride are added. The mixture is heated at 120°C for 32 h and every 8 h fresh additions of the same amounts of sodium
10 azide and ammonium chloride are carried out. When the starting material has disappeared, the mixture is evaporated and the residue is washed with 30 ml of water in the presence of CH₂Cl₂. The organic phase is dried, evaporated and chromatographed. 0.24 g of a beige-colored solid is obtained. Yld = 25%. - M.p. = 287°C - TLC (DM20): R_f = 0.33.

¹H NMR δ (ppm): 2.35 (s, 3H); 2.7 (s, 3H); 3.15 (m, 1H); 3.35 (m, 1H); 3.95 (m, 1H); 4.55 (m,
15 1H); 6.95 (m, 1H); 7.05 (m, 1H); 7.4-7.6 (m, 7H); 8.15 (m, 2H); 8.25 (s, 1H).

IR: 3300, 1670, 1620, 1580, 1560, 1440, 1380, 1350, 1290, 1270, 1230, 1170, 770, 690 cm⁻¹.

EXAMPLE 9

20 **2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-(N-methylcarboxamide).** (I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CONH-CH₃ at position 7 (process A1c)

The compound is prepared as described in Example 8, carrying out the amidation with a solution of methylamine in CH₂Cl₂. The product after chromatographic purifications is obtained in amorphous form and is beige in color. Yld = 25% TLC (Ea): R_f = 0.27.

25 ¹H NMR δ (ppm): 2.4 (s, 3H); 2.8 (s, 3H); 3.0 (d, 3H); 3.1 (m, 1H); 3.3 (m, 1H); 4.0 (q, 1H); 4.7 (q, 1H); 6.0 (s, 1H); 6.4 (d, 1H); 7.0-7.6 (m, 8H); 7.9 (d, 1H); 8.0 (s, 1H); 8.2 (d, 1H).

EXAMPLE 9A

30 **2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-hi]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-N-dimethylcarboxamide.**

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CON(CH₃)₂ at 7 (process D5b)

The compound is prepared as described in Example 8, the amidation being carried out by a solution of dimethylamine in CH₂Cl₂. The product, after chromatographic purifications, is obtained in the form of a yellow powder. Yld = 35%. M.p. = 162-165°C. TLC (DM2): R_f = 0.15.

¹H NMR δ (ppm): 2.35 (s, 3H); 2.7 (s, 3H); 2.9 (s, 3H); 3.15 (m, 1H); 3.4 (m, 1H); 4.0 (q, 1H); 4.55 (t, 1H); 6.95 (s, 1H); 7.05 (s, 1H); 7.4-7.6 (m, 7H); 7.65 (s, 1H); 8.1 (d, 1H).
IR: 2900; 1670; 1640; 1580; 1380; 1230; 1170; 1070; 700 cm⁻¹.

5

EXAMPLE 9B

2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylic acid (2-morpholin-4-yl-ethyl)amide.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CONH(CH₂)₂N-morpholine at 7. (process D5b)

The compound is prepared as described in Example 9C below, the amidation of the
10 product of Example 7B being carried out by a solution of 2-morpholin-4-ylethylamine in CH₂Cl₂.
The product after chromatographic purifications is obtained in the form of a yellow powder.
Yld = 69%. M.p. = 191°C - TLC (DM7): Rf = 0.5.

¹H NMR δ (ppm): 2.3 (s, 3H); 2.5 (t, 4H); 2.6 (t, 2H); 2.75 (s, 3H); 3.0 (m, 1H); 3.3 (m, 1H); 3.6
(q, 2H); 3.7 (t, 4H); 3.9 (q, 1H); 4.6 (m, 1H); 6.9-7.1 (t, 1H) (2s, 2H); 7.2-7.5 (m, 6H); 7.8 (d,
15 1H); 7.9 (s, 1H); 8.2 (d, 1H).

IR: 3300; 2900; 1670; 1580; 1440; 1380; 1290; 1230; 1100; 860; 725; 700 cm⁻¹.

EXAMPLE 9C

2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylic acid (3-(morpholin-4-ylpropyl)amide.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CONH(CH₂)₃N-morpholine at 7 (process D5b)

0.8 g (1.67 mmol) of the racemic acid described in Example 7 and then 0.6 g
(1.84 mmol) of TOTU in 20 ml of CH₂Cl₂ are introduced into a 50 ml round-bottomed flask
protected from moisture and under a nitrogen atmosphere. The medium is cooled in an ice bath
25 and 0.43 g (1.84 mmol) of DIEA is added. The mixture is stirred for 1 min at 0°C and 0.24 g
(1.67 mmol) of 3-morpholin-4-ylpropylamine is added, after which the mixture is stirred for 16 h
at room temperature. The mixture is washed with 1 N HCl and then with saturated NaHCO₃. It is
dried over Na₂SO₄ and the solvent is evaporated off. The product after chromatographic
purification is obtained in the form of a pale yellow powder. Yld = 70%. - M.p. = 140°C. - TLC
30 (DM10): Rf = 0.63.

¹H NMR δ (ppm): 1.7 (t, 2H); 2.3 (s, 3H); 2.5 (m, 6H); 2.7 (s, 3H); 3.1 (m, 1H); 3.3 (m, 3H); 3.6
(m, 4H); 4.0 (q, 1H); 4.6 (t, 1H); 6.9 (s, 1H); 7.05 (s, 1H); 7.5 (m, 6H); 7.9 (d, 1H); 8.2 (m, 2H);
8.8 (t, 1H).

EXAMPLE 9D

2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-(2-amino)ethylcarboxamide.

5 (I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CONH(CH₂)₂NH₂ at 7 (process D5b)

The compound is prepared as described in Example 9C, the amidation being carried out by a solution of 2-aminoethylamine in CH₂Cl₂. The product after chromatographic purifications is obtained in the form of a beige-colored powder. Yld = 21%. - M.p. = 162-165°C. TLC (DMN20): R_f = 0.47.

10 ¹H NMR δ (ppm): 2.2 (s, 3H); 2.7 (s, 3H); 3 (m, 3H); 3.2 (m, 1H); 3.5 (q, 2H); 3.9 (q, 1H); 4.6 (t, 1H); 6.95 (s, 1H); 6.9 (s, 1H); 7 (s, 1H); 7.2-7.5 (m, 7H); 7.9 (d, 1H); 8.1 (s, 1H); 8.15 (d, 1H).

EXAMPLE 9E

The hydrochloride of the product 9D above is prepared in isopropanol, by adding a
15 solution of hydrochloric acid in the same solvent. Yld = 77%. The salt crystallizes with 2.5 molecules of water of solvation.

EXAMPLE 9F

3-{7-[4-(2-hydroxyethyl)piperazine-1-carbonyl]-2-methyl-4-oxo-4*H*-quinazolin-3-yl}-9-methyl-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CON[(CH₂)₂]₂N(CH₂)₂OH at 7 (process D5b)

The compound is prepared as described in Example 9C, the amidation being carried out with a solution of 1-(2-hydroxyethyl)piperazine in CH₂Cl₂. The product after chromatographic purifications is obtained in the form of a white powder. Yld = 71%. TLC (DM10): R_f = 0.6.

25 ¹H NMR δ (ppm): 2.3 (s, 3H); 2.4 (m, 6H); 2.7 (s, 3H); 3.1 (m, 1H); 3.3 (m, 3H); 3.55 (q, 2H); 3.65 (m, 2H); 4 (q, 1H); 4.5 (t, 1H); 4.6 (t, 1H); 6.95 (s, 1H); 7.05 (s, 1H); 7.5 (m, 8H); 8.1 (d, 1H).

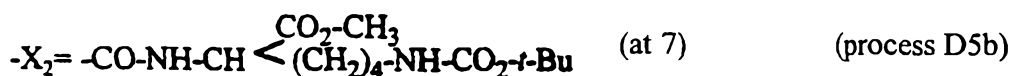
EXAMPLE 9G

30 The hydrochloride of product 9F above is prepared in isopropanol, by adding a solution of hydrochloric acid in the same solvent. Yld = 83%. The salt crystallizes with 2.5 molecules of water of solvation.

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EXAMPLE 9H

Methyl (2S)-6-*t*-butoxycarbonylamino-2-{{2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazolin-7-carbonyl}amino}hexanoate. (I); A = CH₃, Z = CH, B = CH₃, X₁ = H,



5 The compound is prepared as described in Example 9C, the amidation being carried out by a solution of methyl (2S)-2-amino-6-*t*-butoxycarbonylaminohexanoate (methyl Nε-*t*-BOC-(L)-lysinate) in CH₂Cl₂. The product after chromatographic purifications is obtained in the form of a beige-colored powder. Yld = 93%. - TLC (DMN5): Rf = 0.65.

10

EXAMPLE 9I

Methyl (2S)-6-amino-2-{{2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazolin-7-carbonyl}-amino}hexanoate (process D5b).

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CONHCH[(CH₂)₄]NH₂]COOCH₃ at 7

15

The compound is prepared from the product of Example 9H, by dissolving 0.7 g (0.971 mmol) in 17 ml of CH₂Cl₂ and by adding to the mixture 3.8 ml of trifluoroacetic acid dropwise. After 2 h at 20-25°C, an examination by TLC no longer allows the starting material to be detected. The mixture is evaporated; after chromatographic purifications, 0.48 g of product is obtained in the form of a white powder. Yld = 81%. M.p. = 190°C. - TLC (DM10): Rf = 0.32.

20

¹H NMR δ (ppm): 1.4 (m, 2H); 1.6 (m, 2H); 1.8 (q, 2H); 2.3 (s, 3H); 2.65 (d, 3H); 2.8 (m, 2H); 3.2 (m, 2H); 3.4 (m, 1H); 4 (q, 1H); 4.5 (m, 2H); 6.9 (s, 1H); 7 (s, 1H); 7.4-7.6 (m, 6H); 7.9 (d, 1H); 8.1-8.2 (2s, 1d, 3H); 9.1 (d, 1H).

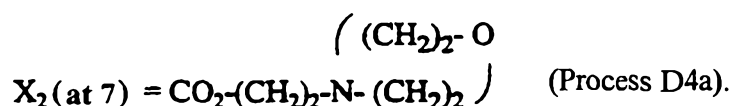
IR: 3300; 3000; 1680; 1420; 1200; 1120; 790; 720; 690 cm⁻¹.

25

EXAMPLE 10

2-(4-morpholinyl)ethyl 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino-[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylate.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H,



In a reactor protected from moisture, 0.3 g (0.63 mmol) of the acid obtained in Example

7 is introduced into 15 ml of sieve-dried DMF, and 0.2 g (1.25 mmol) of carbonyldiimidazole is added. The solution is stirred for 20 h at 20-25°C, 0.246 g (1.88 mmol) of (hydroxyethyl)morpholine is then added and the mixture is heated for 4 h to 60-70°C. After it has returned to approximately 20°C, 75 ml of water are added and the mixture is extracted with 3 times 20 ml of ethyl acetate. The combined organic phases are washed with water and dried and the solvents are then removed. The residue is purified by flash chromatography on a silica column; elution with the solvent D/MN2 enables 0.08 g of purified product to be obtained in amorphous form. Yld = 21.5 % - TLC (D/MN5): Rf = 0.50.

¹H NMR δ (ppm): 2.3 (s, 3H); 2.55 (m, 4H); 2.7-2.8 (m, 5H); 3.0-3.1 (m, 1H); 3.25-3.35 (m, 1H); 3.7 (m, 4H); 3.85-4.0 (m, 1H); 4.45 (t, 2H); 4.65-4.7 (m, 1H); 6.0 (s, 1H); 7.1-7.55 (m, 8H); 8.0 (d, 1H); 8.2 (d, 1H); 8.3 (s, 1H);

IR: 3400, 2900, 1720, 1670, 1580, 1560, 1430, 1290, 1240, 1115, 760, 700 cm⁻¹

EXAMPLE 10A

2-acetoxyethyl 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylate

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CO₂-(CH₂)₂-OCOCH₃ at 7. (Process D4a)

The compound is prepared as described in Example 10, the esterification being carried out with 2-acetoxyethanol. The product, after chromatographic purifications, is obtained in amorphous form and in a beige color. Yld = 36%. M.p. = 115-118°C. - TLC (D/MN2): Rf = 0.9. ¹H NMR δ (ppm): 2.1 (s, 3H); 2.4 (s, 3H); 2.75 (s, 3H); 3.2 (m, 1H); 3.45 (m, 1H); 4 (q, 1H); 4.5 (m, 2H); 4.6 (m, 3H); 7 (s, 1H); 7.1 (s, 1H); 7.5-7.6 (m, 6H); 8.05 (d, 1H); 8.2 (s, 1H); 8.3 (d, 1H).

IR: 3400, 2900, 1740, 1680, 1580, 1560, 1430, 1290, 1240, 760 cm⁻¹.

EXAMPLE 10B

2-Methoxyethyl 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylate

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CO₂-(CH₂)₂-OCH₃ at 7. (Process D4a)

The compound is prepared as described in Example 10, the esterification being carried out with 2-methoxyethanol. The product, after chromatographic purification, is obtained in amorphous form. Yld = 17%. M.p. = 108-111°C. - TLC (D/MN2): Rf = 0.17.

¹H NMR δ (ppm): 2.4 (s, 3H); 2.7 (s, 3H); 3.25 (m, 1H); 3.4 (m, 1H); 3.8 (m, 2H); 4.1 (q, 1H); 4.5 (m, 2H); 4.6 (t, 3H); 7 (s, 1H); 7.55 (t, 2H); 7.65 (m, 4H); 8.1 (d, 1H); 8.25 (s, 1H); 8.3 (d,

1H).

IR: 3400, 2850, 1720, 1680, 1580, 1560, 1380, 1290, 1240, 1100, 760, 690 cm^{-1} .

EXAMPLE 10C

5 **2-Hydroxyethyl 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylate.**
(I); A = CH_3 , Z = CH, B = CH_3 , $\text{X}_1 = \text{H}$, $\text{X}_2 = \text{CO}_2-(\text{CH}_2)_2-\text{OH}$ at 7. (Process D4.a)

The compound is prepared as described in Example 10, the esterification being carried out with ethylene glycol. The product, after chromatographic purification, is obtained in the form
10 of a beige powder. Yld = 47%. M.p. = 257-259°C. - TLC (D/MN2): $R_f = 0.39$.

^1H NMR δ (ppm): 2.35 (s, 3H); 2.7 (s, 3H); 3.2 (m, 1H); 3.4 (m, 1H); 3.75 (m, 2H); 4.0 (q, 1H); 4.4 (m, 2H); 4.6 (t, 1H); 5 (t, 1H); 6.95 (s, 1H); 7.05 (s, 1H); 7.4-7.6 (m, 7H); 8.05 (d, 1H); 8.2 (d, 1H); 8.25 (s, 1H).

15

EXAMPLE 10D

1-(2S)-glyceryl 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylate.

(I); A = CH_3 , Z = CH, B = CH_3 , $\text{X}_1 = \text{H}$, $\text{X}_2 = \text{CO}_2-\text{CH}_2\text{CHOHCH}_2-\text{OH}$ at 7. (Process E1a)

0.3 g of racemic acid of Example 7B (0.626 mmol), 46 mg of (S)-glycidol and 20 mg of
20 tetrabutylammonium bromide are suspended in 30 ml of toluene. The mixture is refluxed for 2.5 h. At the end of the reaction, everything is dissolved. The mixture is evaporated. The products, after chromatographic purification, is obtained (120 mg) in the form of a beige powder. Yld = 47%. - M.p. = 170-175°C - TLC (D/MN10): $R_f = 0.42$.

^1H NMR δ (ppm): 2.3 (s, 3H); 2.65 (m, 1H); 2.8 (s, 3H); 3.3-3.35 (m, 3H); 3.65-3.8 (m, 2H);
25 3.85-4.1 (m, 2H); 4.35-4.5 (m, 2H); 4.6-4.7 (m, 1H); 7.0-7.55 (m, 8H); 7.95 (d, 1H); 8.2 (d, 1H); 8.35 (s, 1H).

IR: 3400, 2900, 1720, 1670, 1580, 1560, 1430, 1290, 1240, 1100, 760, 690 cm^{-1} .

EXAMPLE 10E

30 **2-hydroxy-3-morpholin-4-ylpropyl 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylate.** (Process E)

(I); A = CH_3 , Z = CH, B = CH_3 , $\text{X}_1 = \text{H}$, $\text{X}_2 = \text{CO}_2-\text{CH}_2\text{CHOHCH}_2-4\text{-morpholine}$ at 7.

The compound is prepared as described in Example 10, the esterification being carried out with 1,2-epoxy-3-N-morpholinylpropane. The product, after chromatographic purification, is obtained in the form of a powder. Yld = 56%. - M.p. = 135-140°C - TLC (D/MN3): Rf = 0.35.

¹H NMR δ (ppm): 2.3 (s, 3H); 2.4-2.7 (m, 6H); 2.8 (s, 3H); 3-3.1 (m, 1H); 3.25-3.35 (m, 1H);
5 3.4-3.5 (s, 1H); 3.6-3.7 (m, 4H); 3.85-3.95 (m, 1H); 4 (m, 1H); 4.25-4.40 (m, 2H); 4.6-4.7 (m,
1H); 7.0 (s, 1H); 7.1 (s, 1H); 7.2 (s, 1H); 7.25 (s, 1H); 7.3-7.5 (m, 4H); 7.95 (d, 1H); 8.2 (d, 1H);
8.3 (s, 1H).

IR: 3500, 2950-2800, 1720, 1680, 1580, 1560, 1430, 1290, 1240, 1115, 760, 700 cm⁻¹.

10

EXAMPLE 11

3-(7-hydroxymethyl-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CH₂OH at position 7 (process D2b)

In a reactor protected from moisture, 0.53 g (1.1 mmol) of the acid obtained in Example
15 7 is introduced into 10 ml of sieve-dried THF, and then, after the mixture has been cooled to 0°C,
0.17 ml of ethyl chloroformate and 0.17 ml of triethylamine are introduced. The mixture is
stirred for 2 h at 0°C and the insoluble matter is then filtered off and discarded. 0.5 g of sodium
borohydride dissolved in 0.5 ml of THF is added to the filtrate and the mixture is then kept
stirring for 3 h at 0°C. The solvents are removed by distillation and the residual product is
20 purified by flash chromatography on a silica column. Elution with an ethyl acetate/cyclohexane
mixture enables the product to be obtained in amorphous form. Weight: 0.08 g - Yld = 15.6% -
TLC (D/M5): Rf = 0.60.

¹H NMR δ (ppm): 2.4 (s, 3H); 2.7 (s, 3H); 3.2 (m, 1H); 3.45 (m, 1H); 4.0 (m, 1H); 4.6 (t, 1H);
4.7 (d, 2H); 5.5 (t, 1H); 7.0 (s, 1H); 7.1 (s, 1H); 7.4-7.6 (m, 7H); 7.65 (s, 1H); 8.1 (d, 1H).

25 IR: 3400, 2900, 1660, 1620, 1580, 1560, 1440, 1380, 1230, 1170, 1120, 780, 740, 650 cm⁻¹

EXAMPLE 12

(3S)-3-(5-fluoro-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

30 (I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = F at position 5 (process A1c)

2-Acetylamino-6-fluorobenzoic acid is prepared as described in Example 3 from 2-amino-6-fluorobenzoic acid, and the compound in the title is then prepared according to the procedure described in Example 3.

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Yld = 26% - white solid - M.p. = 238°C - $[\alpha]_D^{25} = 21E$ (c = 1, CH₂Cl₂) - TLC (D/M2): R_f = 0.40
¹H NMR δ (ppm): 2.3 (s, 3H); 2.85 (s, 3H); 3.05 (m, 1H); 3.3 (m, 1H); 3.9 (q, 1H); 4.65 (t, 1H);
7.3 (m, 11H).

5

EXAMPLE 13

3-(5-chloro-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino-[6,7,1-*hi*]indol-4-one.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = Cl at position 5. (process A1c)

This compound is prepared from 2-amino-6-chlorobenzoic acid according to the procedure
described in Example 3.

Yld: 39% - white solid - M.p. = 222°C - TLC (D/M2): R_f = 0.48

¹H NMR δ (ppm): 2.35 (s, 3H); 2.8 (s, 3H); 3.1 (m, 1H); 3.4 (m, 1H); 3.95 (q, 1H); 4.7 (t, 1H);
7.05 (s, 1H), 7.15 (s, 1H); 7.3 (s, 1H); 7.5 (m, 8H).

15

EXAMPLE 14

ethyl 3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-2-carboxylate.

(I); A = CH₃, Z = CH, B = -CO₂Et, X₁ = H, X₂ = H (process A2)

In a reactor under nitrogen and equipped with a CaCl₂ guard tube, 200 mg (0.69 mmol)
of the intermediate 2.a and 122 mg (0.76 mmol) of ethyl 4-oxo-4H-benzo-[d][1,3]oxazine-2-
carboxylate (prepared from N-ethoxalylanthranilic acid according to J. Am. Chem. Soc. **32**, 1910,
122) are introduced into 15 ml of toluene dried over molecular sieve. The mixture is stirred for
14 h at 100°C, the solvent is then evaporated off and the residue is purified by flash
chromatography on silica, eluting with the solvent C/A20. Weight = 0.12 g - Yld: 20% - white
solid - M.p. = 253°C - TLC (C/A30): R_f = 0.37.

¹H NMR δ (ppm): 1.05 (t, 3H); 2.3 (s, 3H); 3.05-3.15 (m, 1H); 3.3-3.4 (m, 1H); 3.7-3.8 (m, 1H);
3.9-4.05 (m, 2H); 4.75-4.85 (m, 1H); 6.6 (s, 1H); 7(s, 1H); 7.3 (s, 1H); 7.4 (t, 2H); 7.5 (d, 1H);
7.55-7.6 (m, 3H); 7.8 (t, 1H); 7.9 (d, 1H); 8.3 (d, 1H)

IR: 3400, 2900, 1740, 1710, 1690, 1590, 1460, 1300, 1230, 1170, 1090, 890, 770, 700 cm⁻¹

30

EXAMPLE 15

Ethyl 5-chloro-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-2-carboxylate.

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(I); A = CH₃, Z = CH, B = -CO₂Et, X₁ = H, X₂ = Cl at position 5 (process A1.a)

In a reactor protected from moisture, 1.0 g (3.43 mmol) of the intermediate 2, 0.617 g of 2-chloro-6-(ethoxycarbonylamino)benzoic acid and 0.34 ml (3.92 mmol) of phosphorus trichloride are introduced into 20 ml of anhydrous CH₂Cl₂. The mixture is stirred at 20-25°C for 18 h and 8.0 ml of 5% aqueous NaHCO₃ solution are then added. After a few minutes of stirring, the organic phase is separated and evaporated. The residue is purified by flash chromatography on a silica column. Elution with the solvent D/A5 enables, after evaporation of the fractions determined pure, 0.52 g of amorphous product to be obtained. Yld = 29%. M.p. = 306°C.- TLC (D/A5): R_f = 0.45.

¹H NMR δ (ppm): 1.0 (t, 3H); 2.4 (s, 3H); 3.1 (m, 1H); 3.3 (m, 1H); 3.7 (m, 1H); 3.9 (m, 2H); 4.7 (m, 1H); 6.4 (s, 1H), 6.9 (s, 1H); 7.2-7.8 (m, 9H).

IR: 3300, 3000, 1630, 1580, 1450, 1380, 1340, 1280, 1140, 1100, 820, 780, 700 cm⁻¹

EXAMPLE 16

Ethyl [3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-2-quinazolinyl]acetate. (I); A = CH₃, Z = CH, B = CH₂-CO₂Et, X₁ = H, X₂ = H. (process A3)

In a reactor protected from moisture, according to a process similar to Example 15, the intermediate 2 and a 60/40 mixture of ethyl (4-oxo-4H-benzo-[d][1,3]oxazin-2-yl)acetate and 2-(2-ethoxycarbonylacetylaminobenzoic acid, obtained by reacting anthranilic acid with ethyl (chlorocarbonyl)acetate, are reacted in CH₂Cl₂ in the presence of triethylamine according to a method adapted from Tetrahedron Lett. 50 (1994) 34, 10331. The product is purified by flash chromatography on a silica column, eluting with the solvent C/A20. Yld = 26% - M.p. = 228-230°C - TLC (C/A30): R_f = 0.30

¹H NMR δ (ppm): 0.75 (t, 3H); 2.3 (s, 3H); 3.1 (m, 1H); 3.3 (s, 2H); 3.4 (m, 1H); 3.5 (m, 1H); 3.8 (m, 3H); 4.0 (q, 1H); 4.55 (t, 1H); 6.85 (s, 1H); 6.95 (s, 1H); 7.45 (m, 4H); 7.55 (m, 3H); 7.7 (s, 1H); 7.9 (m, 1H); 8.15 (s, 1H)

IR: 3400, 2900, 1740, 1670, 1590, 1570, 1470, 1390, 1330, 1300, 1230, 1200, 1150, 770, 710 cm⁻¹

EXAMPLE 17

Methyl 3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-2-quinazolinylacetate. (I); A = CH₃, Z = CH, B = CH₂-O-CO-CH₃, X₁ = H, X₂ = H. (process A1a)

In a reactor protected from moisture, according to a process similar to Example 15, the intermediate 2.a and 2-(2-acetoxyacetyl-amino)benzoic acid, obtained by reacting anthranilic acid with methyl (chlorocarbonyl)acetate, are reacted in CH_2Cl_2 in the presence of triethylamine. The product is purified by chromatography on a silica column, eluting with the solvent C/A20. Yld =

$^1\text{H NMR } \delta$ (ppm): 2.05 (s, 3H); 3.1 (m, 1H); 3.35 (m, 1H); 3.4 (m, 1H); 4.0 (q, 1H); 4.55 (t, 1H); 4.9 (d, 1H); 5.6 (d, 1H); 6.85 (s, 1H); 7.5 (m, 7H); 7.75 (d, 1H); 8.15 (d, 1H); 8.95 (t, 1H)
IR: 3400, 1760, 1690, 1670, 1600, 1560, 1400, 1220, 1180, 780, 700 cm^{-1}

EXAMPLE 17A

9-Methyl-3-(2-methyloxymethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one. (I); A = CH_3 , Z = CH, B = CH_2OCH_3 , $\text{X}_1 = \text{H}$, $\text{X}_2 = \text{H}$ (process A12c).

In the same way as in Example 2A, starting with the intermediate racemic amine 2.a and 2-methoxyacetylaminobenzoic acid, and after chromatographic purification, the product is obtained in the form of a powder (Yld = 17%). - M.p. = 220°C. - TLC (DA5): Rf = 0.15.

$^1\text{H NMR } \delta$ (ppm): 2.3 (s, 3H); 3.1 (m, 1H); 3.2 (s, 3H); 3.4 (m, 1H); 3.65 (d, 1H); 3.9 (q, 1H); 4.4 (d, 1H); 4.55 (dd, 1H); 4.7 (d, 1H); 6.85 (s, 1H); 7.05 (s, 1H); 7.2 (d, 1H); 7.5 (m, 7H); 7.9 (t, 1H); 8.1 (d, 1H).

IR: 3400, 2900, 1670, 1590, 1470, 780, 700 cm^{-1} .

EXAMPLE 17B

9-Methyl-3-(2-hydroxymethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one. (I); A = CH_3 , Z = CH, B = CH_2OH , $\text{X}_1 = \text{H}$, $\text{X}_2 = \text{H}$ (process A12c).

In the same way as in Example 7B, starting with the product of Example 17, and after chromatographic purification, a powder is obtained (Yld = 67%).

$^1\text{H NMR } \delta$ (ppm): 2.3 (s, 3H); 3.1 (m, 1H); 3.4 (m, 1H); 4.0 (m, 1H); 4.4 (q, 1H); 4.6 (t, 1H); 4.8 (d, 1H); 5.05 (m, 1H); 6.9 (s, 1H); 7.0 (s, 1H); 7.5 (m, 7H); 7.7 (d, 1H); 7.9 (m, 1H); 8.1 (d, 1H).

IR: 3400, 1680, 1580, 1560, 780, 700 cm^{-1} .

EXAMPLE 17C

[3-(9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]methyl hydrogen succinate (I); A = CH_3 , Z = CH, B =

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CH₂OCO(CH₂)₂COOH, X₁ = H, X₂ = H (process A13c).

Starting with 0.750 g (1.06 mmol) of the product of Example 17B in 20 ml of CH₂Cl₂, 0.183 g (1.83 mmol) of succinic anhydride and 0.203 g of triethylamine (2 mmol) are added with stirring. After stirring for 4 h at room temperature, the mixture is evaporated and the residue is chromatographed on silica in DM5. 580 mg of powder are obtained. Yld = 63%.

¹H NMR δ (ppm): 2.3 (s, 3H); 2.4 (m, 2H); 2.6 (m, 2H); 3.1 (m, 1H); 3.35 (m, 1H); 4.0 (m, 1H); 4.5 (t, 1H); 4.9 (d, 1H); 5.1 (d, 1H); 6.8 (s, 1H); 7.0 (s, 1H); 7.5 (m, 7H); 7.7 (d, 1H); 7.9 (t, 1H); 8.1 (d, 1H).

IR: 3400, 1740, 1680, 1600, 1160, 780, 700 cm⁻¹.

10

EXAMPLE 17D

[3-(9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]methanol [2-(2-methoxyethoxy)ethoxy]acetate.

(I); A = CH₃, Z = CH, B = CH₂OCOCH₂O[(CH₂)₂O]₂CH₃, X₁ = H, X₂ = H (Process A14c).

15

Starting with 0.300 g (0.666 mmol) of the product of Example 17B in 20 ml of CH₂Cl₂, 0.141 g of triethylamine (1.4 mmol) and then 0.5 g (2.37 mmol) of 3,6,9-trioxadecanoyl chloride are added with stirring. After stirring for 24 h at 20-25°C, the mixture is evaporated, washed with saturated NaHCO₃ solution, dried, evaporated and chromatographed on silica in DM10. 285 mg are obtained. Yld = 42%. - M.p. = 153-155°C. - TLC (DM10): R_f = 0.17.

20

¹H NMR δ (ppm): 2.35 (s, 3H); 3.15 (m, 1H); 3.2 (s, 4H); 3.4 (m, 3H); 3.5 (m, 4H); 3.6 (m, 2H); 4.0 (m, 1H); 4.2 (d, 2H); 4.6 (t, 1H); 5.05 (d, 1H); 5.7 (d, 1H); 6.85 (s, 1H); 7.05 (s, 1H); 7.15 (d, 1H); 7.5 (m, 7H); 7.9 (t, 1H); 8.1 (d, 1H).

IR: 3400, 2900, 1760, 1680, 1600, 1140, 1100, 780, 700 cm⁻¹.

25

EXAMPLE 17E

3-(9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl N-(2-morpholin-4-ylethyl)succinamate.

(I); A = CH₃, Z = CH, B = CH₂OCO(CH₂)₂CONH(CH₂)₂N[(CH₂)₂]₂O, X₁ = H, X₂ = H.

(Process A14c).

30

Starting with 0.400 g (0.73 mmol) of the product of Example 17C in 20 ml of CH₂Cl₂, 0.129 g of phosphorus trichloride (0.94 mmol) is added with stirring, the mixture is left for 20 min then 0.113 g (0.87 mmol) of 2-(N-morpholino)ethylamine is added. After stirring for 24 h at 20-25°C, the mixture is evaporated, washed with saturated NaHCO₃ solution, dried, evaporated and chromatographed on silica in DM2, then DM3 and then DM5. 0.40 g of powder

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is obtained. Yld = 83%. - TLC (DMN5): Rf = 0.22.

¹H NMR δ (ppm): 2.35 (m, 11H); 2.6 (m, 2H); 3.15 (m, 3H); 3.4 (m, 1H); 3.4 (m, 1H); 3.5 (m, 4H); 4.0 (q, 1H); 4.5 (t, 1H); 4.9 (d, 1H); 5.6 (d, 1H); 6.9 (s, 1H); 7.1 (s, 1H); 7.5 (m, 7H); 7.7 (m, 2H); 7.9 (m, 1H); 8.1 (d, 1H).

5 IR: 3400, 2900, 1740, 1680, 1600, 1240, 1160, 1170, 750, 700 cm⁻¹.

EXAMPLE 17F

3-(9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl 2-morpholin-4-ylethyl succinate.

10 (I); A = CH₃, Z = CH, B = CH₂OCO(CH₂)₂COO(CH₂)₂N[(CH₂)₂]₂O, X₁ = H, X₂ = H. (Process A15c).

Starting with 0.500 g (0.9 mmol) of the product of Example 17C in 10 ml of CH₂Cl₂, 0.15 g of phosphorus trichloride (1.1 mmol) is added with stirring, the mixture is left for 20 min and then 0.12 g (0.99 mmol) of 2-(N-morpholino)ethanol is added. After stirring for 24 h at 20-
15 25°C, the mixture is evaporated, washed with saturated NaHCO₃ solution, dried, evaporated and chromatographed, a first time on silica in DMN3 and a second time in DMN1. 0.150 g of a yellow powder is obtained. Yld = 25%. - M.p. = 95°C. - TLC (DMN5): Rf = 0.33.

¹H NMR δ (ppm): 2.35 (m, 7H); 2.45-2.55 (m, 4H); 2.6-2.7 (m, 4H); 3.05-3.02 (m, 1H); 3.3-3.45 (m, 1H); 3.5 (m, 4H); 3.9-4.05 (m, 1H); 4.1 (t, 2H); 4.5-4.6 (m, 1H); 4.9-5 (d, 1H); 5.6-5.7 (d,
20 1H); 6.85 (s, 1H); 7.05 (s, 1H); 7.4-7.65 (m, 7H); 7.7 (d, 1H); 7.9 (t, 1H); 8.1 (d, 1H).

IR: 3450, 2950, 1740, 1670, 1600, 1570, 1300, 1230, 1150, 1110, 1030, 770, 700 cm⁻¹.

EXAMPLE 17G

Methyl 6-*t*-butoxycarbonylamino-2-{3-[3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazolin-2-ylmethoxycarbonyl]propionylamino}hexanoate

25 (I); A = CH₃, Z = CH, B = CH₂OCO(CH₂)₂CONHCH[(CH₂)₄NHCO₂C(CH₃)₃]CO₂CH₃, X₁ = H, X₂ = H (process A15c).

Starting with 0.60 g (1.08 mmol) of the product of Example 17C in 20 ml of CH₂Cl₂,
30 0.25 g of phosphorus trichloride (1.85 mmol) is added with stirring; the mixture is left for 20 min and 0.625 g (1.63 mmol) of methyl (N-ε-*t*-butoxycarbonyl)-(L)-lysinate is then added. After stirring for 24 h at room temperature, the mixture is evaporated, washed with saturated NaHCO₃ solution, dried, evaporated and chromatographed in DM1 and then DM2. 0.170 g of a yellow powder is obtained. Yld = 25%. - M.p. = 95°C. - TLC (DMN5): Rf = 0.33.

¹H NMR δ (ppm): 1.2 (m, 4H); 1.25 (s, 18H); 1.65 (m, 2H); 1.9 (s, 2H); 2.25 (s, 6H); 2.4 (m, 4H); 2.65 (m, 4H); 3.0 (m, 6H); 3.25 (m, 2H); 3.6 (m, 4H); 3.9 (q, 2H); 4.5 (m, 2H); 4.6 (m, 6H); 5.1 (m, 2H); 5.7 (q, 2H); 6.4 (d, 1H); 6.6 (d, 1H); 7.0 (m, 4H); 7.25-7.5 (m, 14H); 7.7 (s, 4H); 8.1 (d, 2H) mixture of two diastereoisomers.

5

EXAMPLE 17H

Ethyl 3-[3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]propanoate.

(I); A = CH₃, Z = CH, B = (CH₂)₂-CO₂Et, X₁ = H, X₂ = H. (Process A1a)

10 In the same way as in Example 15, the intermediate 2 is reacted with 2-(3-ethoxycarbonylpropanoylamino)benzoic acid obtained by reaction of anthranilic acid with ethyl 3-chlorocarbonylpropanoate in CH₂Cl₂ in the presence of triethylamine, according to a method adapted from Tetrahedron Lett. 50 (1994) 34, 10331. The product is purified by flash chromatography on a column of silica, eluting with the solvent C/A30.

15 Yld = 43%. - M.p. = 192°C - TLC (C/A30): R_f = 0.44

¹H NMR δ (ppm): 1.1 (t, 3H); 2.35 (s, 3H); 2.6-2.75 (m, 1H); 2.8-2.95 (m, 1H); 2.95-3.05 (m, 1H); 3.05-3.2 (m, 1H); 3.3-3.4 (m, 1H); 3.45-3.55 (m, 1H); 3.9-4 (m, 3H); 4.5-4.6 (m, 1H); 6.95 (m, 1H); 7.05 (s, 1H); 7.4-7.5 (m, 2H); 7.5-7.6 (m, 5H); 7.62 (d, 1H); 7.85 (t, 1H); 8.1 d (d, 1H). IR: 3800, 2900, 1730, 1670, 1590, 1570, 1470, 1390, 1230, 1170, 880, 770, 700, 660 cm⁻¹.

20

EXAMPLE 18

3-(9-Methyl-3-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one (I); A = CH₃, Z = CH, B = H, X₁ = H, X₂ = H.

25 200 mg (0.4 mmol) of the product of Example 14, dissolved in 5 ml of methanol containing 5% of KOH, are introduced into a reactor, and the mixture is brought to reflux. After 45 min, the mixture is cooled and acidified with a few drops of concentrated hydrochloric acid. A precipitate forms, which is washed with cold water and purified by flash chromatography on silica, eluting with the solvent D/MN10. Weight = 70 mg. Yld: 41% - yellow solid - M.p. = 139°C - TLC (C/A20): R_f = 0.32.

30 ¹H NMR δ (ppm): 2.35 (s, 3H); 3.05-3.2 (m, 1H); 3.3-3.45 (m, 1H); 3.9-4 (m, 1H); 4.4-4.55 (m, 1H); 6.3 (s, 1H); 7.05 (s, 1H); 7.4-7.65 (m, 7H); 7.75 (d, 1H); 7.85-7.95 (t, 1H); 8.15 (d, 1H); 8.7 (s, 1H).

IR: 3400, 2900, 1670, 1610, 1560, 1470, 1380, 1270, 1240, 1160, 880, 780, 700 cm⁻¹

EXAMPLE 19

(3S)-3-(2-Methyl-4-oxo-4H-pyrido[3,4-d]-pyrimidin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-hi]indol-1-one.

5 (I); A = CH₃, Z = N, B = CH₃, X₁ = H, X₂ = H (process A1b)

In a reactor protected from moisture and under a nitrogen atmosphere, 0.515 g (2.86 mmol) of 3-acetamidoisonicotinic acid and 0.316 g (3.13 mmol) of N-methylmorpholine are dissolved in 20 ml of CH₂Cl₂ dried over molecular sieve. The mixture is cooled to 0°C and 3.13 mmol of isobutyl chloroformate are added dropwise to the mixture, which is then stirred for 3 h at 0°C. 0.833 g (2.86 mmol) of the intermediate amine 2.b of R configuration dissolved in 3 ml of CH₂Cl₂ is added. The mixture is maintained for 2 h at 0°C and then for 12 h at room temperature. The solvent is evaporated off under vacuum and the residue weighing 1.87 g is purified by flash chromatography on a silica column, eluting successively with the solvents D/A4, D/A6, D/M3 and D/M5. The intermediate fractions are pooled and chromatographed again, eluting with the solvent D/M2. The fractions determined pure by TLC are pooled, the solvent is evaporated and 0.07 g of a white foam is obtained.

Yld = 5.6% - M.p. = 245°C - ee = 97% (HPLC, DNBPG covalent Pirkle column)

TLC (D/M5): R_f = 0.6

¹H NMR δ (ppm): 2.3 (s, 3H); 2.85 (s, 3H); 3.1 (m, 1H); 3.3 (m, 1H); 3.90 (q, 1H); 4.7 (t, 1H); 7-7.6 (m, 8H); 8 (d, 1H); 8.65 (d, 1H); 9.15 (d, 1H).

IR: 3500, 1680, 1580, 1420, 1400, 1260, 1220, 700 cm⁻¹.

EXAMPLE 19A

3-(2-Methyl-4-oxo-4H-pteridin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-hi]indol-4-one.

25 (I); A = CH₃, Z = CH, Z₁ = N, Z₂ = N, B = CH₃, X₁ = H, X₂ = H. (Process A11c).

The compound is prepared in two steps, using 2.0 g of methyl 3-aminopyrazolecarboxylate, which is refluxed for 6 h in 6.27 g of trimethyl orthoacetate. The volatile products are evaporated and stripped off under high vacuum. The intermediate compound is not purified, and is used directly in the following step. 1.25 g of the amine 2.a in 20 ml of methanol are added and the mixture is refluxed for 16 h under a nitrogen atmosphere. The product is purified by flash chromatography on silica in the mixture D/M1. Mass: 0.30 g. Yld: 16% - Solid - M.p. = 178-183°C. - TLC (D/MN5): R_f = 0.44.

¹H NMR δ (ppm): 2.3 (s, 3H); 2.85 (s, 3H); 3.0 - 3.15 (m, 3H); 3.3-3.4 (m, 1H); 3.85-4.0 (m,

1H); 4.6-4.7 (m, 1H); 7.0-7.5 (m, 8H); 8.7 (s, 1H); 8.9 (s, 1H).

IR: 3400, 2850, 1680, 1580, 1540, 1460, 1430, 1380, 1260, 1210, 1100, 720, 700.

EXAMPLE 20

5 **3-(2-Methyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino-[6,7,1-*hi*]indol-4-one.**

(I); A = NO₂, Z = CH, B = CH₃, X₁ = H, X₂ = H (process A1c)

In a reactor protected from moisture and at 0°C, 14.7 g (45.6 mmol) of the intermediate amine 3.a are dissolved with stirring in 250 ml of anhydrous CH₂Cl₂. At a temperature in the region of 20°C, 9 g (50 mmol) of 2-acetamidobenzoic acid and 14.96 g (45.6 mmol) of OTUT are then added. The mixture is cooled to 0°C and 11.79 g (91.2 mmol) of DIEA are added. The mixture is maintained for 1 min at 0°C and then for 12 h at room temperature. 14.96 g of OTUT and 11.79 g of DIEA are then added under the same conditions; the mixture is kept stirring for 1 h and the solvent is then evaporated off under vacuum. The residue is purified by chromatography on silica, eluting with the solvent D/A1 and then D/A1.5. Weight = 17 g - Yld: 80%.
 15 ¹H NMR δ (ppm): 2.75 (s, 3H); 3.25 (m, 1H); 3.45 (m, 1H); 4.05 (m, 1H); 4.7 (m, 1H); 7.2 (s, 1H); 7.35-7.55 (m, 6H); 7.7 (m, 1H); 7.75 (m, 1H); 8.15 (m, 2H); 8.3 (s, 1H).

The products of Examples 21 to 26 are prepared according to the process A1c (Table 1) from the nitro intermediate 3.a and the appropriate substituted 2-acetamidobenzoic acids.

20

Table 1: Synthesis

Ex. No.	A	Z	B	X ₁	X ₂	Process	Yld	M.p.	Rf
20	NO ₂	CH	CH ₃	H	H	A1c	75%	-	-
21	NO ₂	CH	CH ₃	H	5-CH ₃	A1c	24%	-	0.85 (D/M5)
22	NO ₂	CH	CH ₃	H	6-CH ₃	A1c	27%	250°C	0.38 (D/M2)
23	NO ₂	CH	CH ₃	H	7-CH ₃	A1c	30%	215°C	0.36 (D/M2)
24	NO ₂	CH	CH ₃	H	8-CH ₃	A1c	13%	-	0.47 (D/M2)
25	NO ₂	CH	CH ₃	6-CH ₃	8-CH ₃	A1c	27%	172°C	0.79 (D/M2)
26	NO ₂	CH	CH ₃	6-CH ₃	8-Br	A1c	2%	-	0.81 (D/M2)
27	NO ₂	N	CH ₃	H	H	B	44%	-	0.55 (D/M5)

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EXAMPLE 21

3-(2,5-Dimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino-[6,7,1-*hi*]indol-4-one.

5 ¹H NMR δ (ppm): 2.7 (d, 6H); 3.3 (2m, 2H); 4.1 (q, 1H); 4.7 (m, 1H); 7.2 (m, 2H); 7.4 (m, 7H); 8.1 (s, 1H); 8.2 (s, 1H).

EXAMPLE 22

3-(2,6-Dimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino-[6,7,1-*hi*]indol-4-one.

10 ¹H NMR δ (ppm) 2,4 (s, 3H); 2.7 (s, 3H); 3.2 (m, 1H); 3.4 (m, 1H); 4.1 (q, 1H); 4.7 (t, 1H); 7.2 (s, 1H); 7.5 (m, 7H); 7.9 (s, 1H); 8.2 (s, 1H); 8.3 (s, 1H).

EXAMPLE 23

3-(2,7-Dimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino-[6,7,1-*hi*]indol-4-one.

15 ¹H NMR δ (ppm): 2.4 (s, 3H); 2.7 (s, 3H); 3.15 (m, 1H); 3.35 (m, 1H); 4 (q, 1H); 4,7 (t, 1H); 7.4 (m, 8H); 8.0 (d, 1H); 8.1 (s, 1H); 8.2 (s, 1H).

EXAMPLE 24

3-(2,8-Dimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino-[6,7,1-*hi*]indol-4-one.

20 ¹H NMR δ (ppm): 2.7 (s, 3H); 2.8 (s, 3H); 3.3 (m, 1H); 3.5 (m, 1H); 4.2 (q, 1H); 4.8 (t, 1H); 7.4 (m, 8H); 8 (d, 1H); 8.2 (s, 1H); 8.3 (s, 1H).

EXAMPLE 25

3-(2,6,8-Trimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]-indol-4-one.

25 ¹H NMR δ (ppm): 2.4 (s, 3H); 2.6 (s, 3H); 2.7 (s, 3H); 3.2 (m, 1H); 3.4 (m, 1H); 4 (q, 1H); 4.7 (t, 1H); 7.2 (s, 1H); 7.4 (m, 6H); 7.7 (s, 1H); 8.1 (s, 1H); 8.2 (s, 1H).

EXAMPLE 26

3-(8-Bromo-2,6-dimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino-[6,7,1-*hi*]indol-4-one.

30 ¹H NMR δ (ppm): 2.4 (s, 3H); 2.7 (s, 3H); 3.2 (m, 1H); 3.4 (m, 1H); 4.1 (q, 1H); 4.7 (t, 1H); 7.1

(s, 1H); 7.4 (m, 5H); 7.8 (s, 1H); 7.9 (s, 1H); 8.2 (s, 1H); 8.3 (s, 1H).

EXAMPLE 27

**(3S)-3-(2-Methyl-4-oxo-4H-pyrido[3,4-d]-pyrimidin-3-yl)-9-nitro-1-phenyl-
5 6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.**

(I); A = NO₂, Z = N, B = CH₃, X₁ = H, X₂ = H. (process B)

Stage 1: Preparation of **(3R)-3-acetylamino-N-(9-nitro-4-oxo-1-phenyl-3,4,6,7-tetrahydro-
[1,4]diazepino[6,7,1-*hi*]indol-3-yl)isonicotinamide.**

In a 500-ml round-bottomed flask equipped with a CaCl₂ guard tube, 5.1 g (11.5 mmol)
10 of (3R)-3-amino-N-(9-nitro-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-
3-yl)isonicotinamide, the preparation of which is described under the intermediate 5, are
introduced into 100 ml of pyridine, 50 ml of acetic anhydride are added and the mixture is stirred
for 16 h at 20-25°C. The mixture is cooled in ice, and 250 ml of water are added. After stirring
for 4 h at room temperature, the mixture is extracted with ethyl acetate and the organic phase is
15 washed with saturated NaHCO₃ and then with water. The solvent is evaporated off and the
residue purified by flash chromatography on silica, eluting with D/A10, D/A20, and then D/A30.
Weight = 2.7 g - Yld = 49%.

Stage 2: In a 100-ml round-bottomed flask protected from moisture and under nitrogen, 1.7 g
(3.5 mmol) of the acetylated derivative obtained in the preceding step are introduced into 40 ml
20 of 1,2-dichlorobenzene. The medium is brought to 190°C for 24 h; after cooling, the reaction
medium is purified directly on a silica column, eluting with D/M1.

Weight = 0.7 g - Yld = 43% - TLC (D/M5): R_f = 0.55.

¹H NMR δ (ppm): 2.8 (s, 3H); 3.4 (2m, 2H); 4.2 (q, 1H); 4.8 (m, 1H); 7.1 (m, 1H); 7.4-7.6 (m,
5H); 8.0 (s, 1H); 8.2 (s, 1H); 8.4 (s, 1H); 8.7 (s, 1H); 9.1 (s, 1H).

25

EXAMPLE 28

**(3S)-9-Amino-3-(2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-
3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.**

(I) (3S); A = NH₂, Z = CH, B = CH₃, X₁ = H, X₂ = H (process A1c)

30 The compound is prepared according to the procedure of Example 3 from the intermediate 4 of R
configuration and N-acetylanthranilic acid.

¹H NMR δ (ppm): 2.8 (s, 3H); 3 (m, 1H); 3.2 (m, 1H); 3.85 (q, 1H); 4.5 (q, 1H); 6.4 (s, 1H); 6.8
(s, 1H); 7.1 (s, 1H); 7.4-7.6 (m, 7H); 7.7 (m, 2H); 7.9 (m, 1H); 8.15 (d, 1H).

IR: 3300, 1660, 1580, 1480, 1380, 1300, 1240, 1100, 880, 780, 700 cm^{-1} .

EXAMPLE 28A

Methyl 3-(9-amino-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-2-methyl-4-oxo-3,4-dihydroquinazoline-7-carboxylate

(I); A = NH_2 , Z = CH, B = CH_3 , X_1 = H, X_2 = CO_2CH_3 (process A4)

The compound is prepared from the intermediate 4 and an ester derivative of 2-aminoterephthalic acid:

Stage 1: Preparation of **Dimethyl 2-(1-methoxyethylideneamino)terephthalate**

10 3.8 g (32 mmol) of 1,1,1-trimethoxyethane and 1.5 g (7.17 mmol) of dimethyl 2-aminoterephthalate are introduced into a reactor. The medium is stirred and refluxed for 5 h, and then concentrated to dryness at 50°C under a vacuum of less than 1 mm Hg. 1.4 g of a thick brown oil are obtained. - TLC (99/1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$): R_f = 0.7 - 0.8.

$^1\text{H NMR } \delta$ (ppm): 1.8 (s, 3H); 3.78 (s, 3H); 3.82 (s, 3H); 3.90 (s, 3H); 7.4 (s, 1H); 7.65 (d, 1H);
15 7.85 (d, 1H).

Stage 2: 3 ml of methanol and 1.5 g (5.13 mmol) of the intermediate 4 are added to the product obtained in stage 1 above. The solution is refluxed for 16 h. A yellow suspension is obtained, which is diluted with methanol and filtered off. 10 ml of methanol are added to the precipitate to purify it, and the mixture is brought to reflux. 1.2 g (Yld = 47.4%) are obtained. - M.p. = 276°C -

20 TLC (95/5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$): R_f = 0.8.

$^1\text{H NMR } \delta$ (ppm): 2.85 (s, 3H); 3-3.1 (m, 1H); 3.25-3.35 (m, 1H); 3.6-3.85 (m, 2H); 3.85-3.95 (m, 1H); 3.95 (s, 3H); 4.6-4.7 (m, 1H); 6.45 (s, 1H); 6.85 (s, 1H); 7.15 (s, 1H); 7-7.6 (m, 5H); 8.0 (d, 1H); 8.25 (d, 1H); 8.45 (s, 1H).

IR: 3400, 3300, 3220, 1770, 1650, 1620, 1590, 1560, 1480, 1440, 1380, 1300, 1240, 1160, 1090,
25 1010, 760, 710 cm^{-1} .

EXAMPLE 28B

The enantiomers are separated on a preparative HPLC system (of the *Merck* type, by injecting the racemate onto a *Chiralcel* OJ 20 \times 250 mm chiral column, particles of 10 μm ,
30 thermostatically adjusted to 35°C), or an analytical column (*Chiralcel* OJ 250 \times 4.5 mm column, thermostatically adjusted to 35°C, eluent: 50/50 hexane/ethanol, flow rate 1.2 ml/min). Under the latter conditions, the enantiomer A has a retention time of 9.3 min.

EXAMPLE 28C

Under these same conditions, the enantiomer B has a retention time of 16.5 min.

EXAMPLE 28D

5 **3-(9-Amino-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-2-methyl-4-oxo-3,4-dihydroquinazoline-7-carboxylic acid**

(I); A = NH₂, Z = CH, B = CH₃, X₁ = H, X₂ = CO₂H

0.6 g (1.22 mmol) of the product of Example 28A and 30 ml of THF are introduced into a reactor. After solubilization, a solution of 0.135 g of KOH in 8 ml of water is added and the
10 mixture is kept stirring for 3 h at 20-25°C. The mixture is neutralized with 0.1 N HCl to pH 6.8 and the THF is evaporated off at 50°C under a vacuum of 20 mm Hg. The residue is chromatographed, eluting with CH₂Cl₂ progressively enriched with methanol. The product obtained is crystallized from 10 ml of CH₂Cl₂ and the precipitate is filtered off. 0.25 g is obtained (Yld = 42.7%). M.p. > 275°C - TLC (85/15 CH₂Cl₂/MeOH): Rf = 0.35.

15 ¹H NMR δ (ppm): 2.7 (s, 3H); 3.0-3.1 (m, 1H); 3.3-3.4 (m, 1H); 3.4-3.7 (m, 3H exch.); 3.8-3.95 (m, 1H); 4.45-4.55 (m, 1H); 6.45 (s, 1H); 6.9 (s, 1H); 6.95 (s, 1H); 7.4-7.6 (m, 5H); 7.95-8.2 (m, 3H).

IR: 3350, 1680, 1480, 1380, 1300, 1240, 1170, 1110, 1010, 790, 690 cm⁻¹.

20

EXAMPLE 29

9-Amino-3-(2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

(I); A = NH₂, Z = CH, B = CH₃, X₁ = H, X₂ = H (process C1)

The compound is prepared by reduction of the product of Example 20 with sodium
25 sulfide, which is the preferred agent according to the process C1: 0.5 g (1.07 mmol) of the product of Example 20, 0.672 g (2.8 mmol) of Na₂S.9H₂O and 3.21 ml of ethanol are introduced into a reactor. The mixture is heated to 60°C with stirring for 2 h. The solvent is evaporated off and the residue taken up with water and extracted with CH₂Cl₂. After purification by flash chromatography on silica, eluting with the solvent D/A2, 190 mg of a yellow solid are obtained.
30 Weight = 0.19 g - Yld: 41% - M.p. = 291°C.

¹H NMR δ (ppm): identical to the product of Example 28 above.

An alternative process consists in using titanium trichloride as reducing agent. Thus, in a reactor under nitrogen, protected from moisture and equipped with a magnetic stirrer, 5.0 g (10.7 mmol) of the product of Example 20 are introduced into 42.8 ml of acetic acid. 64 mmol of TiCl₃

(in 30% solution in 2N HCl) are added dropwise and the mixture is kept stirring for 30 min. It is then alcalinized with sodium hydroxide to a pH of 9, the medium being cooled by adding ice. The mixture is then extracted with ethyl acetate. After evaporation of the solvent, the product is purified by flash chromatography on silica. Yld: 10%.

5

EXAMPLE 30

9-Amino-3-(2,5-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

(I); A = NH₂, Z = CH, B = CH₃, X₁ = H, X₂ = CH₃ at position 5 (process C1)

10

The product is obtained by reducing the compound of Example 21 with Na₂S.

¹H NMR δ (ppm): 2.65 (s, 3H); 2.7 (s, 3H); 3 (m, 1H); 3.3 (m, 1H); 4.4 (q, 1H); 4.5 (t, 1H); 5.7 (s, 1H); 6.4 (s, 1H); 6.9 (d, 2H); 7.5 (m, 9H).

EXAMPLE 31

15

9-Amino-3-(2,6-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

(I); A = NH₂, Z = CH, B = CH₃, X₁ = H, X₂ = CH₃ at position (process C1)

The product is obtained by reducing the compound of Example 22 with Na₂S.

20

¹H NMR δ (ppm): 2.4 (s, 3H); 2.7 (s, 3H); 3 (m, 1H); 3.3 (m, 1H); 3.9 (q, 1H); 4.5 (t, 1H); 5.4 (s, 2H); 6.4 (s, 1H); 6.9 (d, 2H); 7.5 (m, 7H), 7.9 (s, 1H).

EXAMPLE 32

9-Amino-3-(2,8-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indole-4-one.

25

(I); A = NH₂, Z = CH, B = CH₃, X₁ = H, X₂ = CH₃ at position 8 (process C2)

In a 100-ml round-bottomed flask equipped with a condenser, 550 mg (1.15 mmol) of the product of Example 24 are introduced into 20 ml of absolute ethanol. The medium is heated to permit dissolution. 1.3 g (5.75 mmol) of SnCl₂·2H₂O are added. The temperature is maintained for 1 h at 50°C, 30 ml of ice are then introduced and the mixture is alcalinized to a pH of 12 with 1N NaOH. The medium is extracted with CH₂Cl₂; the organic phase is washed with saturated aqueous NaCl solution and then dried over Na₂SO₄. The product is purified by flash chromatography on a silica column, eluting with the solvent D/M1 and then D/M2. A yellow solid is obtained - Weight = 60 mg - Yld = 12%.

30

¹H NMR δ (ppm): 2.6 (s, 3H); 2.7 (s, 3H); 3 (m, 1H); 3.3 (m, 1H); 3.9 (q, 1H); 4.5 (t, 1H); 5.4 (s,

2H); 6.4 (s, 1H); 6.95 (d, 2H); 7.5 (m, 6H); 7.7 (d, 1H); 7.9 (d, 1H).

EXAMPLE 33

9-Amino-3-(2,6,8-trimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-

5 **[1,4]diazepino[6,7,1-*hi*]indol-4-one.**

(I); A = NH₂, Z = CH, B = CH₃, X₁ = CH₃ at position 6, X₂ = CH₃ at position 8 (process C2)

The product is obtained in the form of a yellow solid from the compound of Example 25, the reducing agent being SnCl₂.

¹H NMR δ (ppm): 2.4 (s, 3H); 2.55 (s, 3H); 2.7 (s, 3H); 3 (m, 1H); 3.3 (m, 1H); 3.9 (q, 1H); 4.5
10 (t, 1H); 5.4 (s, 2H); 6.4 (s, 1H); 6.9 (s, 1H); 6.95 (s, 1H); 7.5 (m, 6H); 7.7 (s, 1H).

EXAMPLE 34

9-Amino-3-(2-methyl-4-oxo-4H-pyrido[3,4-d]pyrimidin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

15 (I); A = NH₂, Z = N, B = CH₃, X₁ = X₂ = H (process C2)

The product is obtained in the form of a yellow solid from the compound of Example 19, the reducing agent being SnCl₂.

¹H NMR δ (ppm): 2.7 (s, 3H); 3.05 (m, 1H); 3.3 (m, 1H); 3.9 (q, 1H); 4.5 (t, 1H); 5.4 (s, 2H); 6.4
20 (s, 1H); 6.85 (s, 1H); 6.9 (s, 1H); 7.5 (m, 5H); 7.9 (d, 1H); 8.7 (d, 1H); 9.1 (s, 1H).

EXAMPLE 34A

5-Chloro-2-methyl-3-(9-nitro-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline.

(I); A = NO₂, Z = CH, B = CH₃, X₁ = H, X₂ = Cl at 5 (process A2)

25 A mixture of 7 g (35.7 mmol) of 5-chloro-2-methyl-4-oxo-4H-benzo[d][1,3]oxazine (prepared from 6-chloro-2-aminobenzoic acid and acetic anhydride, according to J. Am. Chem. Soc. (1907) 29: p. 86) and 8.87 g (27.5 mmol) of the intermediate 3.a in 50 ml of CH₂Cl₂ is maintained at 100°C under a pressure of 4 bar for 8 h in an autoclave. The medium is cooled, the solvent is evaporated off and the residue is purified by flash chromatography on a column of
30 silica, eluting with the solvents D/M0.5 and D/M1.5. The fractions of interest are combined and evaporated. 6.7 g of an amorphous solid are obtained. Yld = 43%. - TLC: (D/M0.5): R_f = 0.35.
¹H NMR δ (ppm): 2.35 (s, 3H); 2.65 (s, 3H); 3.1 (m, 1H); 3.35 (q, 1H); 3.95 (q, 1H); 4.45 (t, 1H); 6.95 (s, 1H); 7.05 (s, 1H); 7.4-7.55 (m, 6H); 8.0 (d, 1H); 8.1 (d, 2H).

EXAMPLE 34B

9-Amino-3-(5-chloro-2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-hi]indol-4-one.

5 (I); A = NH₂, Z = CH, B = CH₃, X₁ = H, X₂ = Cl at 5 (process C1).

The compound is prepared by reduction of 3.54 g (7.14 mmol) of the product of Example 34A with Na₂S, which is the preferred agent according to the process C1, as in Example 29, with heating for 12 h. After purification by chromatography on silica, eluting with the solvent DM2, 530 mg of a yellow solid are obtained. Yld = 31%. - M.p. = 272°C. - TLC (D/M2): Rf =
10 0.35.

¹H NMR δ (ppm): 2.8 (s, 3H); 3.0 (m, 1H); 3.4 (m, 1H); 3.9 (q, 1H); 4.7 (); 6.5 (s, 1H); 6.9 (s, 1H); 7.2-7.8 (m, 9H).

IR: 3300, 3200, 1660, 1580, 1450, 1380, 1320, 1270, 1160, 780, 700 cm⁻¹.

15

EXAMPLES 35 TO 35I

Preparation of the common intermediate:**Pentafluorophenyl 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxylate.**

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ = CO₂-C₆F₅ at 7. (Process D11a)

20 4.6 g (9.6 mmol) of the acid obtained in Example 7 in 200 ml of CH₂Cl₂ dried over sieves are introduced into a reactor protected from moisture; 3.54 g (19 mmol) of pentafluorophenol, 8.3 g (4.3 mmol) of N-ethyl-N-3-dimethylaminopropylcarbodiimide hydrochloride and 0.48 g (0.25 mmol) of 4-dimethylaminopyridine para-toluenesulfonate are added. The solution is stirred for 5 h at 20-25°C. It is washed with 200 ml of water and then with 200 ml
25 of 5% NaHCO₃ solution. The organic phase is dried and evaporated. The product is recrystallized from ether (60 ml). 5.54 g of white powder are obtained. Yld = 89% - TLC (D/M2): Rf = 0.92.

EXAMPLE 35

General process

30 185 mg (0.1 mmol) of Fmoc-valine (9-fluorenylmethoxycarbonyl-(L)-valine) which are bound to a Wang resin, are placed in 4.8 ml of DMF with stirring; after stirring for 1 h which is intended to make the resin swell, 1.2 ml of piperidine are added with stirring for a further 1.5 h, and the resin is rinsed three times with 5 ml of DMF and then with three times 5 ml of methanol and finally three times with 5 ml of CH₂Cl₂. 100 mg (0.15 mmol) of the above pentafluorophenyl

ester in 8 ml of CH₂Cl₂ are added and the mixture is stirred for 20 h at room temperature. The phases are separated after settling has taken place and the resin is rinsed three times with 5 ml of DMF and then three times with 5 ml of methanol and finally three times with 5 ml of CH₂Cl₂. The coupling operation is repeated a second time. The rinsed resin is stirred in a 50/50 (v/v) trifluoroacetic acid/CH₂Cl₂ mixture for 1 h at 25°C. The resin is filtered off and rinsed with CH₂Cl₂. It is concentrated and stripped off the CH₂Cl₂ several times. The purity is determined by high-pressure chromatography on a Nucleosil C18 column, the mobile phase being a 65/35 (v/v) KH₂PO₄ buffer/acetonitrile mixture. The flow rate is 1 ml/min; the UV absorption at 240 nm is recorded.

10 TLC (66/17/17 *n*-butanol/acetic acid/water): R_f = 0.89.

50 mg of N-(2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carbonyl)valine are obtained.

Nine other products are prepared in the same way:

15

EXAMPLE 35A

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxyl)tyrosine.

EXAMPLE 35B

20 **N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxyl)alanine.**

EXAMPLE 35C

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxyl)phenylalanine.

EXAMPLE 35D

25 **N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxyl)glycine.**

EXAMPLE 35E

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxyl)leucine.

30

EXAMPLE 35F

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxyl)aspartic acid.

EXAMPLE 35G

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxyl)proline.

EXAMPLE 35H

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxyl)glutamic acid.

EXAMPLE 35I

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazoline-7-carboxyl)lysine.

Example:	Resin	Mass (mg)	Purity (%)	Rf (TLC)	Retention time (HPLC)
35	N-Fmoc-valine	50	94.6	0.89	10.95 min
35A	N-Fmoc-O- <i>t</i> -Bu-tyrosine	40	77.5	0.94	16.55
35B	N-Fmoc-alanine	40	78.4	0.94	18.63
35C	N-Fmoc-phenylalanine	20	87.8	0.93	28.77/30.63
35D	N-Fmoc-glycine	60	97.6	0.83	8.09
35E	N-Fmoc-leucine	40	94.1	0.97	40.36/44.13
35F	N-Fmoc- γ -O- <i>t</i> -Bu- aspartic acid	40	94.4	0.78	6.09
35G	N-Fmoc-proline	80	97.5	0.79	10.89
35H	N-Fmoc- δ -O- <i>t</i> -Bu- glutamic acid	60	96.0	0.86	7.53
35I	N-Fmoc- ϵ -N-Boc-lysine	70	96.6	0.38	8.84

10

EXAMPLE 36

Ethyl 2-{{2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydroquinazolin-7-carbonyl}amino}-3-phenyl-(L)-propionate.

(I); A = CH₃, Z = CH, B = CH₃, X₁ = H, X₂ (at 7) = CONHCH(CH₂C₆H₅)CO₂CH₂CH₃

15

(Process D11a)

The compound is prepared as described in Example 35, the amidation being carried out by a solution of ethyl (L)-phenylalaninate in CH₂Cl₂. The product, after chromatographic purifications, is obtained in the form of a white powder. Yld = 81%. M.p. = 135°C. - TLC (50/50

AEC): Rf = 0.30.

¹H NMR δ (ppm): 1.7 (t, 3H); 2.3 (s, 3H); 2.8 (s, 3H); 3.0 (m, 1H); 3.3 (m, 1H); 3.9 (q, 2H); 4.2 (m, 1H); 4.6 (dt, 1H); 5.0 (m,); 6.7 (d, 1H); 7.0 (s, 1H); 7.1 (m, 1H); 7.2 (m, XH); 7.3 (m, H); 7.4 (m, H); 7.5 (d,); 7.7 (d,); 7.9 (t,); 8.2 (d,).

5 IR: 3350, 3000, 2900, 1720, 1680, 1620, 1580, 1560, 1480, 1440, 1420, 1400, 1340, 1180, 1120, 1020, 960, 740, 700 cm⁻¹.

BIOLOGICAL ACTIVITY

10 Phosphodiesterase-inhibiting activity

The capacity of the compounds of formula (I) of the invention to inhibit cyclic nucleotide phosphodiesterases is evaluated by measuring their IC₅₀ (concentration necessary for inhibiting 50% of the enzyme activity). In the case of the PDE4 enzymes, this value is compared with that of rolipram, a specific PDE4 inhibitor. The different types of phosphodiesterases are
 15 obtained partially purified on a DEAE-cellulose column from guinea pig trachea and dog aorta according to a method adapted from W.J. Thompson et al., 1979, *Advances in Cyclic Nucleotide Research*, Vol. 10: 69-92, ed. G. Brooker et al. Raven Press, New York, and from P.J. Silver et al., 1988, *Eur. J. Pharmacol.* 150: 85-94, and from the cell line of human origin U937 according to a method adapted from T.J. Torphy *et al.*, 1992, *J. Pharm. Exp. Ther.* 263: 1195 - 1205.
 20 Measurement of the enzyme activity of the different types of PDE, and especially of the PDE4 enzymes, is then carried out according to a method adapted from W.J. Thompson, *ibidem*. For the determination of the IC₅₀, the enzyme activity is measured in the presence of the inhibitor in a concentration range from 10⁻¹⁰ to 10⁻⁴ M.

25 The following table illustrates PDE4-inhibiting activity of Examples according to the invention on an enzyme preparation obtained from the U937 cell line.

Example	Enzyme
1	0.448
2	0.146
2A	0.183
2B	0.067
2C	0.108

Example	Enzyme
16	0.260
17	0.746
17A	0.137
17B	0.221
17C	0.339

3	0.141
4	0.553
5	0.832
6	3.016
6A	0.133
6B	1.418
6C	0.838
6D	0.372
6E	>100.000
6F	>100.000
7	0.052
7A	0.157
7B	0.057
7C	0.066
7D (R)	0.982
7E (S)	0.035
8	0.050
8A	n.t.
8B	0.028
9	0.063
9A	0.122
9B	0.095
9C	0.069
9D	0.119
9E	n.t.
9F	0.192
9G	0.137
9H	n.t.
9I	0.119
10	0.183

17D	0.286
17E	0.222
17F	0.147
17G	0.516
17H	0.184
18	0.823
19	0.193
19A	1.477
20	n.t.
21	n.t.
22	1.734
23	0.497
24	30.564
25	>100.000
26	90.620
27	n.t.
28	0.005
28A	0.005
28B	0.003
28C	0.070
28D	0.009
29	0.013
30	0.008
31	0.087
32	0.055
33	0.155
34	0.042
34A	n.t.
34B	0.003
35	0.106

10A	0.108
10B	0.155
10C	0.081
10D	0.042
10E	0.075
11	0.079
12	0.088
13	0.083
14	0.310
15	0.082

n.t.: not tested

35A	0.088
35B	0.190
35C	0.111
35D	0.065
35E	0.082
35F	0.547
35G	0.291
35H	0.219
35I	0.120
36	0.312
rolipram	0.792

Inspection of the results in the above table shows that the products of the invention generally inhibit the PDE4 enzyme of human origin much more effectively than rolipram, and in some cases are approximately 100 times as active as rolipram.

Moreover, tests carried out on PDEs of different types, purified from guinea pig trachea or from dog aorta, show that the IC_{50} values obtained with the products of the invention with respect to PDEs of type 3 and of type 1 and 5 are much higher than those measured for the type 4 PDEs. These results are evidence of a potent and selective inhibitory activity for the products of the invention with respect to the PDE4 enzymes.

Examples 28A, 28B, 28C, 28D, 34, and 34B at concentrations lower than 5×10^{-6} M have proved capable of inhibiting bacterial LPS-induced production of TNF- α in whole human blood.

Anti-inflammatory and anti-allergic activity in vivo

The effects of the products of the invention were studied in rats in a model of eosinophil infiltration induced by an antigenic stimulation, according to a methodology adapted from Lagente V. *et al.*, (1994) Br. J. Pharmacol. 112, 83P.

The administration a number of products of the Examples at 10 mg/kg p.o. significantly decreased the number of eosinophils in the bronchoalveolar lavage fluid.

These results demonstrate the anti-inflammatory and/or anti-allergic activity of the products of the invention. Hence the products of the invention will be especially useful for the treatment or prevention of:

- allergic pathologies, and in particular asthma and atopic dermatitis; inflammatory pathologies, in particular those affecting the bronchus, but also rheumatoid arthritis and inflammatory intestinal complaints (hemorrhagic rectocolitis and Crohn's disease); including, where it is present, an autoimmune component.

5

PHARMACEUTICAL FORMULATION

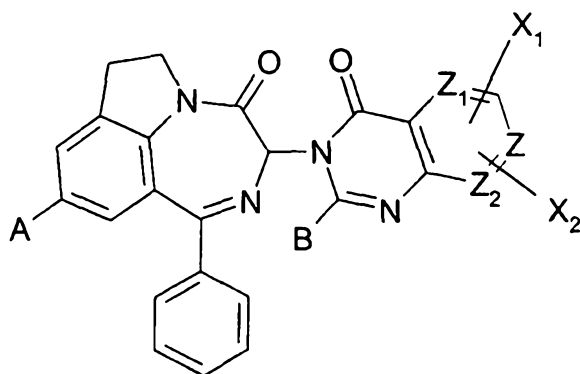
The products of the invention are administered in the form of compositions suited to the nature and extent of the complaint to be treated. The daily dosage in man is usually between 2 mg and 1 g of product, which can be taken in one or several doses. The compositions are prepared in forms which are compatible with the administration route envisaged, such as, for example, tablets, dragées, capsules, mouthwashes, aerosols, powders for inhalation, suppositories, gels or suspensions. These compositions are prepared by methods familiar to a person skilled in the art, and comprise from 0.5 to 60% by weight of active principle (compound of formula I) and 40 to 99.5% by weight of suitable pharmaceutical vehicle which is compatible with the active principle and the physical form of the composition envisaged. The composition and preparation of tablets containing a compound of the invention are presented by way of example:

Active substance	
of formula (I)	1 to 75 mg
Lactose	124 to 74 mg
Microcrystalline	
cellulose	36 to 60 mg
Polyvinylpyrrolidone	6 mg
Sodium carboxymethyl	
starch	8 mg
Magnesium stearate	1 mg

Mix the active substance, lactose, microcrystalline cellulose and carboxymethyl starch. Wet and granulate using an aqueous or alcoholic solution of polyvinylpyrrolidone of appropriate concentration. Dry and size the granule. Mix the magnesium stearate homogeneously. Tablet on the basis of 200 mg per tablet.

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CLAIMS

1). Diazepinoindolone (I) of formula



I

5 wherein :

-A is hydrogen, C₁-C₄alkyl, OR¹, hydroxy, nitro, cyano, -NH₂, -NHR¹, or -NR¹R²;

R¹ and R² independently are C₁-C₄alkyl, cyclopropyl, cyclopropylmethyl, or NR¹R² taken together with the nitrogen to which they are bound complete a ring having 4 or 5 carbon atoms;

10 -B is hydrogen, C₁-C₄alkyl, -CH₂OM, -CH₂OC(=O)(CH₂)_a(CO)_bY¹-Y², or

-(CH₂)_cC(=O)OM;

Y¹ is -(VCH₂CH₂)_c-, with V = -NH- or -O-; or Y¹ is -NHCHR^A-C(=O)-;

Y² is hydrogen, hydroxy, -OCH₃, or 4-morpholinyl;

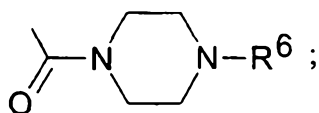
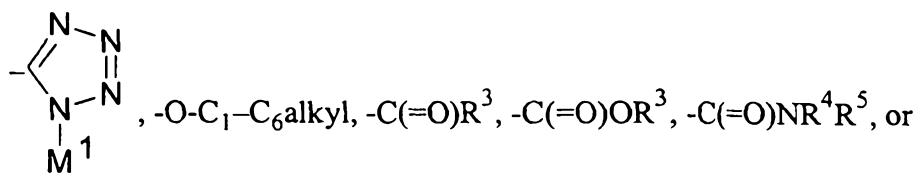
M is hydrogen or C₁-C₄alkyl;

15 a = 1 or 2; b = 0 or 1; c = 0, 1, or 2;

-Z is CH, then Z₁ and Z₂ both are CH or N; or

Z is N, then Z₁ and Z₂ are CH;

-X₁ and X₂ independently are hydrogen, C₁-C₄alkyl, -(CH₂)_n-OR³, halogen, cyano,



20

R^3 is hydrogen, C_1 - C_6 alkyl, benzyl, phenethyl, or $-Q^1-Q^2$;

R^4 is hydrogen, or C_1 - C_4 alkyl;

R^5 is hydrogen, C_1 - C_4 alkyl, $-CHR^A-C(=O)OM^1$, or $-Q^3-Q^4$;

R^6 is hydrogen, C_1 - C_4 alkyl, or $-Q^3-Q^5$;

5 R^A is a residue of a natural α -amino-acid, the carbon atom to which it is linked having either a S configuration, or a R configuration;

Q^1 is $-(CH_2)_n-(CHOH)_m-(CH_2)_p-$;

Q^2 is hydroxy, $-O-C_1-C_6$ alkyl, $-OC(=O)-C_1-C_6$ alkyl, or 4-morpholinyl;

Q^3 is $-(CH_2)_n-$;

10 Q^4 is $-NHM^1$, $-NM^1M^2$, or 4-morpholinyl;

Q^5 is $-M^1$ or $-OM^1$;

M^1 and M^2 are independently hydrogen or C_1 - C_4 alkyl;

n is 1, 2, or 3; m is 0, 1, 2, 3, or 4; p is 0, 1, 2, or 3, provided that if m is not 0, then p is not 0;

15 -its racemic form and each of its isomers, in particular those whose configuration is determined by carbon 3 of the [1,4]diazepino[6,7,1-*hi*]-indol-4-one ring system,
-and the pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof.

2) A compound of Claim 1 wherein carbon 3 of the [1,4]diazepino[6,7,1-*hi*]-indol-4-one ring
20 system has the S configuration.

3) A compound of Claim 1 or 2 wherein:

A is hydrogen, methyl, hydroxy, $-OCH_3$, $-NH_2$, $-NHCH_3$; $-N(CH_3)_2$ or 1-pyrrolidinyl;

B is C_1 - C_4 alkyl, $-CH_2OH$, $-CH_2OCH_3$, $-CO_2-CH_2-CH_3$; and

25 X_1 et X_2 are independently hydrogen, methyl, methoxy, $-CH_2OH$, F, Cl, Br, $-C(=O)OR^3$, or $C(=O)NR^4R^5$;

R^3 , R^4 , and R^5 being as defined in Claim 1.

4) A compound of Claim 1, 2, or 3 wherein

A is -CH₃ or -NH₂; and

B is -CH₃ or -CH₂OCH₃.

5) A compound of Claim 1, 2, 3, or 4 wherein

5 Z, Z₁, Z₂ are CH ; and

X₁ or X₂ is methyl, F, Cl, or Br at position 5 of the quinazoline ring system.

6) A compound of Claim 1, 2, 3, 4, or 5 wherein

Z, Z₁, Z₂ are CH ;

10 A is -NH₂ ; and

X₁ or X₂ is -C(O)OR³ or -C(=O)NR⁴R⁵ at position 7 of the quinazoline ring system;

R³, R⁴, and R⁵ being as defined in Claim 1.

7) The compounds:

15 (3S)3-(2-Methyl-4oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H[1,4]diazepino[6,7,1-*hi*]indol-4-one ;

9-Methoxy-3-(2-methyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

20 2-Methyl-3-(9-methoxy-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid methyl ester;

2-Methyl-3-(9-methoxy-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid.

8) The compounds:

25 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid methyl ester;

30 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid;

D-Glucamine 2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-

[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylate salt;

(3R) 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid;

5 (3S) 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 2-morpholin-4-yl-ethyl ester;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 2-acetoxy-ethyl ester;

10 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 2-methoxy-ethyl ester;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 2-hydroxy-ethyl ester;

15 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 1-(2S)-glycerol ester;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid 2-hydroxy-3-morpholin-4-yl-propyl ester.

20 9) The compounds:

9-Methyl-3-(2-methyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

(3S)9-Methyl-3-(2,5-dimethyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

25 (3S)9-Methyl-3-(2,6-dimethyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

(3S)9-Methyl-3-(2,6-dimethyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.;

30 (3S)9-Methyl-3-(2,8-dimethyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(5-Methoxy-2-methyl-4-oxo-4H-quinazolin-3yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(7-Methoxy-2-methyl-4-oxo-4H-quinazolin-3yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(6-Methoxy-2-methyl-4-oxo-4H-quinazolin-3yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(6-Bromo-2-methyl-4-oxo-4H-quinazolin-3yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

5 3-(5-Hydroxymethyl-2-methyl-4-oxo-4H-quinazolin-3yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-5-carboxylic acid tertiobutyl ester ;

10 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-5-carboxylic acid;

3-(7-Hydroxymethyl-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

(3*S*)-3-(5-Fluoro-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

15 3-(5-Chloro-2-methyl-4-oxo-4H-quinazolin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

(9-Methyl-3-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino [6,7,1-*hi*]indol-4-one.

20 **10) The compounds:**

3-(9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid ethyl ester;

5-Chloro-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid ethyl ester;

25 [3-(9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-acetic acid ethyl ester;

Acetic acid 3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl ester;

30 9-Methyl-3-(2-methyloxymethyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

9-Methyl-3-(2-hydroxymethyl-4-oxo-4H-quinazolin-3yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

Succinic acid mono-[3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl] ester;

[2-(2-Methoxy-ethoxy)-ethoxy]-acetic acid mono-[3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl] ester;

N-(2-Morpholin-4-yl-ethyl)-succinamic acid 3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl-methyl ester;

5 Succinic acid 3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl ester 2-morpholin-4-yl-ethyl ester;

6-*t*-Butoxycarbonylamino-2-{3-[3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxycarbonyl]-propionylamino}-hexanoic acid methyl ester;

10 3-[3-(9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-propanoic acid ethyl ester.

11) The compounds:

(3S) 3-(2-Methyl-4-oxo-4*H*-pyrido[3,4-*d*]pyrimidin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one;

3-(2-Methyl-4-oxo-4*H*-pteridin-3-yl)-9-methyl-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

9-Amino-3-(2-methyl-4-oxo-4*H*-pyrido[3,4-*d*]pyrimidin-3-yl)-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

20

12) The compounds:

3-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

25 3-(2,5-Dimethyl-4-oxo-4*H*-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(2,6-Dimethyl-4-oxo-4*H*-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(2,7-Dimethyl-4-oxo-4*H*-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

30 3-(2,8-Dimethyl-4-oxo-4*H*-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(2,6,8-Trimethyl-4-oxo-4*H*-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

3-(8-Bromo-2,6-dimethyl-4-oxo-4H-quinazolin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

(3S)3-(2-Methyl-4-oxo-4H-pyrido[3,4-*d*]pyrimidin-3-yl)-9-nitro-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

5 5-Chloro-2-methyl-3-(9-nitro-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline.

13) The compounds:

(3S)9-Amino-3-(2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

10 3-(9-Amino-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-2-methyl-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid methyl ester, and its enantiomers;

3-(9-Amino-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-2-methyl-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid;

15 9-Amino-3-(2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

9-Amino-3-(2,5-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

20 9-Amino-3-(2,6-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

9-Amino-3-(2,8-dimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

9-Amino-3-(2,6,8-trimethyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

25 9-Amino-3-(5-chloro-2-methyl-4-oxo-4H-quinazolin-3-yl)-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one.

14) The compounds:

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxamide;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carbonitrile;

9-Methyl-3-[2-methyl-4-oxo-7-(1H-tetrazol-5-yl)-4H-quinazolin-3-yl]-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-*hi*]indol-4-one;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-N-methylcarboxamide;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-N-dimethylcarboxamide;

5 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid (3-(morpholin-4-yl-propyl)-amide);

10 2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-(2-amino)-ethylcarboxamide, and the hydrochloride salt thereof;

3-{7-[4-(2-Hydroxy-ethyl)-piperazine-1-carbonyl]-2-methyl-4-oxo-4*H*-quinazolin-3-yl}-9-methyl-1-phenyl-6,7-dihydro-3*H*-[1,4]diazepino[6,7,1-*hi*]indol-4-one, and the hydrochloride salt thereof;

15 (2*S*) 6-*t*-Butoxycarbonylamino-2-{{2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carbonyl}-amino}-hexanoic acid methyl ester;

(2*S*) 6-Amino-2-{{2-methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazolin-7-carbonyl}-amino}-hexanoic acid methyl ester.

20

15) The compounds:

2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid pentafluorophenyl ester;

25 N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxyl)-tyrosine;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxyl)-alanine;

30 N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxyl)-phenylalanine;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxyl)-glycine;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxyl)-leucine;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxyl)-aspartic acid;

N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxyl)-glutamic acid;

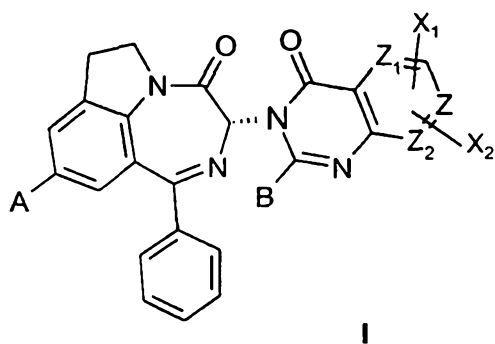
5 N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxyl)-lysine;

2{[2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carbonyl]-amino}-3-phenyl-(L)-propionic acid ethyl ester;

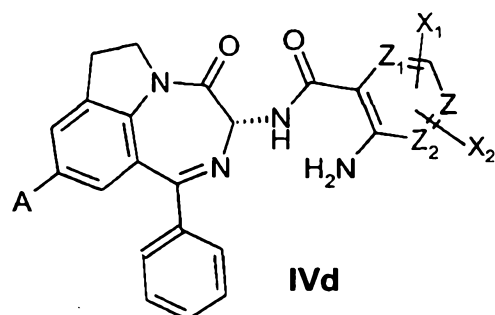
10 N-(2-Methyl-3-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indol-3-yl)-4-oxo-3,4-dihydro-quinazoline-7-carboxyl)-proline.

16) Process for the preparation of the compounds (I) according to Claim 1 which consists:

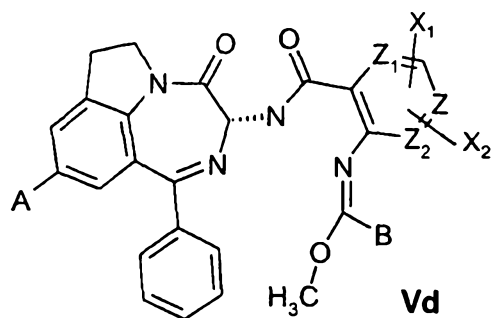
i) - for preparing optically active compounds (I)



15 in reacting an optically active amine (IVd)

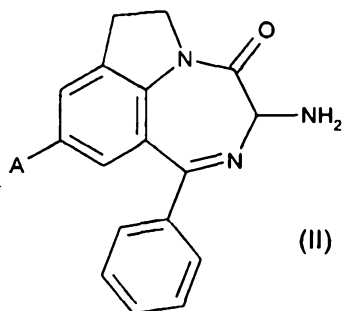


with an ortho-ester B-C(OMe)₃, to obtain the imine derivative (Vd)



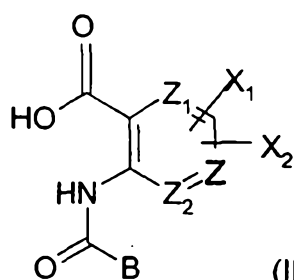
and cyclizing this intermediate in a neutral solvent with an acid catalyst ;

- ii*) - for preparing compounds (I) in which A and Z have the designations of (I), B the designations of (I) except for those comprising a carboxylic acid function, and X₁ and X₂ the meanings of (I) except for those comprising a reactive hydroxyl function, in reacting an intermediate aminodiazepinoindolone (II) of formula



in which A has the designations of (I),

- with an aromatic 2-amido acid (IIIa) of formula

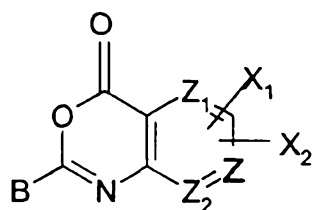


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in which B, Z, Z₁, Z₂, X₁ and X₂ have the designations defined

above, or

- with a 4-oxo-4H-oxazine (IIIb) of formula



(III_b)

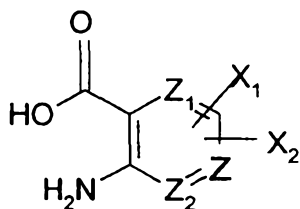
in which B, Z, X₁ and X₂ have the designations defined above,

or

- with a mixture comprising from 95 to 5% by weight of an intermediate (IIIa) with from 5 to 95% of an intermediate (IIIb), in which B, Z, X₁ and X₂, which are identical for both intermediates, have the designations defined above,

the intermediates (IIIa) and (IIIb) being isolated or otherwise after their preparation by N-

5 acylation and then, where appropriate, cyclization of an aromatic 2-amino acid (III) of formula



(III)

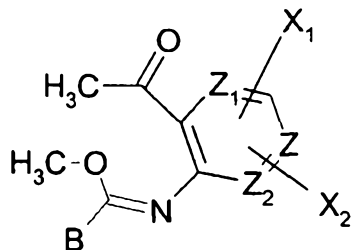
with 1,1,1-trimethoxyethane, or with a reactant (B-CO)_nW in which B has the designations of

(I) except for those comprising a carboxylic acid function, and W is halogen, in particular

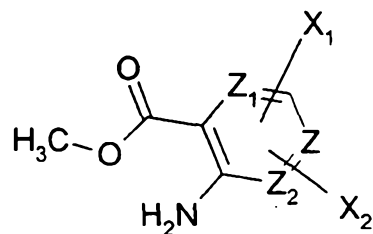
chlorine or bromine, when n has the value 1, or alternatively is oxygen when n has the value 2; or

10 finally

-with an imine of formula (IIIc) :



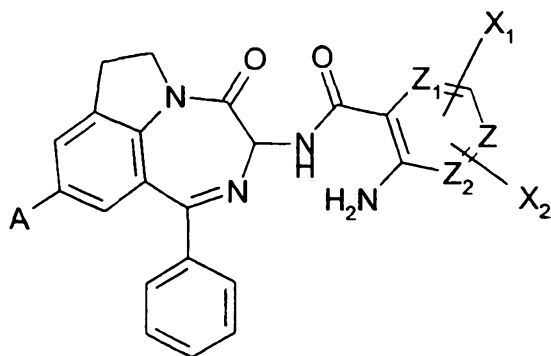
and in cyclizing the intermediate obtained ; the imine (IIIc) is first obtained by condensation of an aromatic amine of formula (IVc)



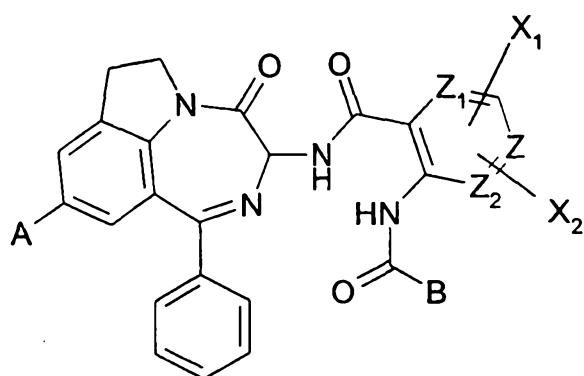
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with a 1,1,1-trimethoxy-alkane ;

iii) - for preparing compounds (I) in which B and Z have the designations of (I), A the designations of (I) except for amino and X₁ or X₂ the meanings of (I) except for those comprising a reactive hydroxyl function, in N-acylating an intermediate diazepinoindolone (IV) of formula



in which A, Z, X₁ and X₂ have the designations defined above, with a reactant (B-CO)_nW defined above in which B has the meanings designated above, to obtain an intermediate (V) of formula



- 5 which is cyclized to a diazepinoindolone (I);
- iv*) - for preparing a compound (I) in which A is amino and where B, Z, X₁ and X₂ have the meanings of (I), in reducing with sodium sulfide or a metal chloride, in particular tin chloride, a compound (I) in which A is nitro; or
- v*) - for preparing a compound (I) in which A and Z have the meanings of (I) and B and/or X₁
- 10 and/or X₂ are functionalized:
- in hydrolyzing in an acid or alkaline medium a compound (I) comprising an amide (-CO-N<) or ester (-CO-O- or -O-CO-) function, to obtain a corresponding acid or alcohol compound (I);
 - in reducing with a complex metal hydride or organometallic hydride a compound (I)

15 comprising an acid (-CO-OH) or ester (-CO-O-) function, to obtain a corresponding alcohol compound (I);
 - in carrying out the hydrogenolysis in the presence of a metal catalyst of a compound (I) comprising an ether, in particular a benzyl ether (-O-CH₂-C₆H₅), function, to obtain a corresponding alcohol compound (I);

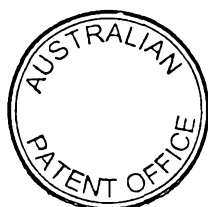
20 - in esterifying or transesterifying with an alcohol a compound (I) having an acid (-CO₂H) or ester (-CO-O-) function, to obtain a compound (I) ester of said alcohol; or

in amidating with ammonia or a primary or secondary amine a compound (I) comprising an acid (-CO-OH) or ester (-CO-O) function, to obtain a corresponding primary, secondary or tertiary amide compound (I).

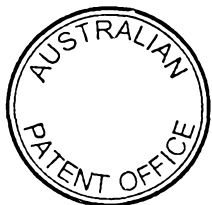
- 5 17. Use of a therapeutically effective amount of a compound of one of Claims 1 to 15 for preparing a pharmaceutical composition suitable for treating, including by the oral route, a patient in need of a phosphodiesterase 4 inhibitor.
18. The use of Claim 17 wherein the patient is suffering from asthma, atopic dermatitis, or rheumatoid arthritis.
- 10 19. The use of Claim 17 wherein the patient is suffering from an inflammatory bowel disease: ulcerative colitis or Crohn's disease.
20. The use of Claim 17 wherein the patient is suffering from primary or secondary pulmonary hypertension.
21. The use of Claim 17 wherein the patient is suffering from hepatic failure, including
15 following immunologic or inflammatory liver injury.
22. The use of Claim 17 wherein the patient is suffering from bone loss, in particular osteoporosis or osteomalacia.
23. The use of Claim 17 wherein the patient is suffering from septic shock.
24. The use of Claim 17 wherein the patient is suffering from multiple sclerosis.
- 20 25. Medicament comprising a therapeutically effective amount of a compound of one of Claims 1 to 15.

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26. A method of treatment of a patient in need of a phosphodiesterase 4 inhibitor including the step of administering to said patient a therapeutically effective amount of a compound of any one of Claims 1 to 15.
27. A method of treatment according to Claim 26 wherein the patient is suffering from
5 asthma, atopic dermatitis or rheumatoid arthritis.
28. A method according to Claim 26 wherein the patient is suffering from an inflammatory bowel disease, ulcerative colitis or Crohn's disease.
29. A method according to Claim 26 wherein the patient is suffering from primary or secondary pulmonary hypertension.
- 10 30. A method according to Claim 26 wherein the patient is suffering from hepatic failure, including hepatic failure following immunologic or inflammatory liver injury.
31. Method according to Claim 26 wherein the patient is suffering from bone loss, in particular osteoporosis or osteomalacia.
- 15 32. Method according to Claim 26 wherein the patient is suffering from septic shock.
33. A method according to Claim 26 wherein the patient is suffering from multiple sclerosis.
34. A diazepinoindolone of formula 1 substantially as herein described with reference to any one of the examples.
- 20 35. A process for preparing a diazepinoindolone of formula 1 substantially as herein described with reference to any one of the examples.
36. The use of a therapeutically effective amount of a diazepinoindolone of formula 1 from the manufacture of a medicament substantially as herein described.



37. A method of treatment of a patient in need of phosphodiesterase 4 inhibitor substantially as herein described with reference to any one of the examples.

DATED this 7th Day of June 2000

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