Description

SUBSTITUTED BETA-CARBOLINES WITH I_KB-KINASE INHIBITING ACTIVITY

The invention relates to novel substituted beta-carbolines, a process for their preparation and use thereof as pharmaceuticals.

United States Patent 4,631,149 discloses beta-carbolines useful as antiviral, antibacterial and antitumor agents. United States Patent 5,604,236 discloses beta-carboline derivatives containing an acidic group, useful as thromboxane syntheses inhibitors. DE 198 07 993 A1 discloses beta-carboline-derivatives useful for the treatment of TNF-α dependent diseases.

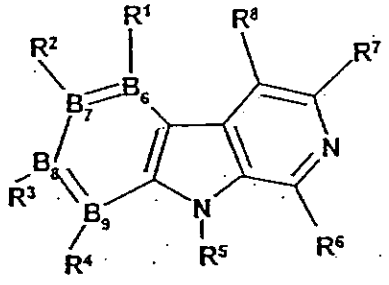
NFkB is a heterodimeric transcription factor which can activate a large number of genes which code, inter alia, for proinflammatory cytokines such as IL-1, IL-2, TNFα or IL-6. NFkB is present in the cytosol of cells, building a complex with its naturally occurring inhibitor IkB. The stimulation of cells, for example by cytokines, leads to the phosphorylation and subsequent proteolytic degradation of IkB. This proteolytic degradation leads to the activation of NFkB, which subsequently migrates into the nucleus of the cell and there activates a large number of proinflammatory genes.

In disorders such as rheumatoid arthritis (in the case of inflammation), osteoarthritis, asthma, cardiac infarct, Alzheimer's disease or atherosclerosis, NFkB is activated beyond the normal extent. Inhibition of NFkB is also of benefit in cancer therapy, since it is employed there for the reinforcement of the cytostatic therapy. It was possible to show that pharmaceuticals such as glucocorticoids, salicylates or gold salts, which are employed in rheumatic therapy, intervene in an inhibitory manner at various points in the NFkB-activating signal chain or interfere directly with the transcription of the genes. The first step in the signal cascade mentioned is the degradation of IkB. This phosphorylation is regulated by the specific IkB kinase. To date, no inhibitors are known which specifically inhibit IkB kinase.

In the attempt to obtain active compounds for the treatment of rheumatoid arthritis (in the case of inflammation), osteoarthritis, asthma, cardiac infarct, Alzheimer's disease, carcinomatous disorders (potentiation of cytotoxic

therapies) or atherosclerosis, it has now been found that the benzimidazoles according to the invention are strong and very specific inhibitors of IkB kinase.

In a first aspect of the present invention there is provided a compound of the formula I



(I)

and/or a stereoisomeric form of the compounds of the formula I and/or a physiologically tolerable salt of the compounds of the formula I,

where B_6, B_7, B_8 and B_9 are independently selected from the group consisting of carbon atom and nitrogen atom, where B_6, B_7, B_8 and B_9 together are no more than two nitrogen atoms at the same time; wherein

in case a)

the substituents R^1, R^2 and R^3 independently of one another are

1.1. hydrogen atom,

1.2. halogen,

1.3. -CN,

1.4. -COOH,

1.5. $-NO_2$,

1.6. $-NH_2$,

1.7. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted independently of one another by

1.7.1 phenyl, which is unsubstituted or mono- to penta-substituted by halogen or $-O-(C_1-C_4)$-alkyl,

1.7.2 halogen,

1.7.3 $-NH_2$,

1.7.4 -OH,

1.7.5 $-COOR^{16}$, wherein R^{16} is hydogen atom or $-(C_1-C_{10})$-alkyl,

1.7.6 $-NO_2$,

1.7.7 $-S(O)_y-R^{14}$, wherein y is zero, 1 or 2, R^{14} is $-(C_1-C_{10})$-alkyl, phenyl, which phenyl is unsubstituted or mono to penta-

substituted by substituents independently chosen from those defined under 1.7.1 to 1.7.11, amino or $-N(R^{13})_2$,

wherein R^{13} is independently of one another hydrogen atom, phenyl, $-(C_1-C_{10})$-alkyl, $-C(O)-(C_1-C_7)$-alkyl, -C(O)-phenyl, $-C(O)-NH-(C_1-C_7)$-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, $-C(O)-O-(C_1-C_7)$-alkyl, $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined in 1.7.7, and wherein the R^{13} alkyl or phenyl in each case are unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 , or

R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

1.7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted independently of one another as defined under 1.7.1 to 1.7.11 above,

1.7.9 a radicale selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

1.7.10 $-(C_3-C_7)$-cycloalkyl or

1.7.11 =O,

1.8. $-N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above,

1.9. $-NH-C(O)-R^{15}$, wherein R^{15} is

1.9.1 a radicale selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

wherein said radical is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, $-CF_3$, by benzyl or by $-(C_1-C_{10})$-alkyl, wherein the $-(C_1-C_{10})$ alkyl is mono to tri- substituted by substituents

independently chosen from those as defined under 1.7.1 to 1.7.11 above,

1.9.2 -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above or by -O-(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted independently chosen from those as defined under 1.7.1 to 1.7.11 above,

1.9.3 -(C_3-C_7)-cycloalkyl,

1.9.4 -$N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above, or

1.9.5 phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, by -O-(C_1-C_{10})-alkyl, -CN, by -CF_3 by –(C_1-C_{10})-alkyl, wherein alkyl is mono to tri- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, or by two substituents of said phenyl which form a dioxolan ring,

1.10. -$S(O)_y$-R^{14} , wherein R^{14} and y are as defined in 1.7.7 above,

1.11. -C(O)-R^{12}, wherein R^{12} is phenyl or -(C_1-C_7)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

1.12. -C(O)-O-R^{12}, wherein R^{12} is as defined in 11. above,

1.13. -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

1.14. -O-(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl,

1.15. -O-(C_0-C_4)-alkyl-(C_3-C_7)-cycloalkyl,

1.16. -(C_1-C_4)-alkyl-$N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above

1.17. -CF_3 or

1.18. -CF_2-CF_3,

R^4 is 1. -(C_1-C_{10})-alkyl, wherein alkyl is mono- to penta- substituted by substituents independently chose from those as defined under 1.7.1 to 1.7.11 above,

2. $-CF_3$,

3. $-CF_2-CF_3$,

4. -CN,

5. $-S(O)y-R^{14}$, wherein R^{14} and y are as defined in 1.7.7 above,

6. $-NH_2$,

7. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is mono- to penta- substituted independently of one another by

7.1 phenyl, which is unsubstituted or mono- to penta- substituted by substituents independently chosen from halogen or $-O-(C_1-C_4)$-alkyl,

7.2 halogen,

7.3 $-NH_2$,

7.4 -OH,

7.5 $-COOR^{16}$, wherein R^{16} is hydogen atom or $-(C_1-C_{10})$-alkyl,

7.6 $-NO_2$,

7.7 $-S(O)_y-R^{14}$, wherein y is zero, 1 or 2, R^{14} is $-(C_1-C_{10})$-alkyl, phenyl, which phenyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, amino or,

wherein R^{13} is independently of one another chosen from hydrogen atom, phenyl, $-(C_1-C_{10})$-alkyl, $-C(O)-(C_1-C_7)$-alkyl, -C(O)-phenyl, $-C(O)-NH-(C_1-C_7)$-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, $-C(O)-O-(C_1-C_7)$-alkyl, $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined in 7.7 above,
and wherein R^{13} alkyl or phenyl groups in each case are unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, or

R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

7.9 a radical selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan,

morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, thiophene, 2-isoxazoline, isothiazolidine, 2-isothiazoline, or thiomorpholine,

7.10 -(C_3-C_7)-cycloalkyl or

7.11 =O,

8. -$N(R^{17})_2$, wherein R^{17} is independently of one another chosen from those hydrogen atom, phenyl, -(C_1-C_{10})-alkyl, -C(O)-phenyl, -C(O)-NH-(C_1-C_7)- alkyl,

-C(O)-(C_1-C_{10})-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C_1-C_7)-alkyl, -$S(O)_y$-R^{14}, wherein R^{14} and y are as defined as in 7.7 above,

and wherein alkyl or phenyl in each case are unsubstituted or mono- to penta- substituted independently of one another as defined under 1.7.1 to 1.7.11 above, or

R^{17} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms.

R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

9. -NH-C(O)-R^{15}, wherein R^{15} is

9.1 a radical selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

wherein said radical is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, -CF_3, benzyl or by -(C_1-C_{10})-alkyl, wherein alkyl is mono to tri- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

9.2 -(C_1-C_{10})-alkyl, wherein alkyl is mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above or by -O-(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

9.3 -(C_3-C_7)-cycloalkyl,

9.4 -$N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above

provided that

-$N(R^{13})_2$ is not -NH_2, or

9.5 phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, by –O-(C_1-C_{10})-alkyl, by –CN, by -CF_3, by -(C_1-C_{10})-alkyl, wherein alkyl is mono to tri- substituted independently of one another as defined under 1.7.1 to 1.7.11 above or two substituents of the phenyl radical form a dioxolan ring ,

10. -C(O)-R^{12}, wherein R^{12} is phenyl or -(C_1-C_7)-alkyl, wherein alkyl or phenyl are mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

11. -C(O)-O-R^{12}, wherein R^{12} is as defined in 10. above,

12. -O-(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl,

13. -O-(C_0-C_4)-alkyl-(C_3-C_7)-cycloalkyl or

14. -(C_1-C_4)-alkyl-$N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above,

R^5 is 1. a hydrogen atom,

2. -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.4 above,

3. -C(O)-R^9, wherein R^9 is

-NH_2, -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 7.1 to 7.4, or –$N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above, or

4. -S(O)$_2$-R^9, wherein R^9 is as defined in 3. above, or

R^4 and R^5 together with the atom to which they are bonded form a heterocycle, or

R^3 and R^5 together with the atom to which they are bonded form a heterocycle containing an additional oxygen atom in the ring and

R^6, R^7 and R^8 independently of one another are hydrogen atom or methyl, or

in case b)

the substituents of R^1, R^2 and R^4 independently ~~of one another~~chosen from those as defined under 1.1 to 1.18 in case a) above,

R^3 is 1. $-CF_3$,

2. $-CF_2-CF_3$,

3. -CN,

4. -COOH,

5. $-NO_2$,

6. $-NH_2$,

7. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is mono- to penta substituted by substituents independently chosen from

7.1 phenyl, which is unsubstituted or mono- to penta-substituted by substituents independently chosen from halogen or $-O(C_1-C_4)$-alkyl,

7.2 halogen,

7.3 $-NH_2$,

7.4 -OH,

7.5 $-COOR^{16}$, wherein R^{16} is hydogen atom or $-(C_1-C_{10})$-alkyl,

7.6 $-NO_2$,

7.7 $-S(O)_y-R^{14}$, wherein y is zero, 1 or 2, R^{14} is $-(C_1-C_{10})$-alkyl, phenyl, which phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, amino or , wherein R^{13} is independently of one another chosen from hydrogen atom, phenyl, $-(C_1-C_{10})$-alkyl, $-C(O)-(C_1-C_7)$-alkyl, -C(O)-phenyl, $-C(O)-NH-(C_1-C_7)$-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, $-C(O)-O-(C_1-C_7)$-alkyl, $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined in 7.7 above, and wherein the R^{13} alkyl or phenyl groups in each case are unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, or

R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as define under 1.7.1 to 1.7.11 above,

7.9 a radicale selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

7.10 -(C_3-C_7)-cycloalkyl or

7.11 =O,

8. $-N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above,

9. $-NH-C(O)-R^{15}$, wherein R^{15} is

9.1 a radicale selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine, wherein said radical is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, $-CF_3$, benzyl or by -(C_1-C_{10})-alkyl, wherein alkyl is mono to tri- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

9.2 -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above or by -O-(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

9.3 -(C_3-C_7)-cycloalkyl,

9.4 $-N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above, or

9.5 phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, by -O-(C_1-C_{10})-alkyl, by –CN, by -CF_3, by -(C_1-C_{10})-alkyl, wherein alkyl is mono to tri- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above or two substituents of the phenyl radical form a dioxolan ring ,

10. -S(O)y-R^{14} , wherein R^{14} and y are as defined in 1.7.7 above,

11. -C(O)-R^{12}, wherein R^{12} is phenyl or -(C_1-C_7)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

12. -C(O)-O-R^{12}, wherein R^{12} is phenyl or -(C_1-C_7)-alkyl, wherein phenyl or alkyl are unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

13. -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

14. -O-(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl,

15. -O-(C_0-C_4)-alkyl-(C_3-C_7)-cycloalkyl or

16. -(C_1-C_4)-alkyl-N(R^{13})$_2$, wherein R^{13} is as defined in 1.7.7 above,

R^5 is as defined as R^5 in case a) above,

R^6, R^7 and R^8 independently of one another are chosen from hydrogen atom or methyl, with the following provisos for case b):

when R^6 is methyl, R^3 is not an O-(C_1-C_{10})- alkyl monosubstituted by either an unsubstituted phenyl or a –COO-(C_1-C_{10})-alkyl; and

when R^3 is an O-(C_1-C_{10})-alkyl monosubstituted by a –(C_3-C_7)-cycloalkyl, R^6 is hydrogen.

One embodiment may be compounds of formula I, wherein in case a)

B_6, B_7, B_8, and B_9 are each a carbon atom,

R^1, R^2 and R^3 independently of one another are hydrogen atom, halogen, cyano, nitro, amino, -O-(C_1-C_7)-alkyl, wherein alkyl is unsubstituted or substituted by phenyl,

-CF_2-CF_3, -CF_3, -N(R^{18})$_2$,

wherein R^{18} is independently of one another hydrogen atom, -(C_1-C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1-C_4)-alkyl or -C(O)-(C_1-C_7)-alkyl, wherein alkyl, pyridyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another as defined under

1.7.1 to 1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

$S(O)_y$-R^{14},

wherein y is zero, 1 or 2, and R^{14} is -(C_1-C_{10})-alkyl, phenyl, which is unsubstituted or mono- to penta- substituted as defined for substituents under 1.7.1 to 1.7.11, amino or -$N(R^{18})_2$, wherein R^{18} is as defined above, wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 1.7.1 to 1.7.11, or

-C(O)-O-R^{12}, wherein R^{12} is as defined above,

R^4 is cyano, amino, -O-(C_1-C_7)-alkyl, wherein alkyl is substituted by phenyl; -CF_2-CF_3, -CF_3, -$N(R^{18})_2$,

wherein R^{18} is independently of one another hydrogen atom, -(C_1-C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1-C_4)-alkyl or -C(O)-(C_1-C_7)-alkyl, wherein alkyl, pyridyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another as defined under 1.7.1 to 1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

$S(O)_y$-R^{14},

wherein y is zero, 1 or 2, and R^{14} is -(C_1-C_{10})-alkyl, phenyl, which is unsubstituted or mono- to penta- substituted as defined for substituents under 1.7.1 to 1.7.11, amino or -$N(R^{18})_2$, wherein R^{18} is as defined above, wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 1.7.1 to 1.7.11, or

-C(O)-O-R^{12}, wherein R^{12} is as defined above,

R^6, R^7 and R^8 independently of one another are hydrogen atom or methyl, and R^5 is as defined in the above aspect,

or in case b)

the substituents R^1, R^2 and R^4 independently of one another are hydrogen atom, halogen, cyano, nitro, amino, -O-(C_1-C_7)-alkyl, wherein

alkyl is unsubstituted or substituted by phenyl,

$-CF_2-CF_3$, $-CF_3$, $-N(R^{18})_2$,

wherein R^{18} is independently of one another hydrogen atom, $-(C_1-C_7)$-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, $-C(O)-O-(C_1-C_4)$-alkyl or $-C(O)-(C_1-C_7)$-alkyl, wherein alkyl, pyridyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another as defined under 1.7.1 to 1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

$S(O)_y-R^{14}$,

wherein y is zero, 1 or 2, and R^{14} is $-(C_1-C_{10})$-alkyl, phenyl, which is unsubstituted or mono- to penta- substituted as defined for substituents under 1.7.1 to 1.7.11, amino or $-N(R^{18})_2$, wherein R^{18} is as defined above,

wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 1.7.1 to 1.7.11,

or

$-C(O)-O-R^{12}$, wherein R^{12} is as defined above,

R^3 is cyano, nitro, amino, $-O-(C_1-C_7)$-alkyl, wherein alkyl is substituted by phenyl;

$-CF_2-CF_3$, $-CF_3$, $-N(R^{18})_2$,

wherein R^{18} is independently of one another hydrogen atom, $-(C_1-C_7)$-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, $-C(O)-O-(C_1-C_4)$-alkyl or $-C(O)-(C_1-C_7)$-alkyl, wherein alkyl, pyridyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another as defined under 1.7.1 to 1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

$S(O)_y-R^{14}$,

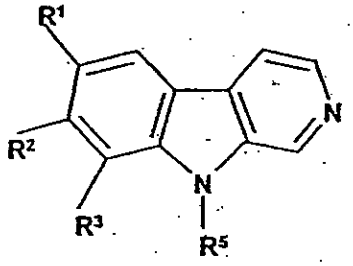
wherein y is zero, 1 or 2, and R^{14} is $-(C_1-C_{10})$-alkyl, phenyl, which is unsubstituted or mono- to penta- substituted as defined for substituents under 1.7.1 to 1.7.11, amino or $-N(R^{18})_2$, wherein R^{18} is as defined above,

wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 1.7.1 to 1.7.11, or

$-C(O)-O-R^{12}$, wherein R^{12} is as defined above,

R^6, R^7 and R^8 independently of one another are hydrogen atom or methyl, and R^5 is as defined above.

In a second aspect of the invention, there is provided a compound of formula (II)



(II)

and/or a stereoisomeric form of the compound of the formula II and/or a physiologically tolerable salt of the compound of the formula II, wherein;

R^1 and R^2 are independently of one another chosen from hydrogen atom, halogen, cyano amino, $-O-(C_1-C_4)$-alkyl, nitro, $-CF_3$, $-CF_2-CF_3$, $-S(O)_y-R^{14}$, wherein y is 1 or 2,

R^{14} is amino, $-(C_1-C_7)$-alkyl or phenyl, which is unsubstituted or mono- to tri-substituted as defined for substituents under 1.7.1 to 1.7.11 above,

$-N(R^{18})_2$, wherein R^{18} is independently of one another hydrogen atom $-(C_1-C_7)$-alkyl-C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-(C_1-C_4)-alkyl, -C(O)-O-phenyl, -C(O)-O-(C_1-C_4)-alkyl or $-(C_1-C_{10})$-alkyl, wherein pyridyl, alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another as defined under 1.7.1 to 1.7.11 as defined in the first aspect, or

R^{18} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

R^3 is cyano, amino, $-O-(C_1-C_4)$-alkyl, nitro, $-CF_3$, $-CF_2-CF_3$, $-S(O)_y-R^{14}$, wherein y is 1 or 2, R^{14} is amino, $-(C_1-C_7)$-alkyl or phenyl, which is unsubstituted or mono- to tri- substituted as defined for substituents under 1.7.1 to 1.7.11 as defined in the first aspect,

$-N(R^{18})_2$, wherein R^{18} is independently of one another hydrogen atom, $-(C_1-C_7)$-alkyl-C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-O-phenyl, -C(O)-NH-(C_1-C_4)-alkyl, -C(O)-O-(C_1-C_4)-alkyl or $-(C_1-C_{10})$-alkyl, wherein pyridyl, alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another as defined under 1.7.1 to 1.7.11 as defined in the first aspect,

R^{18} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms, and

R^5 is hydrogen atom, $-(C_1-C_{10})$-alkyl,

wherein alkyl is unsubstituted or mono- to tri- substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.4 as defined in the first aspect,

$-C(O)-R^9$ or $-S(O)_2-R^9$, wherein

R^9 is $-(C_1-C_{10})$-alkyl, $-O-(C_1-C_{10})$-alkyl,

wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 1.7.1 to 1.7.4 as defined in the first aspect, or

phenyl, which is unsubstituted or mono- to tri- substituted as defined under 1.7.1 to 1.7.11, or $-N(R^{18})_2$, wherein R^{18} is independently of one another chosen from hydrogen atom, $-(C_1-C_7)$-alkyl, -C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl, C(O)-pyridyl, -C(O)-NH-(C_1-C_4)-alkyl, -C(O)-O-phenyl, -C(O)-O-(C_1-C_4)-alkyl or $-(C_1-C_{10})$-alkyl, wherein pyridyl, alkyl or phenyl are unsubstituted or mono- to tri-substituted independently of one another as defined under 1.7.1 in to 1.7.11 as defined in the first aspect, or R^{18} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms.

In a third aspect of the present invention, there is provided a compound of formula (II), wherein

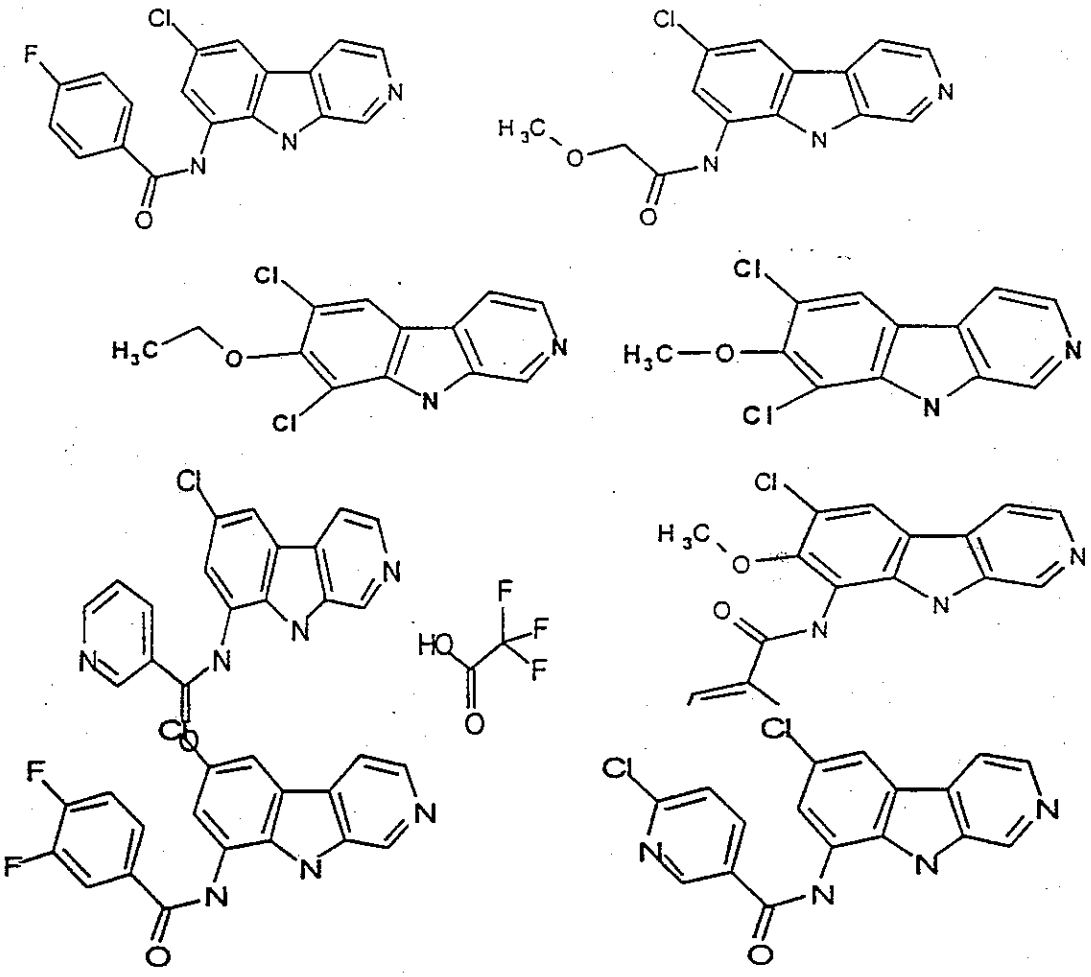
R^1 is bromo, $-CF_3$ or chloro,

R^2 is hydrogen atom or O-(C_1-C_2)-alkyl,

R^3 is $-N(R^{18})_2$, wherein R^{18} is independently of one another chosen from hydrogen atom, -N-C(O)-pyridyl, -C(O)-phenyl, $-(C_1-C_7)$-alkyl, -C(O)-(C_1-C_4)-alkyl or -C(O)-O-(C_1-C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri- substituted by substituents independently chosen from by halogen or –O-(C_1-C_2)-alkyl, and

R^5 is hydrogen atom, methyl or $-S(O)_2-CH_3$.

Specific preferred compounds and all pharmaceutically acceptable salts thereof which are illustrative of the compounds of the invention include the following;



Especially preferred are the compounds N-(6-Chloro-9H-β-carbolin-8-yl)-nicotinamide, as well as the bismesylate salt, bistrifluoracetate salt and bishydrochloride salt of N-(6-Chloro-9H-β-carbolin-8-yl)-nicotinamide, N-(6-Chloro-9H-β-carbolin-8-yl)-3,4-difluoro-benzamide, as well as the hydrochloride salt of N-(6-Chloro-9H-β-carbolin-8-yl)-3,4-difluoro-benzamide, N-(6-Chloro-7-methoxy-9H-β-carbolin-8-yl)-nicotinamide as well as the bistrifluoracetate salt and bishydrochloride salt of N-(6-Chloro-7-methoxy-9H-β-carbolin-8-yl)-nicotinamide and 6-Chloro-N-(6-chloro-9H-β-carbolin-8-yl)-nicotinamide.

The term "alkyl" by itself or as part on another substituent, unless otherwise stated means a straight or branched chain hydrocarbon radical having 1 to 10 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary-butyl, pentyl, hexyl, heptyl, nonyl, octyl, decanyl or cycloalkyl having 3 to 7 carbon atoms such as cylopropyl, cyclobutyl, cyclohexyl or cycloheptyl .

The term "alkoxy" by itself or as part on another substituent, unless otherwise stated means -O-alkyl or -O-substituted alkyl.

The term "heterocycle having 5 to 7 ring atoms" represents a radical of a monocyclic saturated system having 5 to 7 ring members, which contains 1, 2 or 3 heteroatoms as ring members. Examples of heteroatoms are N, O and S. Examples of the term heterocycle having 5 to 7 ring atoms are pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine.

The term "aryl" by itself or as part on another substituent, unless otherwise stated refers to an organic radical derived from an aromatic molecule by removal of one atom; such as phenyl, pyridyl, thiazoly, morpholinyl and naphthyl.

The term "substituted alkyl" means an alkyl radical substituted at one or more positions by one or more radicals of the group halogen, nitro, sulfo, amino, substituted amino, carboxyl, alkoxy, -O-aryl, -O-substituted aryl, and hydroxyl.

The term "substituted aryl" means an aryl radical substituted at one or more positions by one or more radicals of the group halogen, alkyl, substituted alkyl, nitro, sulfo, amino, alkoxy, aryl, substituted aryl, or hydroxyl groups, preferred is an aryl radical substituted at 1 to 3 positions by 1 to 3 groups.

The term "substituted amino" refers to $-N(R^{13})_2$ wherein R^{13} is independently of one another hydrogen atom, sulfo, alkyl, aryl, -C(O)-alkyl, C(O)-NH-aryl, -C(O)-O-aryl, -C(O)-O-alkyl, or C(O)-O-aryl, wherein each alkyl or aryl may be independently substituted.

The term "sulfo" refers to $-S(O)y-R^{14}$, wherein R^{14} is an alkyl, aryl, substituted aryl, substituted alkyl, amino, or substituted amino and y is zero, one or two.

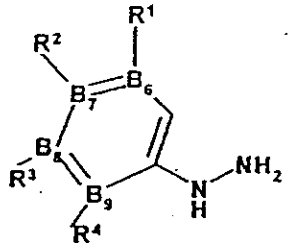
The term "halogen" is understood as meaning fluorine, chlorine, bromine or iodine.

The term "$-(C_1-C_4)$-alkyl" is understood as meaning hydrocarbon radicals whose carbon chain is linear or branched and contains 1 to 4 carbon atoms.

In a fourth aspect of the present invention there is provided a process for the preparation of the compounds of the formula I as defined in the first aspect,

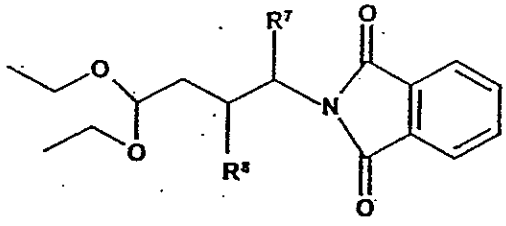
which comprises

a) reacting a compound of formula III



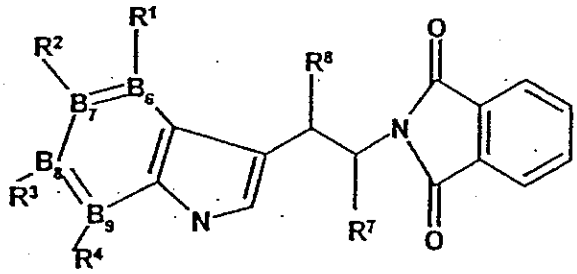
(III)

in which R^1, R^2, R^3, R^4, B_6, B_7, B_8 and B_9 are each as defined in formula I, with a compound of the formula IV,



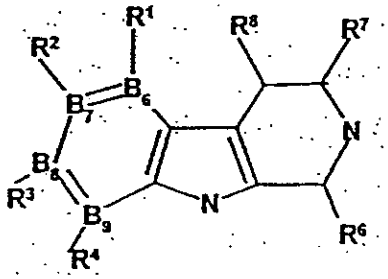
(IV)

in the presence of a acid, converting into a compound of the formula V,



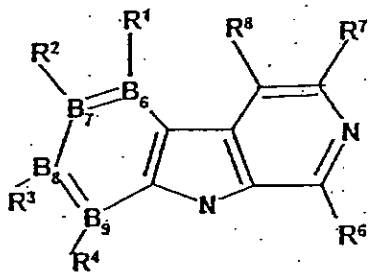
(V)

and is reacted with hydrazine hydrate and later with formaldehyde (R^6 is H) or R^6CHO to give a compound of formula VI



(VI)

and then oxidizing formula VI to give a compound of the formula VII,



(VII)

where R^1 to R^4, R^6 to R^8 and B_6 to B_9 are as defined in formula I, a compound of formula (I)

Another embodiment may relate to a compound of the formula VII reacted with a compound of the formula VII

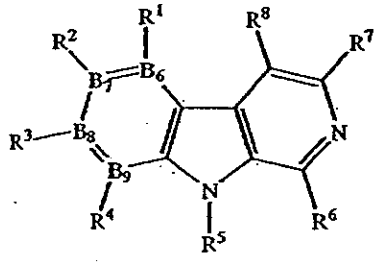
$$Y\text{-}R^5 \quad \text{(VIII)}$$

where Y may be halogen or –OH and R^5 is as defined in formula I, to give a compound of the formula I, or

resolving a compound of the formula I, which on account of its chemical structure may occur in enantiomeric forms, prepared by process a) or b) into the pure enantiomers by salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as amino acids, separation of the diastereomers thus obtained, and removal of the chiral auxiliary groups, or

isolating the compound of the formula I prepared by process a), b) or c) either in free form or, in the case of the presence of acidic or basic groups, converting it into physiologically tolerable salts.

In a fifth aspect of the present invention, there is provided a method for the production of a pharmaceutical for the prophylaxis or therapy of disorders in whose course an increased activity of I_k B kinase is involved, comprising bringing into a suitable administration form at least one compound chosen from a compound of formula I,



(I)

a stereoisomeric form of a compound of formula I or a physiologically tolerable salt of a compound of formula I, together with a pharmaceutically suitable and physiologically tolerable excipient,

wherein B_6, B_7, B_8 and B_9 are ring atoms independently chosen from carbon atoms and nitrogen atoms and wherein B_6, B_7, B_8 and B_9 together are no more than two nitrogen atoms at the same time;

where the substituents R^1, R^2, R^3, R^4 and R^8 may be independently chosen from

1. hydrogen atom,

2. halogen,

3. -OH,

4. -CN,

5. sulfo,

6. $-NO_2$,

7. $-NH_2$,

8. alkoxy,

9. substituted amino,

10. -NH-C(O)-R^{15}, wherein R^{15} is a heterocycle having 5 to 7 ring atoms, an alkyl, an aryl, a substituted aryl or a substituted alkyl,

11. -COOH,

12. -O-R^{10}, wherein R^{10} is alkyl, substituted alkyl or aryl,

13. -C(O)-R^{12}, wherein R^{12} is alkyl, substituted alkyl or aryl,

14. -C(O)-O-R^{12}, wherein R^{12} is alkyl, substituted alkyl or aryl,

15. aryl,

16. -O-aryl,

17. substituted aryl,

18. -O-substituted aryl,

19. alkyl,

20. substituted alkyl,

21. $-CF_3$ or

22. $-CF_2-CF_3$,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,

R^5 is

1. hydrogen atom,

2. alkyl,

3. alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,

4. -C(O)-R^9 or

5. $-S(O)_2-R^9$, in which

R^9 is

a) alkyl,

b) alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,

c) aryl,

d) aryl radical, substituted at one or more positions by one or more of the radicals, halogen, amino, or hydroxyl,

e) $-NH_2$,

f) alkoxy or

g) substituted amino, and

R^6 and R^7 may be independently chosen from

1. hydrogen atom,

2. halogen,

3. -OH,

4. methyl,

5. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to tri-substituted by substituents independently chosen from

5.1 aryl,

5.2 halogen,

5.3 $-NO_2$,

5.4 sulfo,

5.5 -COOH,

5.6 -NH_2,

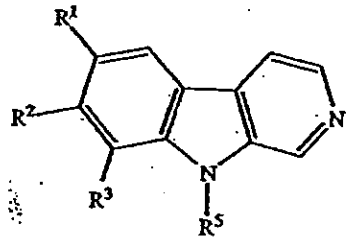
5.7 -O-(C_1 -C_4)-alkyl or

5.8 -OH, or

6. -$N(R^{13})_2$, wherein R^{13} is independently of one another chosen from hydrogen atom, aryl, -C(O)-(C_1 -C_4)-alkyl or substituted aryl or alkyl,

wherein said -C(O)-(C_1 -C_4)-alkyl is unsubstituted or mono- or tri-substituted independently of one another as defined under 5.1 to 5.8, or
R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms.

In a sixth aspect of the present invention, there is provided a method for the production of a compound for the prophylaxis or therapy of disorders in whose course an increased activity of I_k B kinase is involved, comprising bringing into a suitable administration form at least one compound chosen from a compound of formula II,



(II)

wherein R^1, R^2 and R^3 are independently chosen from hydrogen atom, halogen, cyano, amino, -O-(C_1 -C_4)-alkyl, nitro, -CF_3 or

wherein R^{13} is independently of one another chosen from hydrogen atom, -(C_1 -C_4)-alkyl, -C(O)-(C_1 -C_7)-alkyl, -C(O)-pyridyl, -C(O)-phenyl or -C(O)-O-(C_1 -C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri-substituted by substituents independently chosen from halogen or -O-(C_1 -C_4)-alkyl, and

R^5 is hydrogen atom, -C(O)-OH_3 -, methyl, -$S(O)_2$ -CH_3, -C(O)-morpholinyl, -CH_2 -CH_2 -OH or -CH_2 -C(O)-NH_2,
provided that no more than two of R^1, R^2, R^3 and R^5 are a hydrogen atom.

In a seventh aspect of the present invention, there is provided a composition which comprises an efficacious amount of at least one compound chosen from the compounds of formula I as defined in the first aspect, a physiologically tolerable salt of the compounds of the formula I or an optionally stereoisomeric form of the compounds of the formula I, together with at least one pharmaceutically suitable and physiologically tolerable excipient, additive, active compound or auxiliary.

The preparation of physiologically tolerable salts of compounds of the formula I capable of salt formation, including their stereoisomeric forms, may be carried out in a manner known per se. With basic reagents such as hydroxides, carbonates, hydrogencarbonates, alkoxides and also ammonia or organic bases, for example trimethyl- or triethylamine, ethanolamine or triethanolamine or alternatively basic amino acids, for example lysine, ornithine or arginine, the carboxylic acids form stable alkali metal, alkaline earth metal or optionally substituted ammonium salts. If the compounds of the formula I contain basic groups, stable acid addition salts can also be prepared using strong acids. For

this, both inorganic and organic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, benzenesulfonic, p-toluenesulfonic, 4-bromobenzenesulfonic, cyclohexylamidosulfonic, trifluoromethylsulfonic, acetic, oxalic, tartaric, succinic or trifluoroacetic acid are suitable.

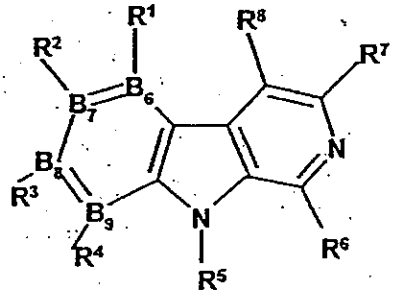
Yet another embodiment may relate to pharmaceuticals which may comprise of an efficacious amount of at least one compound of the formula I and/or of a physiologically tolerable salt of the compounds of the formula I and/or an optionally stereoisomeric form of the compounds of the formula I, together with a pharmaceutically suitable and physiologically tolerable excipient, additive and/or other active compounds and auxiliaries.

On account of the pharmacological properties, the compounds may be suitable for the prophylaxis and therapy of all those disorders in whose course an increased activity of IkB kinase is involved. These may include, for example, asthma, rheumatoid arthritis (in the case of inflammation), osteoarthritis, Alzheimer's disease, carcinomatous disorders (potentiation of cytotoxic therapies), cardiac infarct or atherosclerosis.

The pharmaceuticals may generally be administered orally or parentally or by rectal, inhale or transdermal administration.

In an eighth aspect of the present invention, there is provided the use of a therapeutically effective amount of at least one compound chosen from a compound of formula I as defined in the first aspect, a stereoisomeric form of a compound of the formula I, or a physiologically tolerable salt of a compound of the formula I in the manufacture of a medicament for treating a patient experiencing at least one disorder involving an increased activity of $I_{\kappa}B$ kinase.

Still another embodiment may relate to the use of the compounds of the formula I



(I)

and/or a stereoisomeric form of the compounds of the formula I and/or a physiologically tolerable salt of the compounds of the formula I,

for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of I_KB kinase is involved.

wherein B_6, B_7, B_8 and B_9 are independently selected from the group consisting of carbon atom and nitrogen atom and wherein B_6, B_7, B_8 and B_9 together are no more than two nitrogen atoms at the same time;

where the substituents R^1, R^2, R^3, R^4 and R^8 independently of one another are

1. hydrogen atom,
2. halogen,
3. -OH,
4. -CN,
5. sulfo,
6. $-NO_2$,
7. $-NH_2$,
8. alkoxy,
9. substituted amino,
10. -NH-C(O)-R^{15}, wherein R^{15} is a heterocycle having 5 to 7 ring atoms, alkyl, aryl, substituted aryl or substituted alkyl,
11. -COOH,
12. -O-R^{10}, wherein R^{10} is alkyl, substituted alkyl or aryl,
13. -C(O)-R^{12}, wherein R^{12} is alkyl, substituted alkyl or aryl,
14. -C(O)-O-R^{12}, wherein R^{12} is as defined above,
15. aryl,
16. -O-aryl,
17. substituted aryl,
18. –O-substituted aryl,
19. alkyl,
20. substituted alkyl,
21. $-CF_3$ or
22. $-CF_2-CF_3$,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,

R^5 is

1. hydrogen atom,
2. alkyl,
3. alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,
4. -C(O)-R^9 or
5. $-S(O)_2-R^9$, in which

R^9 is a) alkyl,

b) alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,

c) aryl,

d) aryl radical, substituted at one or more positions by one or more of the radicals, halogen, amino, or hydroxyl,

e) $-NH_2$,

f) alkoxy or

g) substituted amino, and

R^6 and R^7 independently of one another are

1. hydrogen atom,
2. halogen,
3. -OH,
4. methyl,
5. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to tri-substituted independently of one another by
   - 5.1 aryl,
   - 5.2 halogen,
   - 5.3 $-NO_2$,
   - 5.4 sulfo,
   - 5.5 -COOH,
   - 5.6 $-NH_2$,
   - 5.7 $-O-(C_1-C_4)$-alkyl or
   - 5.8 -OH, or
6. $N(R^{13})_2$, wherein R^{13} is independently of one another hydrogen atom, aryl, $-C(O)-(C_1-C_4)$-alkyl or substituted aryl or alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 5.1 to 5.8, or R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms.

Preferred is the use of the compounds of formula I, wherein

B_6, B_7, B_8, and B_9 are each a carbon atom,

R^1, R^2, R^3, R^4 and R^8 independently of one another are

1. hydrogen atom,
2. halogen,
3. -CN,
4. -COOH,
5. $-NO_2$,
6. $-NH_2$,
7. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted independently of one another by
   - 7.1 phenyl, which is unsubstituted or mono- to penta-substituted by halogen or $-O-(C_1-C_4)$-alkyl,
   - 7.2 halogen,
   - 7.3 $-NH_2$,
   - 7.4 -OH,
   - 7.5 $-COOR^{16}$, wherein R^{16} is hydogen atom or $-(C_1-C_{10})$-alkyl,
   - 7.6 $-NO_2$,
   - 7.7 $-S(O)_y-R^{14}$, wherein y is zero, 1 or 2, R^{14} is $-(C_1-C_{10})$-alkyl, phenyl, which is unsubstituted or mono- to penta-substituted as defined for substituents under 7.1 to 7.11, amino or $-N(R^{13})_2$,
     wherein R^{13} is independently of one another hydrogen atom, phenyl, $-(C_1-C_{10})$-alkyl, $-C(O)-(C_1-C_7)$-alkyl, -C(O)-phenyl, $-C(O)-NH-(C_1-C_7)$-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, $-C(O)-O-(C_1-C_7)$-alkyl, $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined above,
     and wherein alkyl or phenyl in each case are unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.11 above, or
     R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.11 above,

7.9 a radicale selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

7.10 -(C_3-C_7)-cycloalkyl or

7.11 =O,

8. -N(R^{13})$_2$, wherein R^{13} is as defined in 7.7 above,

9. -NH-C(O)-R^{15}, wherein R^{15} is

9.1 a radicale selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine, wherein said radical is unsubstituted or mono- to penta-substituted independently of one another as defined under 7.1 to 7.11 above, -CF_3, benzyl or by -(C_1-C_{10})-alkyl, wherein alkyl is mono to tri- substituted independently of one another as defined under 7.1 to 7.11 above,

9.2 -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.11 above or by -O-(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted independently of one another as defined under 7.1 to 7.11 above,

9.3 -(C_3-C_7)-cycloalkyl,

9.4 -N(R^{13})$_2$, wherein R^{13} is as defined in 7.7 above, or

9.5 phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.11 above, by -O-(C_1-C_{10})-alkyl, by

–CN, by -CF_3, by -(C_1-C_{10})-alkyl, wherein alkyl is mono to tri- substituted independently of one another as defined under 7.1 to 7.11 above or two substituents of the phenyl radical form a dioxolan ring ,

10. -S(O)y-R^{14} , wherein R^{14} and y are as defined in 7.7 above,

11. -C(O)-R^{12}, wherein R^{12} is phenyl or -(C_1-C_7)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.11 above,

12. -C(O)-O-R^{12}, wherein R^{12} is as defined in 11. above,

13. -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted independently of one another as defined under 7.1 to 7.11 above,

14. -O-(C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl,

15. -O-(C_0-C_4)-alkyl-(C_3-C_7)-cycloalkyl,

16. -(C_1-C_4)-alkyl-N(R^{13})$_2$, wherein R^{13} is as defined in 7.7 above

17. -CF_3 or

18. -CF_2-CF_3,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,

R^5 is 1. hydrogen atom,

2. -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted independently of one another as defined under 7.1 to 7.4 above,

3. -C(O)-R^9, wherein R^9 is

-NH_2, -(C_1-C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted independently of one another as defined under 7.1 to 7.4, or -N(R^{13})$_2$, wherein R^{13} is as defined in 7.7 above, or

4. -S(O)$_2$-R^9, wherein R^9 is as defined in 3 above,

or R^4 and R^5 together with the atom to which they are bonded form a heterocycle,

or R^3 and R^{15} together with the atom to which they are bonded form a heterocycle containing an additional oxygen atom in the ring and

R^6 and R^7 independently of one another are hydrogen atom or methyl.

More preferred is the use of compounds of formula I for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of I_KB kinase is involved, wherein

B_6, B_7, B_8, and B_9 are each a carbon atom,

R^1, R^2, R^3 and R^4 independently of one another are hydrogen atom, halogen, cyano, nitro, amino, -O-(C_1-C_7)-alkyl, phenyl, -O-phenyl, -CF_2-CF_3, -CF_3, N(R^{13})$_2$,

wherein R^{13} is independently of one another hydrogen atom, -(C_1-C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-(C_1-C_7)-alkyl or -(C_1-C_{10})-alkyl, wherein alkyl, pyridyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.11, or R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

S(O)$_y$-R^{14},

wherein y is zero, 1 or 2, and R^{14} is -(C_1-C_{10})-alkyl, phenyl, which is unsubstituted or mono- to penta- substituted as defined for substituents under 7.1 to 7.11, amino or -N(R^{13})$_2$, wherein R^{13} is as defined above,

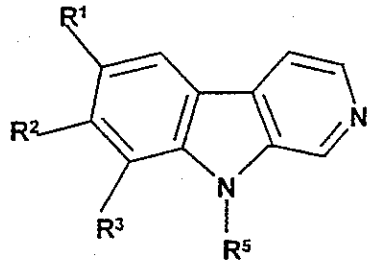
wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.11, or

-C(O)-O-R^{12}, wherein R^{12} is as defined above,

R^6, R^7 and R^8 independently of one another are hydrogen atom, methyl, amino, -N(R^{13})$_2$, wherein R^{13} is as defined above,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom, and R^5 is as defined above.

Even more preferred is the use of compounds of formula II



(II)

and/or a stereoisomeric form of the compounds of the formula II and/or a physiologically tolerable salt of the compounds of the formula II,
for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of I_kB kinase is involved, wherein;

R^1, R^2 and R^3 are independently from one another hydrogen atom, halogen, cyano, amino, -O-(C_1-C_4)-alkyl, nitro, $-CF_3$, $-CF_2-CF_3$, $-S(O)_y-R^{14}$, wherein y is 1 or 2,

R^{14} is amino, -(C_1-C_7)-alkyl, phenyl, which is unsubstituted or mono- to tri- substituted as defined for substituents under 7.1 to 7.9, or $-N(R^{13})_2$, wherein

R^{13} is independently of one another -C(O)-pyridyl, hydrogen atom, -(C_1-C_7)-alkyl-C(O)-(C_1-C_7)-alkyl, -C(O)-phenyl, -(C_1-C_{10})-alkyl, -C(O)-NH-(C_1-C_4)-alkyl, -C(O)-O-phenyl or -C(O)-O-(C_1-C_4)-alkyl, wherein
pyridyl, alkyl or phenyl are unsubstituted or mono- to tri-substituted independently of one another as defined under 7.1 to 7.11, or
R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

provided that at least one of R^1, R^2 and R^3 is not a hydrogen atom, and

R^5 is hydrogen atom, -(C_1-C_{10})-alkyl,
wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.4,
$-C(O)-R^9$ or $-S(O)_2-R^9$, wherein
R^9 is -(C_1-C_{10})-alkyl, -O-(C_1-C_{10})-alkyl,
wherein alkyl is unsubstituted or mono- to tri- substituted independently of one another as defined under 7.1 to 7.4,

phenyl, which is unsubstituted or mono- to tri- substituted as defined under 7.1 to 7.11, or -$N(R^{13})_2$,
wherein R^{13} is as defined above.

Most preferred is the use of the compounds of formula II for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of I_KB kinase is involved, wherein
R^1, R^2 and R^3 are independently from one another hydrogen atom, halogen, cyano, amino, -O-(C_1-C_4)-alkyl, nitro, -CF_3 or $N(R^{13})_2$,
wherein R^{13} is independently of one another hydrogen atom, -(C_1-C_7)-alkyl, -C(O)-(C_1-C_7)-alkyl, -C(O)-pyridyl, -C(O)-phenyl or -C(O)-O-(C_1-C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri-substituted independently of one another by halogen or -O-(C_1-C_4)-alkyl, and
R^5 is hydrogen atom, –C(O)-CH_3, methyl, –$S(O)_2$-CH_3, -C(O)-morpholinyl, -CH_2-CH_2-OH or -CH_2-C(O)-NH_2,
provided that no more than two of R^1, R^2, R^3 and R^5 are a hydrogen atom.
Most highly preferred is the use of the compounds of formula II for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of IkB kinase is involved, wherein
R^1 is bromo, -CF_3 or chloro, R^2 is hydrogen atom or O-(C_1-C_2)-alkyl,
R^3 is hydrogen atom, bromo, chloro or -$N(R^{13})_2$,
wherein R^{13} is independently of one another hydrogen atom, -C(O)-phenyl, -(C_1-C_7)-alkyl, -C(O)-(C_1-C_4)-alkyl or -C(O)-O-(C_1-C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri- substituted independently of one another by halogen or -O-(C_1-C_2)-alkyl, and
R^5 is hydrogen atom, -C(O)-CH_3, methyl or -$S(O)_2$-CH_3,
provided that no more than two of R^1, R^2, R^3 and R^5 are a hydrogen atom.

Specific preferred is the use of the compounds of formula II for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of IkB kinase is involved, wherein
R^1 is chloro, R^2 and R^3 are each hydrogen atom, and R^5 is -C(O)-CH_3, or
R^1 is bromo, R^2 and R^3 are each hydrogen atom, and R^5 is -C(O)-CH_3, or

R^1 is chloro, R^3 is -N-C(O)-CH_2-O-CH_3 and R^2 and R^5 are each hydrogen atom, or R^1 is chloro, R^3 is -N-C(O)-para-fluoro-phenyl and R^2 and R^5 are each hydrogen atom, or R^1 and R^3 are each chloro, R^2 is -C(O)-CH_3 and R^5 is hydrogen atom, or

R^1 and R^3 are each chloro, R^5 is hydrogen atom and R^2 is -C(O)-CH_2-CH_3.

On account of the pharmacological properties, the compounds may be suitable for the prophylaxis and therapy of all those disorders in whose course an increased activity of IkB kinase is involved. Disorders in whose course an increased activity of IkB kinase is involved include, for example the treatment of joint inflammation, including arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis and osteoarthritis. Additionally, the compounds are useful in the treatment of acute synovitis, tuberculosis, atherosclerosis, muscle degeneration, cachexia, Reiter's syndrome, endotoxaemia, sepsis, septic shock, endotoxic shock, gram negative sepsis, gout, toxic shock syndrome, chronic pulmonary inflammatory diseases including asthma and adult respiratory distress syndrome, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, carcinoses, leukemia, sarcomas, lymph node tumors, skin carcinoses, lymphoma, apoptosis, graft versus host reaction, allograft rejection and leprosy. Furthermore, the compounds are useful in the treatment of: infections such as viral infections, for example HIV, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, parasitic infections, for example malaria such as cerebral malaria, and yeast and fungal infections, for example fungal meningitis; fever and myalgias due to infection; AIDS; AIDS related complex (ARC); cachexia secondary to infection or malignancy; cachexia secondary to acquired immune deficiency syndrome (AIDS) or to cancer; keloid and scar tissue formation; pyresis; diabetes; and inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. The compounds may also be useful in the treatment of diseases of or injury to the brain in which over-expression of TNFα has been implicated such as multiple sclerosis, and head trauma. The compounds may also be also useful in the treatment of psoriasis, Alzheimer's disease, carcinomatous disorders (potentiation of cytotoxic therapies), cardiac infarct, chronic

obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS).

Still another embodiment may relate to a process for the production of a pharmaceutical, which comprises bringing at least one compound of the formula I into a suitable administration form using a pharmaceutically suitable and physiologically tolerable excipient and, if appropriate, further suitable active compounds, additives or auxiliaries.

Suitable solid or pharmaceutical preparation forms are, for example, granules, powders, coated tablets, tablets, (micro)capsules, suppositories, syrups, juices, suspensions, emulsions, drops or injectable solutions, and preparations having protracted release of active compound, in whose preparation customary auxiliaries, such as excipients, disintegrants, binders, coating agents, swelling agents, glidants or lubricants, flavourings, sweeteners and solubilizers are used. Frequently used auxiliaries which may be mentioned are magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, lactoprotein, gelatin, starch, cellulose and its derivatives, animal and vegetable oils such as cod liver oil, sunflower, groundnut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and mono- or polyhydric alcohols such as glycerol.

The pharmaceutical preparations are preferably produced and administered in dose units, each unit containing as active constituent a certain dose of the compound of the formula I according to the invention. In the case of solid dose units such as tablets, capsules, coated tablets or suppositories, this dose can be up to approximately 1000 mg, preferably from approximately 50 mg to 300 mg and in the case of injection solutions in ampoule form up to approximately 300 mg, preferably from approximately 10 mg to 100 mg.

For the treatment of an adult patient weighing approximately 70 kg, depending on the efficacy of the compound according to formula I, daily doses of approximately 20 mg to 1000 mg of active compound, preferably from approximately 100 mg to 500 mg, are indicated. Under certain circumstances, however, even higher or lower daily doses may be appropriate. The administration of the daily dose can be carried out both by single administration in the form of an individual dose unit or else of a number of

smaller dose units and by multiple administration of subdivided doses at specific intervals.
As a rule, final products are determined by mass-spectroscopic methods (FAB-, ESI-MS). Temperatures are given in degrees Celsius, RT means room temperature (22 °C to 26 °C). Abbreviations used are either explained or correspond to the customary conventions.

Example 1, 7-bromo-β-carboline

A solution of norharmane (600 mg, 3.57 mmol) in tetrahydrofuran (THF; 50 ml) was treated with bromine (0.40 ml, 7.80 mmol) at RT while stirring. After stirring for 18 h at RT, the reaction was concentrated under reduced pressure and the resulting residue was sonicated in 10% aqueous Na_2CO_3 (100 ml). The product was filtered and washed with water to give 905 mg of crude product. The crude product was crystallized from xylenes to provide in two crops 580 mg of 7-bromo-β-carboline.

Example 2, 1-acetyl-7-bromo- β -carboline

A solution of Example 1 (25 mg, 0.1 mmol) in dimetylformamide (DMF; 2 ml) was treated with 0.10 ml of 1M aqueous NaOH (0.10 mmol). After stirring at RT for 30 minutes, acetic anhydride (0.010 ml, 0.095 mmol) was added and reaction stirred 18 h at RT. The reaction was partitioned in EtOAc and 5% citric acid and the organic layer washed with water, dried (brine; MgSO4), and concentrated to give 23 mg of crude product. The crude product was chromatographed (7:3 hexane-acetone) on silica gel to give 10 mg of 1-acetyl-7-bromo-β-carboline.

Example 3, 7-fluoro- β -carboline

A mixture of 5-fluorotryptamine hydrochloride (200 mg, 0.93 mmol) in EtOAc (4 ml) and water (2 ml) was treated with glyoxalic acid hydrate (90 mg, 0.98 mmol). The pH of the aqueous layer was adjusted to 5 (with 5% $NaHCO_3$ then 1M HCl) and the mixture stirred vigorously at RT for 18 h. The mixture was then diluted with hexane (4 ml) and the product filtered and washed with water and (1:1) hexane-ethyl acetate.

The crude product from above in 6N HCl (3 ml) was treated 3 times with concentrated HCl (0.050 ml) every 15 min while refluxing. After refluxing for a total of 45 min, the reaction was concentrated to give a residue. The above residue was slurred in xylenes with triethylamine (0.40 ml, 2.9 mmol) and 10% Pd/C (200 mg). The mixture was refluxed for 1 h and then filtered hot through celite. The filtrate was concentrated and the residue chromatographed (5:95 methanol-chloroform) on silica gel to give 25 mg of 7-fluoro-β-carboline.

Example 4, 7-isopropyl- β –carboline hydrochloride

A mixture of 4-isopropylphenylhydrazine hydrochloride (660 mg, 3.55 mmol) and 4-phthalimidobutanal diethyl acetal (1.15 g, 3.95 mmol) in Ethanol (EtOH; 30 ml) was heated at 60 °C to 65 °C for 1 h with water (0.050 ml). The mixture was then treated with concentrated HCl (0.50 ml) and refluxed for 14 h. After concentrating the reaction, the residue was partioned in methylene chloride and saturated aqueous $NaHCO_3$. The aqueous solution was extracted with methylene chloride (3 times) and the combined organic solutions were dried ($MgSO_4$) and concentrated to give after chromatography (4:1 hexane-ethyl acetate) on silica gel 146 mg of product.

The above product was treated with hydrazine hydrate (1 ml) in EtOH (4 ml) and water (1 ml) and stirred at RT overnight. After concentrating the reaction to an aqueous mixture, the product was extracted with methylene chloride (3 times). The combined organic solution was dried ($MgSO_4$) and concentrated. The residue was redissolved in methylene chloride and treated with 1M HCl in ether. The precipitate was collected and washed with ether and hexane and dried to provide 102 mg of 6-isopropyltryptamine hydrochloride salt. This tryptamine obtained above was transformed into 7-Isopropyl- β -carboline according to the procedure used in example 3. The hydrochloride salt was obtained by treating a solution of 7-Isopropyl-β-carboline in methylene chloride with 1M HCl in ether and concentrating. The residue was triturated with (1:1) methylene chloride-hexane to give 15 mg of 7-isopropyl-β-carboline hydrochloride.

Example 5, 7-cyano- β -carboline

A dark solution of example 1 (190 mg, 0.62 mmol) and CuCN (110 mg, 1.22 mmol) in N-methyl 2-pyrrolidone (1.5 ml) was heated in a sealed reaction tube at 200 °C for 48 h. The mixture was filtered and the filtrate was diluted with water (50 ml). A brown solid that precipitated was filtered, washed with water, saturated aqueous $NaHCO_3$, and then methanol. This material was dissolved in DMSO and diluted with aqueous HCl. This homogeneous dark solution was decolorized with charcoal, filtered and concentrated to give a concentrated solution in DMSO. This DMSO solution was partitioned in (1:1) EtOAc-THF and saturated aqueous $NaHCO_3$. The organic solution was dried ($MgSO_4$) and concentrate to give 8 mg of 7-cyano- β -carboline.

Example 6, 7-nitro-β- carboline hydrochloride

Norharmane (100 mg, 0.60 mmol) was treated with concentrated nitric acid (1.0 ml) and the resulting suspension was heated to 65 °C until the mixture became homogeneous (3 to 4 min). The solution was carefully poured into water (20 ml), and the precipitate filtered and washed with water then methanol. The solid was suspended in saturated aqueous $NaHCO_3$ and stirred vigorously before filtering and washing with water. The solid was taken up in hot methanol and this solution treated with 1M HCl in ether (5 ml). The solution was concentrated and the residue triturated with ether to provide 58 mg of a 7:3 mixture of 7-nitro- β -carboline hydrochloride and 9-nitro- β - carboline hydrochloride.

Example 7, 7-carboxy- β - carboline trifluoroacetat

Crude product from example 5 (from 210 mg of example 1, 0.85 mmol) was treated with 6 M HCl in a sealed reaction tube for 15 h at 110 °C. The reaction was evaporated to give a concentrated solution of product in N-methyl 2-pyrrolidone. A portion (half) was purified by preparative HPLC using a C_{18} - packed column and eluting with a gradient (5:95 to 50:50) of water-acetonitril (with 0.1% trifluoracetic acid). The pure fractions were combined and lyophilized to provide 11 mg of 7-carboxy- β -carboline trifluoroacetate.

Example 8, 7,9-dibromo- β - carboline hydrochloride

A solution of the product from example 1 (140 mg, 0.58 mmol) in THF (2 ml) was treated with bromine (0.50 ml). After 10 min at RT, the reaction was diluted with chloroform and the product was filtered. The filtered product was taken up in methanol and treated with 1M HCl in ether and concentrated. The residue was triturated with ether to provide 160 mg of 7,9-dibromo- β - carboline hydrochloride.

Example 9, 7,9-dichloro- β - carboline

To a suspension of norharmane (84 mg, 0.50 mmol) in water (3 ml) at RT was added 1M aqueous HCl (1.1 ml, 1.1 mmol). To this homogenous solution was added N-chlorosuccinimide (747 mg, 5.58 mmol) portionwise and the resulting solution was stirred at 60 °C to 70 °C for 3h. The reaction was partitioned in EtOAc and saturated aqueous $NaHCO_3$ and the organic layer was dried (brine; $MgSO_4$) and then concentrated. The residue was chromatographed (2:3 THF-hexane) on silica gel to give 24 mg of 7,9-dichloro- β -carboline after triturating with (1:1) methylene chloride-hexane, then with hexane.

Example 10, 1-acetyl-7-bromo- β - carboline

To a suspension of NaH (95%, 14 mg, 0.60 mmol) in DMF (1.0 ml) at 5 °C to 10 °C was added the product from example 1 (74 mg, 0.30 mmol). The resulting mixture was stirred for 15 min at 5 °C to 10 °C before adding methanesulfonylchloride (0.030 ml, 0.38 mmol). The reaction was allowed to warm to RT and stirred for 2 h before partitioning into saturated aqueous $NaHCO_3$ and EtOAc. After stirring the mixture overnight, the organic layer was washed with water, dried (brine; $MgSO_4$), and concentrated. The residue was purified by chromatography (1:1 hexane-ethyl acetate) on silica gel to give 23 mg of 1-acetyl-7-bromo- β –carboline.

Example 11, 7-bromo-1-methyl- β - carboline

To a suspension of NaH (95%, 6 mg, 0.24 mmol) in DMF (2.0 ml) at 5 °C to 10 °C was added the product from example 1 (50 mg, 0.20 mmol). The resulting mixture was stirred for 15 min at 5 °C to 10 °C before adding methyl-iodide (0.030 ml, 0.20 mmol) at 0 °C to 5 °C. The reaction stirred for 12 h at

0 °C to 5 °C before partitioning into water and EtOAc. The organic layer was washed with water, dried (brine; $MgSO_4$), and concentrated. The residue was purified by chromatography (gradient, 1:3 hexane-ethyl acetate to ethyl acetate) on silica gel to give 10 mg of 7-bromo-1-metyhl- β –carboline.

Example 12, 7-chloro- β - carboline

To a solution of norharmane (2.0 g, 11.9 mmol) in water (89 ml) and 1M aqueous HCl (29.8 ml, 29.8 mmol) was added N-chlorosuccinimide (3.17 g, 23.8 mmol) portionwise. The resulting solution was stirred at RT for 6 h, and then at 0 °C to 5 °C for 12 h. The reaction was diluted with water (100 ml) and basified cautiously with solid K_2CO_3 (4.3 g). After stirring at RT for 1 h, the product was collected and washed with water. The crude product was refluxed in chloroform for 1 h and filtered after cooling to 15 °C to provide 2.05 g of 7-chloro- β –carboline.

Example 13, 1-acetyl-7-chloro- β - carboline

To a solution of the product from example 12 (104 mg, 0.50 mmol) in DMF (2.0 ml) at 3 °C to 5 °C was added NaH (95%, 15 mg, 0.625 mmol). The resulting mixture was stirred for 15 min before adding acetic anhydride (0.083 ml, 0.875 mmol). The reaction was allowed to warm to RT and stirred for 3 h before pouring into with water (25 ml). The slurry was stirred for 12 h, and the product collected to give after chromatography (1:3 hexane-ethyl acetate) on silica gel 82 mg of 1-acetyl-7-chloro- β –carboline.

Example 14, 7-chloro-9-nitro- β - carboline

A mixture of the product from example 12 (500 mg, 2.48 mmol) in concentrated nitric acid (20 ml) was stirred at RT for 22 h. The reaction mixture was carefully poured into cold (3 °C to 5 °C) water (50 ml), and after stirring for 2 h the precipitate was collected. The solid was suspended in saturated aqueous $NaHCO_3$ (50 ml) and stirred at RT for 12 h. The product was filtered and washed with water to provide 550 mg of 7-chloro-9-nitro- β -carboline

Example 15, 9-amino-7-chloro- β - carboline

To a suspension of the product from example 14 (548 mg, 2.22 mmol) in EtOH (14 ml) at 65 °C to 70 °C was added tin chloride dihydrate (2.5 g, 11.1 mmol). Thereafter, 6M aqueous HCl (14 ml) was added dropwise. The mixture was stirred at 70 °C to 80 °C for 3.5 h and then partitioned slowly into saturated aqueous $NaHCO_3$ (150 ml) and EtOAc (100 ml). The aqueous phase was extracted (2 times) and the combined organic solutions dried (brine; $NaSO_4$) and concentrated to give 484 mg of 9-amino-7-chloro- β -carboline.

Example 16, 9-amino-7-chloro- β - carboline trifuoroacetate

To a solution of the product from example 15 (35 mg, 0.16 mmol) in pyridine (0.80 ml) was added acetic anhydride (0.018 ml, 0.19 mmol). The resulting mixture was allowed to stand at RT for 12 h before pouring into water (15 ml). The crude product was filtered and purified by preparative HPLC using a C_{18} - packed column and eluting with a gradient (5:95 to 60:40) of water-acetonitril (with 0.1% trifluoracetic acid). The pure fractions were combined and lyophilized to provide 18 mg of 9-amino-7-chloro- β -carboline trifluoroacetate.

Example 17, 7-bromo-1-carbonyl-(4'-morpholine)- β - carboline

A solution of the product from example 1 (125 mg, 0.51 mmol) in DMF (2 ml) was treated with 0.55 ml of 1M aqueous NaOH (0.55 mmol). After stirring at RT for 30 minutes, 4-morpholinecarbonyl chloride (0.060 ml, 0.51 mmol) was added and reaction stirred 18 h at RT. The reaction was partitioned in EtOAc and 5% citric acid and the organic layer washed with water, dried (brine; $MgSO_4$), and concentrated. The residue was chromatographed (7:3 hexane-acetone) on silica gel to give 105 mg of 7-bromo-1-carbonyl-(4`-morpholino)- β -carboline.

Example 18, 1-(2'-ethylacetate)-7-chloro- β - carboline

To a suspension of NaH (95%, 28 mg, 1.15 mmol) in DMF (1.0 ml) at 5 °C to 10 °C was added the product from example 12 (202 mg, 1.0 mmol) in DMF (3 ml). The resulting mixture was stirred for 30 min at 5 °C to 10 °C before adding ethyl bromoacetate (0.116 ml, 1.05 mmol). The reaction was allowed to be stirred for 1.5 h and then the reaction was diluted with saturated aqueous $NaHCO_3$ (30 ml). The product was extracted with EtOAc (30 ml; 2 times each

15ml), and the combined organic extracts were dried (brine; $MgSO_4$) then concentrated. The residue was purified by chromatography (1:3 hexane-ethyl acetate) on silica gel to give 270 mg of 1-(2`ethylacetate)-7-chloro-β-carboline.

Example 19, 1-(2'-ethanoyl)-7-chloro- β - carboline

To a solution of the product from example 18 (50 mg, 0.17 mmol) in THF (1.7 ml) at 5 °C to 10 °C was added 1M LAH in THF (0.17 ml, 0.17 mmol). The resulting mixture was stirred for 2 h at 5 °C to 10 °C before adding EtOAc (0.10 ml). The mixture was subsequently diluted with EtOAc (5 ml) and slowly treated with saturated aqueous NaHCO3 (5 ml). After diluting with water (10 ml) and brine (10 ml) the mixture was extracted with EtOAc. The organic solution was dried (brine; $MgSO_4$) then concentrated to give 42 mg of 1-(2`ethanol)-7-chloro- β -carboline.

Example 20, 1-(2'-acetyl)-7-chloro- β - carboline

To a solution of the product from example 18 (107 mg, 0.37 mmol) in MeOH (3.7 ml) at RT was added water (3.7 ml) followed by treatment with 1M aqueous NaOH (0.41 ml, 0.41 mmol). The resulting mixture was stirred for 2 h and the volatile removed under reduced pressure. The mixture was subsequently diluted with water (5 ml) and the pH adjusted to 5 to 6. The precipitate was filtered and washed with water to give 96 mg of 1-(2`-acetyl)-7-chloro- β -carboline.

Example 21, 8-methoxy- β - carboline

Prepared from 6-methoxytryptamine using the procedure as in example 3.

Example 22, see table 1 for structure

To a solution of the product from example 20 (59 mg, 0.23 mmol) in DMF (2.8 ml) at RT was added p-nitrophenol (40 mg, 0.29 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (48 mg, 0.25 mmol). The resulting mixture was stirred for 1.5 h at RT and then ammonium bicarbonate (55 mg, 0.69 mmol) was added. The reaction was stirred for 18 h at RT and then poured into water (20 ml). The aqueous mixture was basified to pH of about 10 with K_2CO_3. The precipitate was filtered and washed with water to give 47 mg of the title compound.

Example 23, 8-hydroxy-2-methyl- β - carboline

A solution of harmine (616 mg, 2.9 mmol) in dichloroethane (20 ml) was treated with 2.0 ml of 1M BBr_3 (4 mmol) in dichloroethane. The reaction was stirred at 60 °C for 48 h and then cooled to 0 °C before quenching with MeOH (5 ml). The reaction was concentrated and the residue triturated with methanol to give 413 mg of 8-hydroxy-2-methyl- β –carboline .

Example 24, 6,8-dibromo-7-methoxy- β - carboline

A solution of the product from example 30 (90 mg, 0.45 mmol) in acetic acid (8 ml) was treated with bromine (0.025 ml, 0.48 mmol). The reaction was stirred at RT for 18 h and then concentrated. The residue was partitioned in EtOAc and aqueous $NaHCO_3$. The organic layer was dried (brine; $MgSO_4$) and concentrated. The residue was purified by chromatography (5:4 hexane-acetone) on silica gel to give 3 mg of 6,8-dibromo-7-methoxy- β –carboline.

Example 25, see table 1 for structure

A solution of the product from example 23 (60 mg, 0.30 mmol) in DMF (3 ml) was treated with K_2CO_3 (100 mg) and t-butyl bromoacetate (0,040 ml, 0.27 mmol). After stirring at RT for 18 h, the reaction was partitioned in EtOAc and water. The organic layer was dried (brine; $MgSO_4$) and then concentrated. The residue was chromatographed (1:1 hexane-EtOAc) on silica gel to give 20 mg of the title compound.

Example 26, see table for structure

A solution of the product from example 23 (50 mg, 0.25 mmol) in DMF (3 ml) was treated with K_2CO_3 (100 mg) and benzyl bromide (0,030 ml, 0.25 mmol). After stirring at RT for 18 h, the reaction was partitioned in EtOAc and water. The organic layer was dried (brine; $MgSO_4$) and then concentrated. The residue was chromatographed (1:1 hexane-EtOAc) on silica gel to give 12 mg of the title compound.

Example 27, 7-ethoxy-2-methyl- β - carboline

A solution of the product from example 23 (60 mg, 0.30 mmol) in DMF (3 ml) was treated with K_2CO_3 (100 mg) and ethyl iodide (0,029 ml, 0.36 mmol). After stirring at RT for 18 h, the reaction was partitioned in EtOAc and water.

The organic layer was dried (brine; $MgSO_4$) and then concentrated. The residue was chromatographed (1:1 hexane-acetone) on silica gel to give 20 mg of 7-ethoxy-2-methyl- β –carboline.

Example 28, 7-bromo-2-methyl- β - carboline

Prepared from harmane using the same procedure as in example 1.

Example 29, see table 1 for structure

A solution of the product from example 23 (60 mg, 0.30 mmol) in DMF (3 ml) was treated with K_2CO_3 (100 mg) and acetic anhydride (0,034 ml, 0.36 mmol). After stirring at RT for 18 h, the reaction was partitioned in EtOAc and water. The organic layer was dried (brine; $MgSO_4$) and then concentrated. The residue was chromatographed (1:1 hexane-acetone) on silica gel to give 18 mg of the title compound.

Example 30, 7-methoxy- β - carboline

Prepared from 5-methoxytryptamine using the procedure in example 3.

Example 31, 8-fluoro- β - carboline

Prepared from 6-fluorotryptamine using the same procedure as in example 3.

Example 32, 7-bromo-2-methyl-8-methoxy- β - carboline

Prepared from harmine using the same procedure as in example 1.

Example 33, 7-hydroxy- β - carboline

Prepared from the product of example 30 using the procedure in example 23.

Example 34, 7-chloro-8-fluoro- β - carboline

Prepared from the product of example 31 using the procedure in example 12.

Example 35, 7-methoxy-1-methyl- β - carboline

Prepared from the product of example 30 using the procedure in example 11.

Example 36 . 9-chloro-8-methoxy-β-carboline trifluoroacetate and Example 37 7,9-dichloro-8- methoxy-β-carboline trifluoroacetate

A solution of the product from example 21 (195 mg, 1.0 mmol) in 1M HCl (3 ml) was treated with N-chlorosuccinimide (270 mg, 2 mmol) portionwise and the resulting solution was stirred at 60 °C to 70 °C for 3h. The reaction was

evaporated and the crude product purified by preparative HPLC using a C_{18}-packed column and eluting with a gradient (5:95 to 50:50) of water-acetonitril (with 0.1% trifluoroacetic acid). The pure fractions of each product were combined and lyophilized to provide 78 mg of 9-chloro-8-methoxy-β-carboline trifluoroacetate and 51 mg of 7,9-dichloro-8- methoxy-β-carboline trifluoroacetate.

Example 38 7,9-dichloro-8-hydroxy-β-carboline

A mixture of the product of example 37 (590 mg, 2.21 mmol) in methylene chloride (25 ml) at 35 °C was treated with a solution of BBr_3 in methylene chloride (1M, 6 ml, 6 mmol). After refluxing for 3h, the reaction was quenched with methanol (5 ml) and then concentrated. The residue was slurred in 60% $NaHCO_3$ solution, the product filtered and washed with water to give 500 mg of 7,9-dichloro-8-hydroxy-β-carboline.

Example 39 7,9-dichloro-8-ethoxy-β-carboline

A mixture of the product of example 38 (35 mg, 0.14 mmol), K_2CO_3 (100 mg), and ethyl iodide (0.014 ml, 0.17 mmol) in acetone (5 ml) was stirred in a closed reaction tube at RT for 3 days. After concentrating the reaction, the residue was partitioned in ethyl acetate and water. The organic layer was dried (MgSO4) and concentrated to give crude product. The crude product was chromatographed (5% methanol in chloroform) on silica gel to give 8 mg of 7,9-dichloro-8-ethoxy- β-carboline.

Example 40 7-chloro-8-fluoro-β-carboline trifluoroacetate

A solution of the product of example 31 (78 mg, 0.42 mmol) in 1M HCl (1 ml) was treated with N-chlorosuccinimide (115 mg, 0.9 mmol) portionwise and the resulting mixture was stirred at 60 °C to 70 °C for 3h. The reaction was evaporated and the crude product purified by preparative HPLC using a C_{18}-packed column and eluting with a gradient (5:95 to 50:50) of water-acetonitril (with 0.1% trifluoroacetic acid). The pure fractions with product were combined and lyophilized to provide 33 mg of the title compound.

Example 41 1-hydroxy-7-trifluoromethyl-β-carboline and Example 42 7-trifluoromethyl-β-carboline

A solution of 3-hydroxy-2-piperdone (96 mg, 0.83 mmol) in methylene chloride (5 ml) was treated with Dess Martin reagent (352 mg, 0.85 mmol) at RT and

the resulting mixture was stirred for 1h. After filtering the salts from the reaction, the ketone in solution was treated with 4-trifluoromethyl-phenyl-hydrazine (145 mg, 0.83 mmol). After 15 min, hexane (20 ml) was added and the hydrazone collected by filtration. This crude hydrazone was heated at 95 °C in formic acid (70%, 10 ml) for 1h. The reaction was evaporated and the residue was chromatographed (ethyl acetate) on silica gel to give 60 mg of dihydro 1-hydroxy-7-trifluoromethyl-β-carboline.

A portion of dihydro 1-hydroxy-7-trifluoromethyl-β-carboline (6 mg) in xylenes (1 ml) was treated with Pd/C (10%, 7 mg) and the mixture heated at 50 °C for one week. The reaction was concentrated after filtering it through celite, and the residue was chromatographed (1:1 hexane-ethyl acetate) on silica gel to give 1 mg of 1-hydroxy-7-trifluoromethyl-β-carboline.

A portion of dihydro 1-hydroxy-7-trifluoromethyl-β-carboline (25 mg) in THF (1 ml) was treated with a solution of lithium aluminum hydride in THF (1M, 0.5 ml). The reaction was stirred at 60 °C for 6h before quenching with water (5 ml) and extracting with ethyl acetate (3 times 10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated to provide tetrahydro 7-trifluoro-methyl-β-carboline. This material was taken up in xylenes (5 ml) and treated with Pd/C (10%, 15 mg). The mixture was stirred at 150 °C for 48h before filtering through celite and concentrating. The residue was chromatographed (ethyl acetate) on silica gel to give 5 mg of 7-tri-fluoromethyl-β-carboline.

Example 43 7-chloro-9-(methylamino)-β-carboline trifluoroacetate

A solution of the product of example 15 (50 mg, 0.23 mmol) in AcOH/methanol (1%, 3 ml) was treated with sodium cyanoborohydride (30 mg, 0.46 mmol) followed by formaldehyde (37%, 0.017 ml, 0.23 mmol). The reaction was stirred at RT for 36 h and then diluted with saturated $NaHCO_3$ (9 ml). After stirring for 15 min, the crude product was filtered and washed with water. The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 13 mg of the title compound.

Example 44 7-chloro-9-(dimethylamino)-β-carboline trifluoroacetate

A solution of the product of example 15 (50 mg, 0.23 mmol) in AcOH/methanol (1%, 3 ml) was treated with sodium cyanoborohydride (30 mg, 0.46 mmol) followed by formaldehyde (37%, 0.060 ml, 0.69 mmol). The reaction was stirred at RT for 36 h and then diluted with saturated $NaHCO_3$ (9 ml). After stirring for 15 min, the crude product was filtered and washed with water. The

crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 40 mg of the title compound.

Example 45 7-chloro-9-(methylsulfonylamino)-β-carboline trifluoroacetate
A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (0.5 ml) was treated with methanesulfonyl chloride (0.024 ml, 0.30 mmol) in two portions over 30h. The reaction was diluted with water (5 ml) and the crude product collected and washed with water (several times). The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 16 mg of the title compound.

Example 46 7-chloro-9-(propylonylamino)-β-carboline trifluoroacetate
A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with propionyl chloride (0.015 ml, 0.17 mmol). After stirring at RT for 4h, the reaction was diluted with water (9 ml) and saturated $NaHCO_3$ (1 ml). The crude product was collected and washed with water (several times). The crude product was purified by preparative HPLC using a C_{18}-packed column and eluting with a gradient (5:95 to 50:50) of water-acetonitril (with 0.1% trifluoroacetic acid). The pure fractions with product were combined and lyophilized to provide 21 mg of the title compound.

Example 47 7-chloro-9-(benzoylamino)-β-carboline trifluoroacetate
A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with benzoyl chloride (0.020 ml, 0.17 mmol). After stirring at RT for 4h, the reaction was diluted with water (9 ml) and saturated $NaHCO_3$ (1 ml). The crude product was collected and washed with water (several times). The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 12 mg of 7-chloro-9-(benzoylamino)-β-carboline trifluoroacetate.

Example 48 7-chloro-9-(Acetyl-methylamino)-β-carboline trifluoroacetate
A solution of the product of example 43 (19 mg, 0.082 mmol) in pyridine (0.40 ml) was treated with acetic anhydride (0.037 ml, 0.36 mmol) in two portions over 48h. The reaction was subsequently concentrated to dryness and the residue coevaporated with AcOH under reduced pressure. The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 9 mg of the title compound.

Example 49 7-chloro-9-(4-fluorobenzoylamino)-β-carboline trifluoroacetate
A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with 4-fluorobenzoyl chloride (0.018 ml, 0.17 mmol). After stirring at RT for 18h, the reaction was diluted with water (10 ml). The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 13 mg of the title compound.

Example 50
A cold (3 °C to 5 °C) solution of the product of example 15 (30 mg, 0.14 mmol) and pyridine (0.014 ml, 0.17 mmol) in THF (0.7 ml) was treated with phenyl chloroformate (0.018 ml, 0.145 mmol). After stirring at RT for 2h, the reaction was partitioned in ethyl acetate and buffer (pH 7.2). The organic layer was dried (brine, $Na2SO_4$) and concentrated to give 43 mg of phenyl carbamate. To a solution of phenyl carbamate (30 mg, 0.089 mmol) in DMSO (0.5 ml) was added 2-methoxyethylamine (0.010 ml, 0.10 mmol). After stirring at RT for 30 min, the crude reaction mixture was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 21 mg of the title compound.

Example 51 7-chloro-9-(methoxyacetylamino)-β-carboline trifluoroacetate
A solution of the product of example 15 (35 mg, 0.16 mmol) in pyridine (1.0 ml) was treated with methoxyacetyl chloride (0.016 ml, 0.18 mmol). After stirring at RT for 2h, the reaction was diluted with water (10 ml). The crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 32 mg of the title compound.

Example 52 7-chloro-9-(3-methoxybenzoxylamino)-β-carboline trifluoroacetate
A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with m-anisoyl chloride (0.027 ml, 0.19 mmol) in two portions over 6h. The reaction was subsequently diluted with water (10 ml) and the crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 33 mg of the title compound.

Example 53 7-chloro-9-(4-methoxybenzoxylamino)-β-carboline trifluoroacetate

A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with p-anisoyl chloride (37 mg, 0.22 mmol) in two portions over 24h. The reaction was subsequently diluted with water (10 ml) and the crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 24 mg of the title compound.

Example 54 7-chloro-9-(methylcarbamylamino)-β-carboline trifluoroacetate
A solution of the product of example 15 (30 mg, 0.14 mmol) in pyridine (1.0 ml) was treated with p-anisoyl chloride (0.017 ml, 0.21 mmol) in two portions over 4h. The reaction was subsequently diluted with water (10 ml) and the crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 35 mg of the title compound.

Example 55 7-chloro-9-(isovalerylamino)-β-carboline trifluoroacetate
A solution of the product of example 15 (35 mg, 0.16 mmol) in pyridine (1.0 ml) was treated with isovalerylchloride (0.033 ml, 0.28 mmol) in two portions over 24h. The reaction was subsequently diluted with water (10 ml) and the crude product was purified as described in example 46. The pure fractions with product were combined and lyophilized to provide 52 mg of the title compound.

Example 60 N-(6-Chloro-9H-β-carbolin-8-yl)-nicotinamide
To a solution of norharmane (2.0 g, 11.9 mmol) in water (89 ml) and 1M aqueous HCl (29.8 ml, 29.8 mmol) was added N-chlorosuccinimide (3.17 g, 23.8 mmol) portionwise. The resulting solution was stirred at RT for 6 h, and then at 0 °C to 5 °C for 12 h. The reaction was diluted with water (100 ml) and basified cautiously with solid K_2CO_3 (4.3 g). After stirring at RT for 1 h, the product was collected and washed with water. The crude product was refluxed in chloroform for 1 h and filtered after cooling to 15 °C to provide 2.05 g of 7-chloro-β-carboline.
A mixture 7-chloro-β-carboline (500 mg, 2.48 mmol) in concentrated nitric acid (20 ml) was stirred at RT for 22 h. The reaction mixture was carefully poured into cold (3 °C to 5 °C) water (50 ml), and after stirring for 2 h the precipitate was collected. The solid was suspended in saturated aqueous $NaHCO_3$ (50 ml) and stirred at RT for 12 h. The product was filtered and washed with water to provide 550 mg of 7-chloro-9-nitro- β -carboline.

To a suspension of 7-chloro-9-nitro- β -carboline (548 mg, 2.22 mmol) in EtOH (14 ml) at 65 °C to 70 °C was added tin chloride dihydrate (2.5 g, 11.1 mmol). Thereafter, 6M aqueous HCl (14 ml) was added dropwise. The mixture was stirred at 70 °C to 80 °C for 3.5 h and then partitioned slowly into saturated aqueous $NaHCO_3$ (150 ml) and EtOAc (100 ml). The aqueous phase was extracted (2 times) and the combined organic solutions dried (brine; $NaSO_4$) and concentrated to give 484 mg of 9-amino-7-chloro- β -carboline.

To a cold (3-5 °C) solution of 9-amino-7-chloro- β -carboline (2.75 g, 12.7 mmol) in pyridine (150 ml) was added nicotinyl chloride hydrochloride (2.82 g, 15.8 mmol). The reaction was allowed to warm to RT and stirred for 20 h before diluting the reaction with water (100 ml) and 1M NaOH (25 ml). After stirring for 1 h at RT, the mixture was poured into water (200 ml). The mixture was allowed to stand for 1 h and the product was filtered to provide 3.80 g of the title compound after washing with water and drying under reduced pressure at RT.

Example 68 N-(6-Chloro-7-methoxy-9H-β-carbolin-8-yl)-nicotinamide

A mixture of 6-methoxytryptamine (9.10 g, 47.8 mmol) in EtOAc (40 ml) and pH 4.5 NaOAc buffer (40 ml) was treated with glyoxalic acid hydrate (5.30, 57.6 mmol). The mixture was stirred vigorously for 2 days and then diluted with hexane (40 ml). The product was filtered and washed with water and (1:1) hexane-ethyl acetate. The crude product was crystallized from methanol after filtration of a hot methanol solution.

The crude product (11.5 g) from above in 6N HCl (100 ml) was treated 3 times with concentrated HCl (5.0 ml) every 15 min while refluxing. After refluxing for a total of 1 h, the reaction was concentrated to give a residue. This residue was slurried and sionicated with 10% Na_2CO_3 (300 ml) and filtered to give the free amine (7.20 g). The above amine was refluxed in xylenes (200 ml) and pyridine (100 ml) with 10% Pd/C (3 g) for 5 h. The hot reaction was filtered thru celite and the filtrate was concentrated to give 6.38 g of 8-methoxy-β-carboline.

To a mixture of 8-methoxy- β -carboline (1.0 g, 5 mmol) in THF (100 ml) was added N-chlorosuccinimide (0.70 g, 5.2 mmol). The reaction was stirred at RT for 4 h before concentrating and washing the residue with 1:1:1 mixture of 10%

Na_2CO_3, hexane, and EtOAc (400 ml). The resulting residue was triturated with xylenes to provide 677 mg of 7-chloro-8-methoxy- β -carboline.

A solution of 7-chloro-8-methoxy- β -carboline (677 mg, 2.9 mmol) in trifluoroacetic acid (10 ml) was treated with $NaNO_3$ (260 mg, 3.06 mmol). The reaction was stirred for 3 h at RT and then concentrated. The crude product was chromatographed on silica eluting with a 5 % to 10% methanol in chloroform gradient to provide 463 mg of 7-chloro-8-methoxy-9-nitro- β -carboline.

A solution of 7-chloro-8-methoxy-9-nitro-β-carboline (460 mg, 1.66 mmol) in EtOH (25 ml) was treated with $SnCl_2$-2 H_2O (450 mg, 2.00 mmol). The reaction was stirred for 5 h at 65 °C and then concentrated. The crude product was chromatographed on silica eluting with a 5 to 10% methanol in chloroform gradient to provide 410 mg of 7-chloro-8-methoxy-9-nitro-β-carboline.

A solution of 7-chloro-8-methoxy-9-nitro-β-carboline (21 mg, 0.085 mmol) in pyridine (1 ml) was treated with nicotinyl chloride hydrochloride (54 mg, 0.30 mmol) and 4-dimethylaminopyridine (5 mg). After stirring at 95 °C - 100 °C for 7 h the reaction was concentrated, the residue slurried with 10% Na_2CO_3, and then chromatographed on silica eluting with a 5 % to 10% methanol in chloroform gradient to provide 4.7 mg of the title compound.

Example 82 N-(6-Chloro-9H-β-carbolin-8-yl)-3,4-difluoro-benzamide

To a cold (3 °C - 5 °C) solution of 9-amino-7-chloro-β-carboline (2.50 g, 11.5 mmol, as prepared in example 60 above) in pyridine (130 ml) was added 3,4-diflourobenzoyl chloride (1.67 ml, 13.25 mmol). The reaction was allowed to warm to RT and stirred for 20 h before diluting the reaction with water (60 ml) and 1M NaOH (15 ml). After stirring for 3 h at RT, the pH of the mixture was adjusted to 8-9 with 1M HCl and then poured into water (250 ml). The mixture was allowed to stand for 30 min and the product was filtered to provide 3.95 g of the title compound after washing with water and drying under reduced pressure at 55 °C - 60 °C.

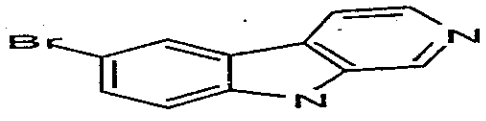
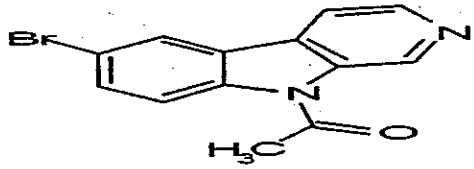
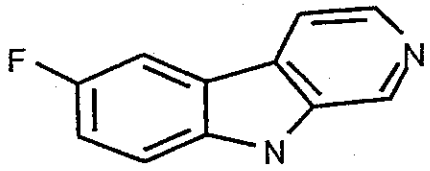
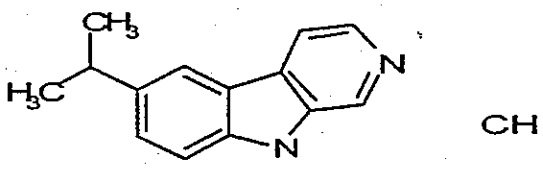
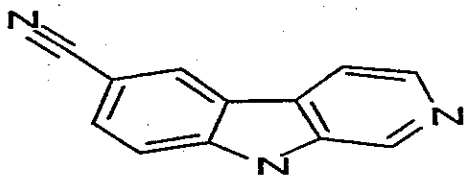
Example 83 6-Chloro-N-(6-chloro-9H-β-carbolin-8-yl)-nicotinamide

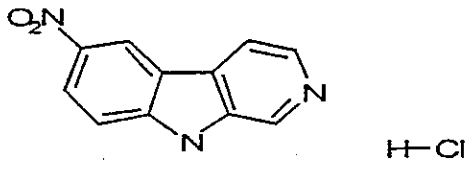
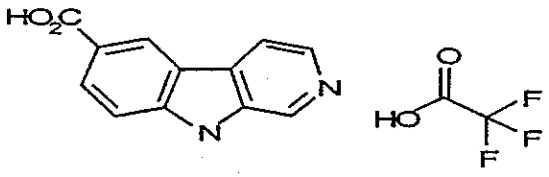
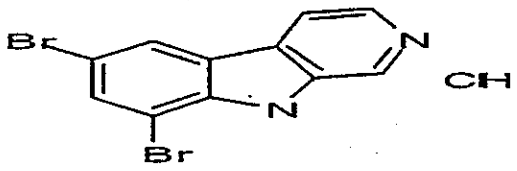
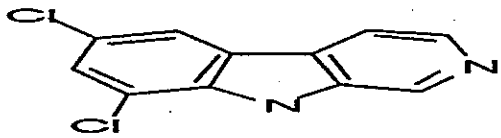
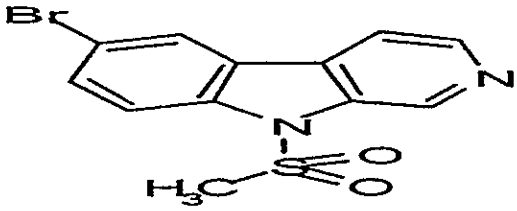
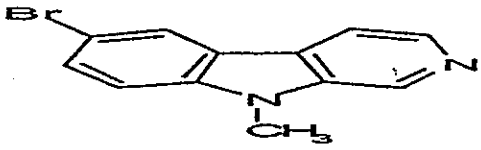
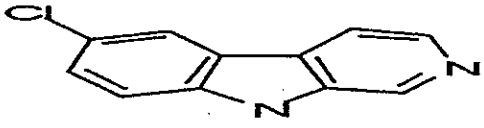
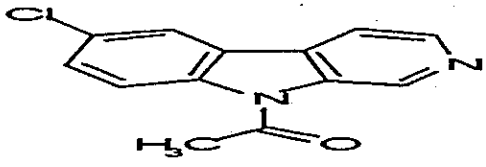
To a cold (3-5 °C) solution of 9-amino-7-chloro-β-carboline (1.40 g, 6.45 mmol, as prepared in example 60 above) in pyridine (72 ml) was added 6-chloro-

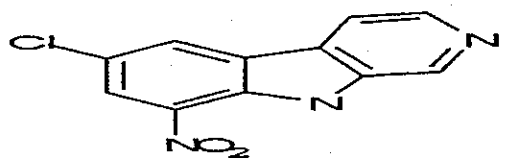
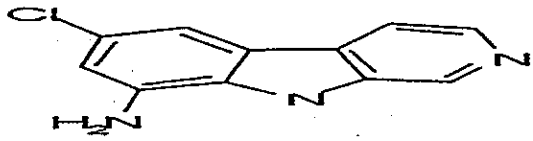
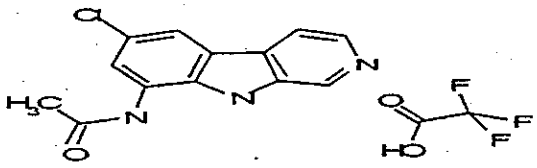
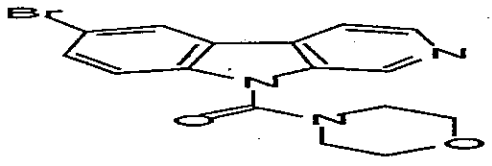
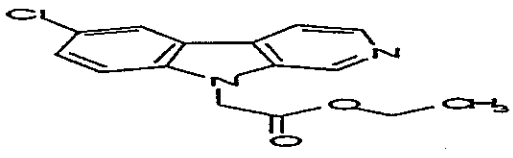
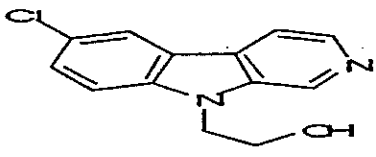
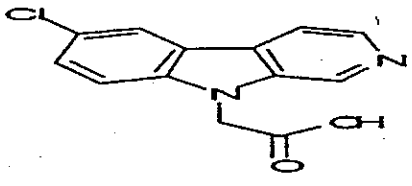
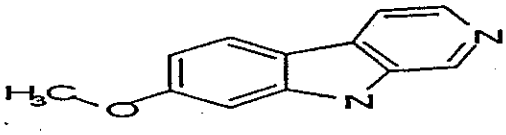
nicotinyl chloride (1.30 g, 7.42 mmol). The reaction was allowed to warm to RT and stirred for 16 h before diluting the reaction with water (60 ml) and 1M NaOH (8 ml). After stirring for 40 min at RT, the mixture was poured into water (200 ml). The mixture was allowed to stand for 30 min and the product was filtered to provide 2.20 g of the title compound after washing with water and drying under reduced pressure at RT.

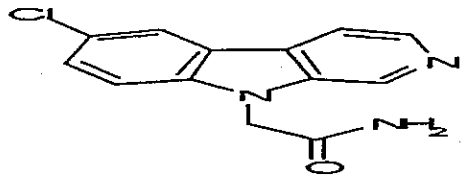
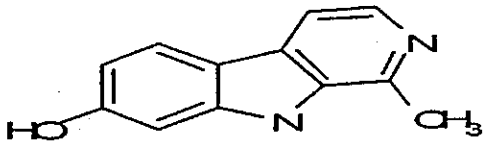
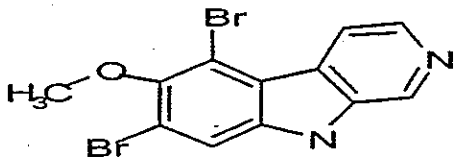
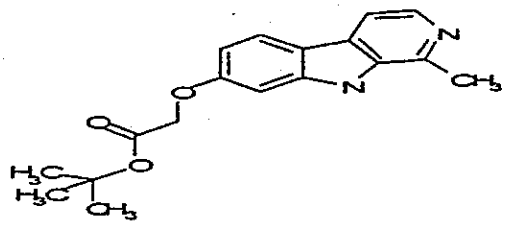
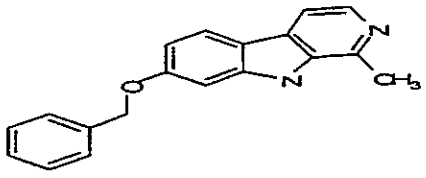
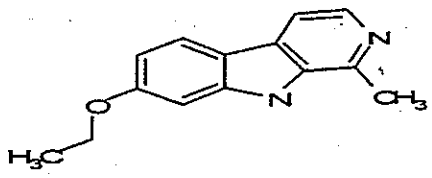
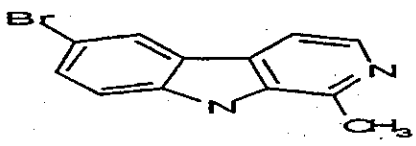
The examples in Table 1 show the structures of the prepared compounds and were prepared according to the previous examples.

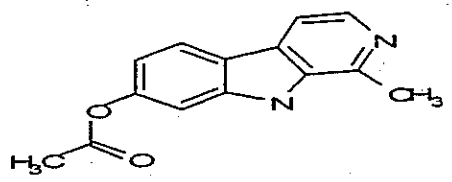
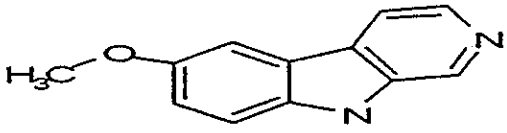
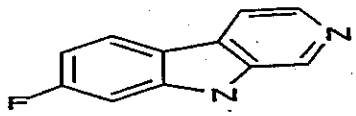
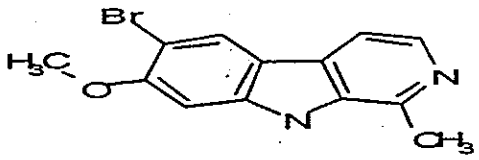
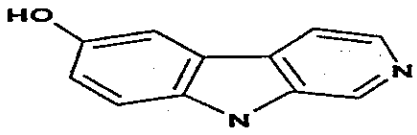
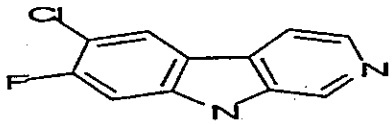
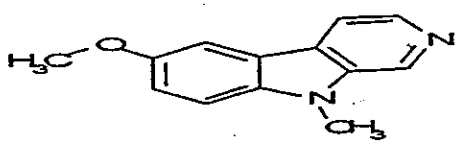
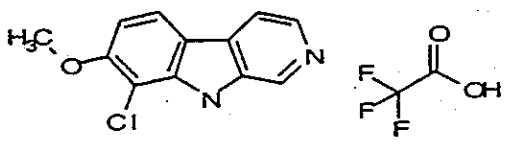
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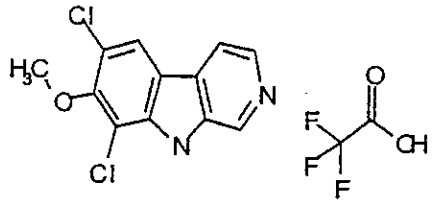
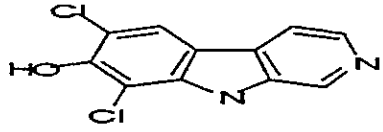
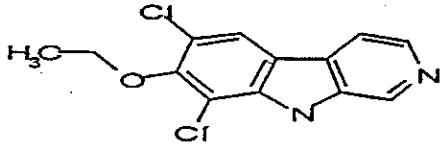
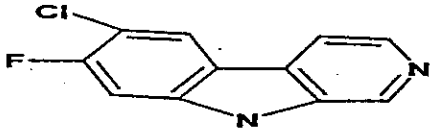
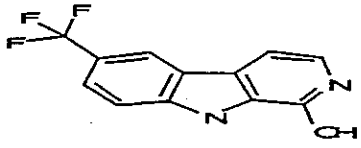
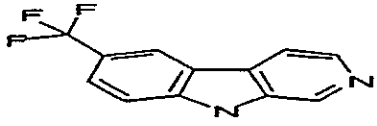
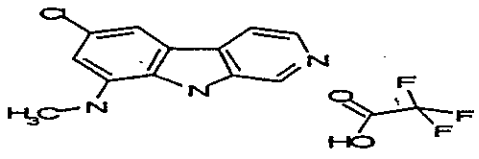
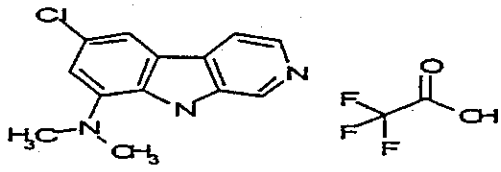
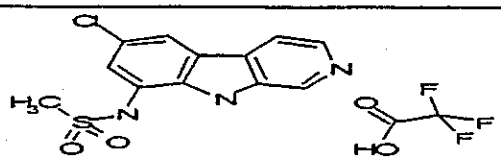
Example	Structure	Empirical formula	MS (M+ H)
1		$C_{11}H_7BrN_2$	248
2		$C_{13}H_9BrN_2O$	290
3		$C_{11}H_7FN_2$	187
4		$C_{14}H_{15}ClN_2$	211
5		$C_{12}H_7N_3$	194

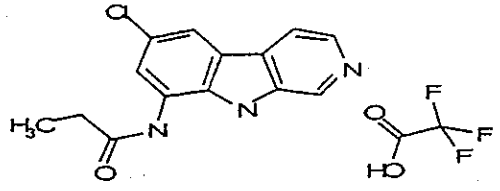
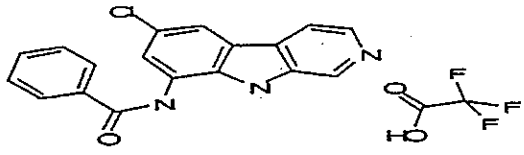
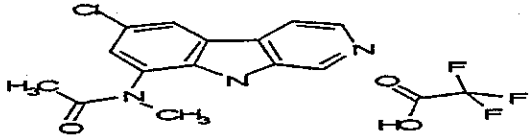
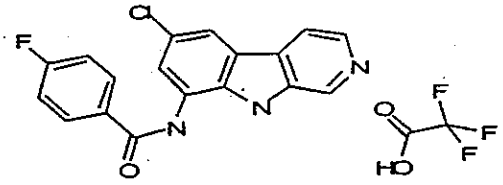
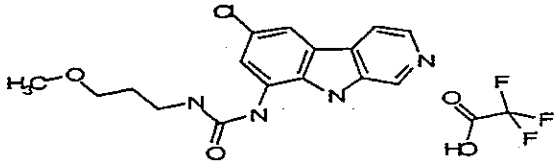
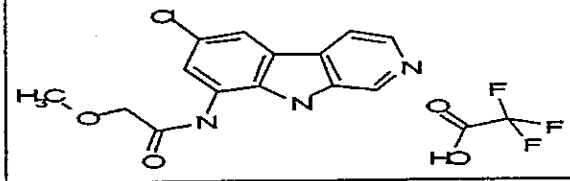
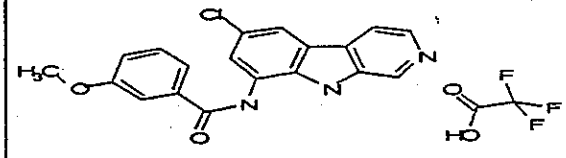
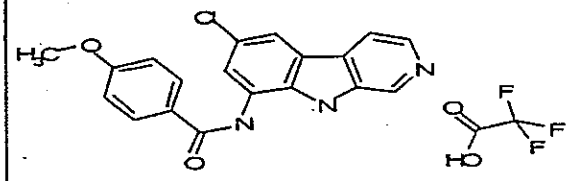
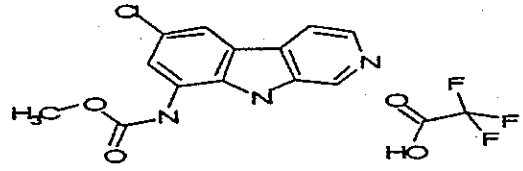
Example	Structure	Empirical formula	MS (M+ H)
6		$C_{11}H_8ClN_3O_2$	214
7		$C_{14}H_9F_3N_2O_4$	213
8		$C_{11}H_7Br_2ClN_2$	327
9		$C_{11}H_6Cl_2N_2$	238
10		$C_{12}H_9BrN_2O_2S$	326
11		$C_{12}H_9BrN_2$	262
12		$C_{11}H_7ClN_2$	204
13		$C_{13}H_9ClN_2O$	246

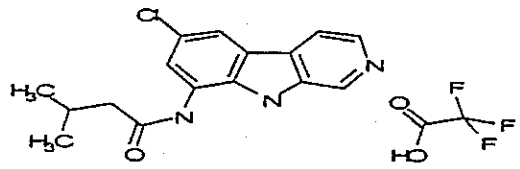
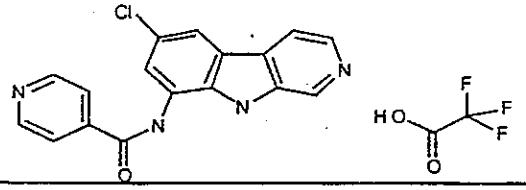
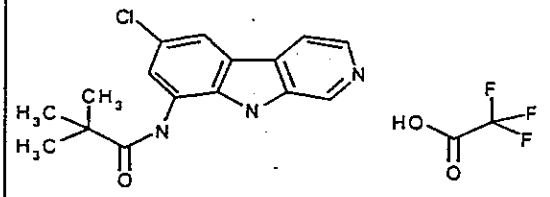
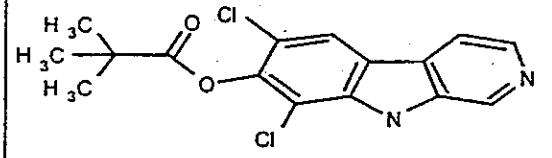
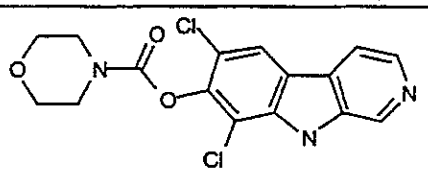
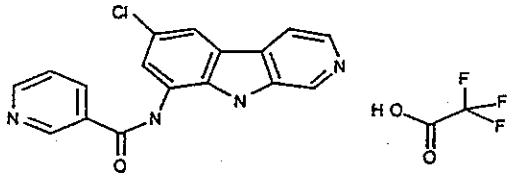
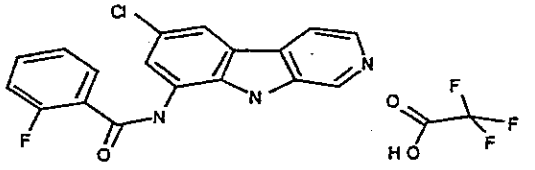
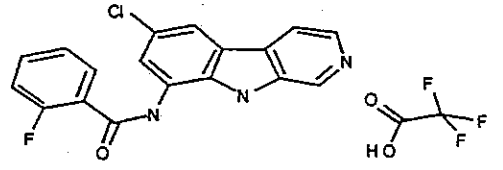
Example	Structure	Empirical formula	MS (M+ H)
14		$C_{11}H_6ClN_3O_2$	249
15		$C_{11}H_8ClN_3$	219
16		$C_{15}H_{11}ClF_3N_3O_3$	261
17		$C_{16}H_{14}BrN_3O_2$	361
18		$C_{15}H_{13}ClN_2O_2$	290
19		$C_{13}H_{11}ClN_2O$	248
20		$C_{13}H_9ClN_2O_2$	262
21		$C_{12}H_{10}N_2O$	199

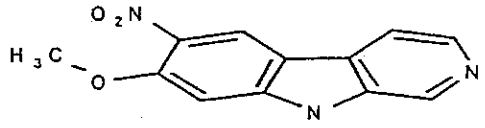
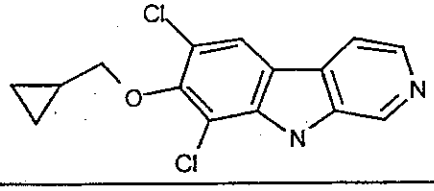
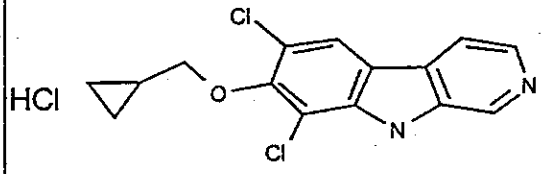
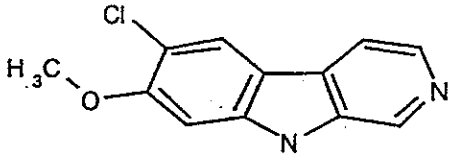
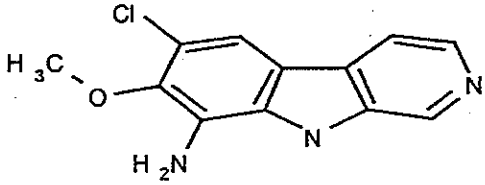
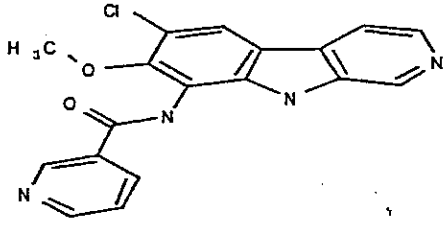
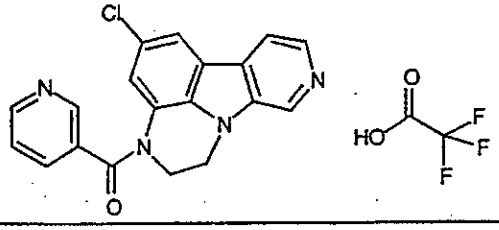
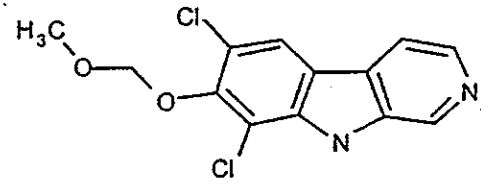
Example	Structure	Empirical formula	MS (M+ H)
22		$C_{13}H_{10}ClN_3O$	261
23		$C_{12}H_{10}N_2O$	199
24		$C_{12}H_8Br_2N_2O$	257
25		$C_{18}H_{20}N_2O_3$	313
26		$C_{19}H_{16}N_2O$	289
27		$C_{14}H_{14}N_2O$	227
28		$C_{12}H_9BrN_2$	262

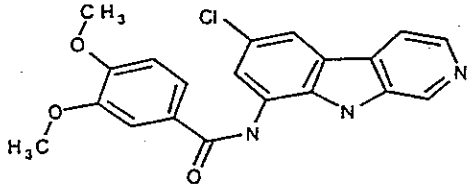
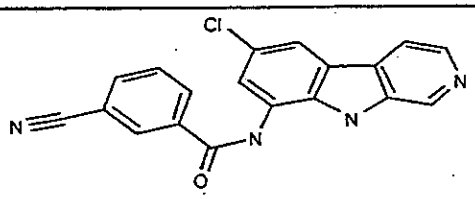
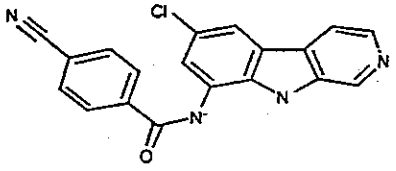
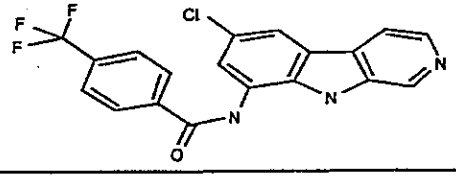
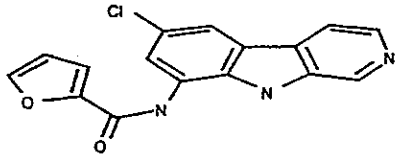
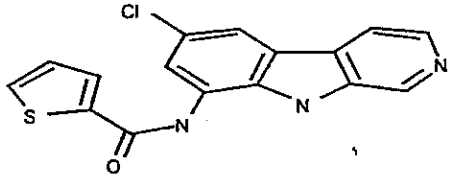
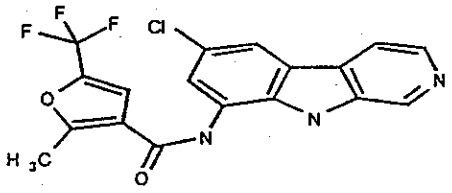
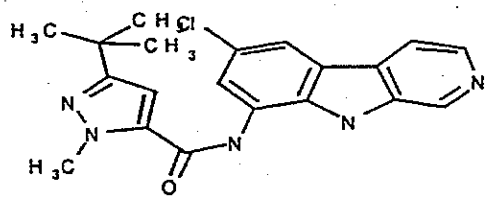
Example	Structure	Empirical formula	MS (M+ H)
29		$C_{14}H_{12}N_2O_2$	241
30		$C_{12}H_{10}N_2O$	199
31		$C_{11}H_7FN_2$	187
32		$C_{13}H_{11}BrN_2O$	292
33		$C_{11}H_8N_2O$	185
34		$C_{11}H_6ClFN_2$	222
35		$C_{13}H_{12}N_2O$	213
36			348

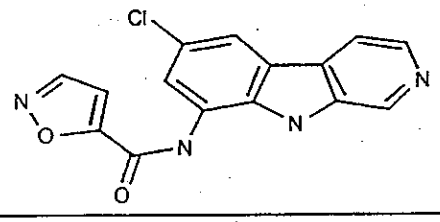
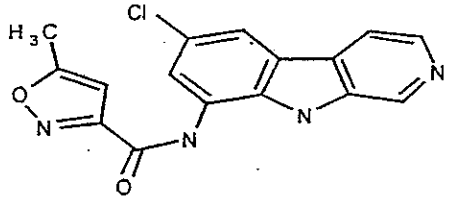
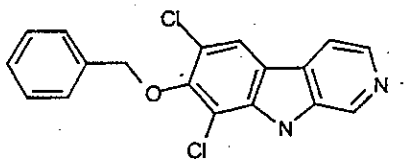
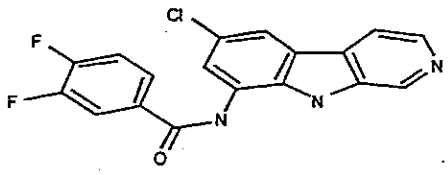
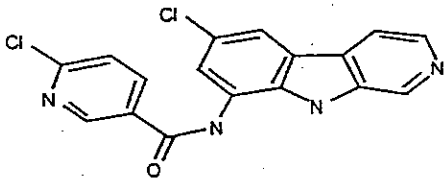
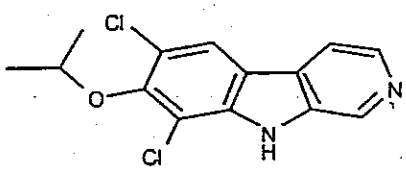
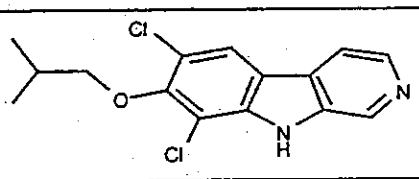
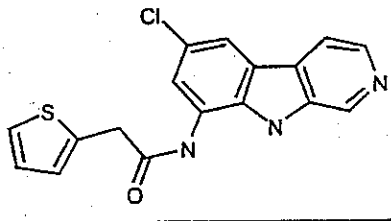
Example	Structure	Empirical formula	MS (M+ H)
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38			254
39			282
40			222
41			253
42			237
43			347
44			361
45			411

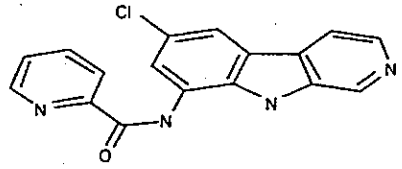
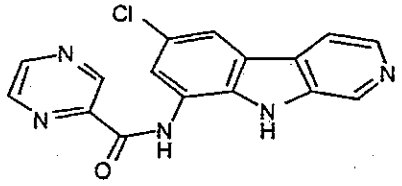
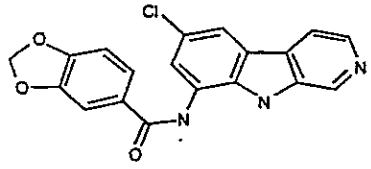
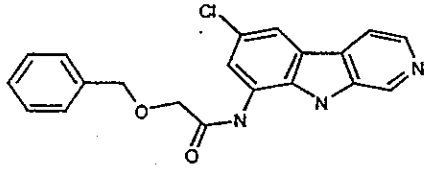
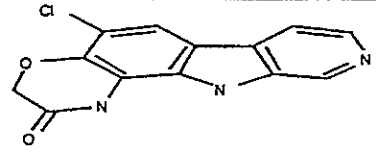
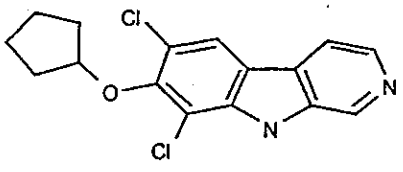
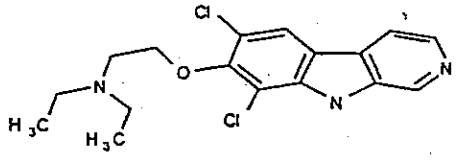
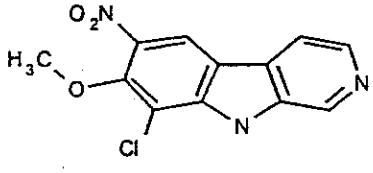
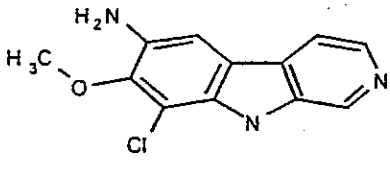
Example	Structure	Empirical formula	MS (M+ H)
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47			437
48			388
49			454
50			448
51			404
52			467
53			467
54			391

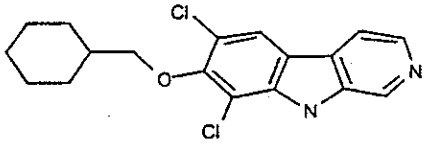
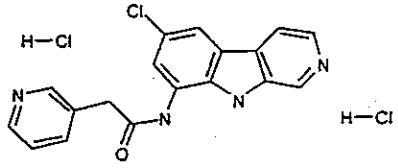
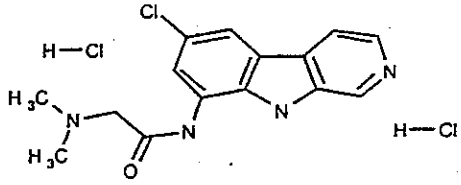
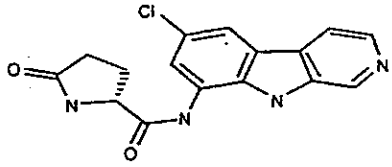
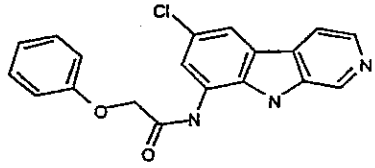
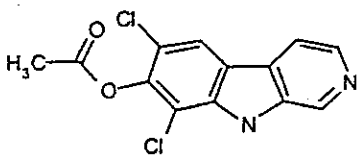
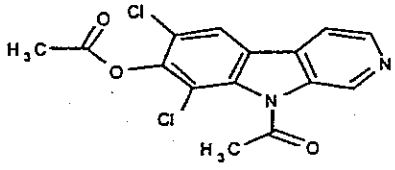
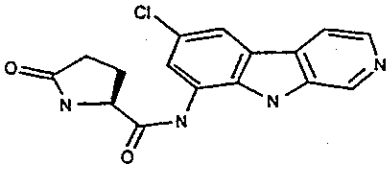
Example	Structure	Empirical formula	MS (M+ H)
55			416
56		$C_{19}H_{12}ClF_3N_4O_3$	323
57		$C_{18}H_{17}ClF_3N_3O_3$	302
58		$C_{16}H_{14}Cl_2N_2O_2$	338
59		$C_{16}H_{13}Cl_2N_3O_3$	367
60		$C_{19}H_{12}ClF_3N_4O_3$	323
61		$C_{20}H_{12}ClF_4N_3O_3$	340
62		$C_{20}H_{12}ClF_4N_3O_3$	340

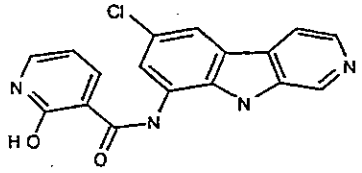
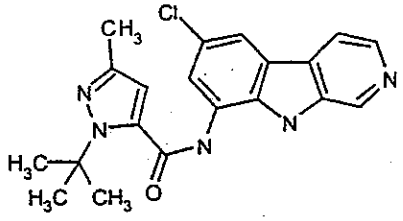
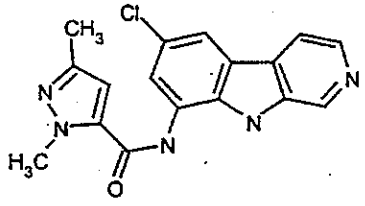
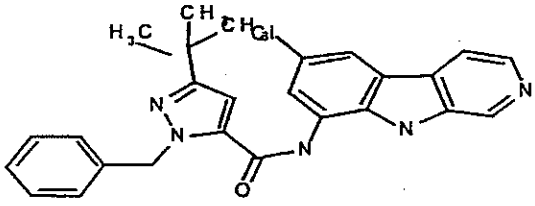
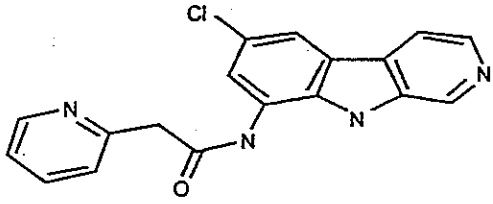
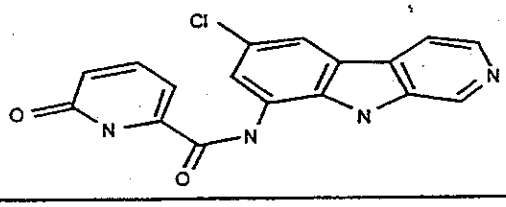
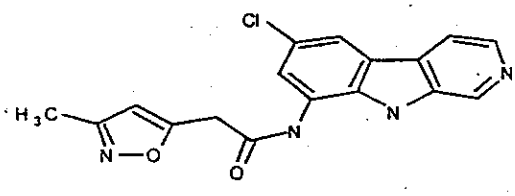
Example	Structure	Empirical formula	MS (M+ H)
63		$C_{12}H_9N_3O_3$	244
64		$C_{15}H_{12}Cl_2N_2O$	308
65		$C_{15}H_{13}Cl_3N_2O$	
66		$C_{12}H_9ClN_2O$	234
67		$C_{12}H_{10}ClN_3O$	249
68		$C_{18}H_{13}ClN_4O_2$	353
69		$C_{21}H_{14}ClF_3N_4O_3$	349
70		$C_{13}H_{10}Cl_2N_2O_2$	298

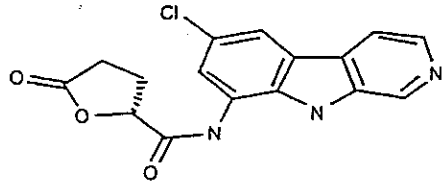
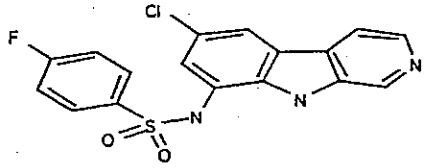
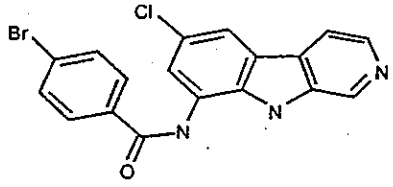
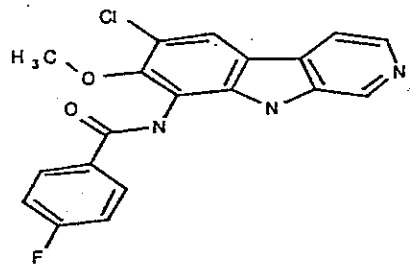
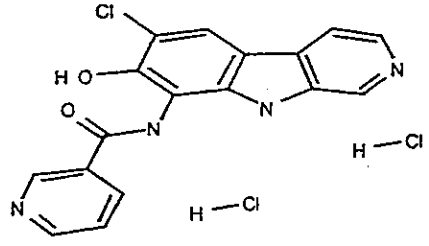
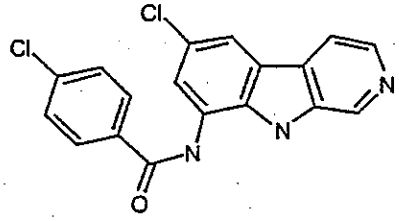
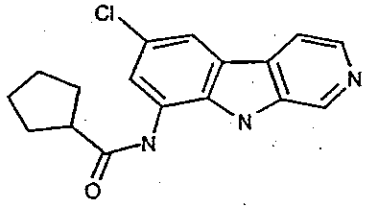
Example	Structure	Empirical formula	MS (M+ H)
71		$C_{20}H_{16}ClN_3O_3$	383
72		$C_{19}H_{11}ClN_4O$	348
73		$C_{19}H_{11}ClN_4O$	348
74		$C_{19}H_{11}ClF_3N_3O$	391
75		$C_{16}H_{10}ClN_3O_2$	313
76		$C_{16}H_{10}ClN_3OS$	329
77		$C_{18}H_{11}ClF_3N_3O_2$	395
78		$C_{20}H_{20}ClN_5O$	383

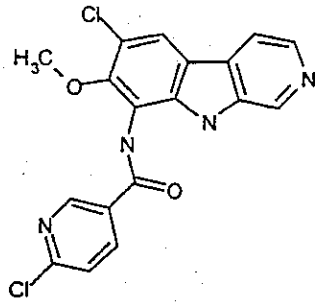
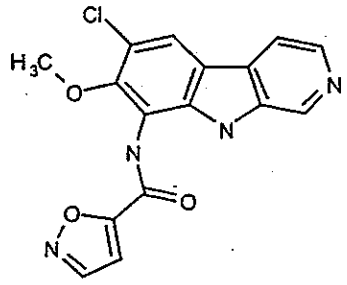
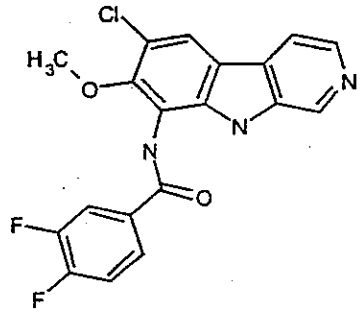
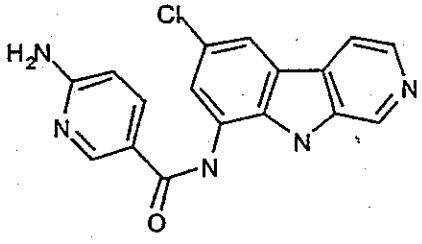
Example	Structure	Empirical formula	MS (M+ H)
79		$C_{15}H_9ClN_4O_2$	314
80		$C_{16}H_{11}ClN_4O_2$	328
81		$C_{18}H_{12}Cl_2N_2O$	344
82		$C_{18}H_{10}ClF_2N_3O$	359
83		$C_{17}H_{10}Cl_2N_4O$	358
84		$C_{14}H_{12}Cl_2N_2O$	296
85		$C_{15}H_{14}Cl_2N_2O$	310
86		$C_{17}H_{12}ClN_3OS$	343

Example	Structure	Empirical formula	MS (M+ H)
87		$C_{17}H_{11}ClN_4O$	323
88		$C_{16}H_{10}ClN_5O$	323
89		$C_{19}H_{12}ClN_3O_3$	367
90		$C_{20}H_{16}ClN_3O_2$	366
91		$C_{13}H_8ClN_3O_2$	274
92		$C_{16}H_{14}Cl_2N_2O$	322
93		$C_{17}H_{19}Cl_2N_3O$	353
94		$C_{12}H_8ClN_3O_3$	279
95		$C_{12}H_{10}ClN_3O$	248

Example	Structure	Empirical formula	MS (M+ H)
96		$C_{18}H_{18}Cl_2N_2O$	350
97		$C_{18}H_{15}Cl_3N_4O$	337
98		$C_{15}H_{17}Cl_3N_4O$	290
99		$C_{16}H_{13}ClN_4O_2$	330
100		$C_{19}H_{14}ClN_3O_2$	353
101		$C_{13}H_8Cl_2N_2O_2$	296
102		$C_{15}H_{10}Cl_2N_2O_3$	338
103		$C_{16}H_{13}ClN_4O_2$	330

Example	Structure	Empirical formula	MS (M+ H)
104		$C_{17}H_{11}ClN_4O_2$	340
105		$C_{20}H_{20}ClN_5O$	383
106		$C_{17}H_{14}ClN_5O$	341
107		$C_{26}H_{24}ClN_5O$	359
108		$C_{18}H_{13}ClN_4O$	338
109		$C_{17}H_{11}ClN_4O_2$	340
110		$C_{17}H_{13}ClN_4O_2$	342

Example	Structure	Empirical formula	MS (M+ H)
111		$C_{16}H_{12}ClN_3O_3$	331
112		$C_{17}H_{11}ClFN_3O_2S$	377
113		$C_{18}H_{11}BrClN_3O$	401
114		$C_{19}H_{13}ClFN_3O_2$	371
115		$C_{17}H_{13}Cl_3N_4O_2$	339
116		$C_{18}H_{11}Cl_2N_3O$	357
117		$C_{17}H_{16}ClN_3O$	314

Example	Structure	Empirical formula	MS (M+ H)
118		$C_{18}H_{12}Cl_2N_4O_2$	388
119		$C_{16}H_{11}ClN_4O_3$	343
120		$C_{19}H_{12}ClF_2N_3O_2$	390
121		$C_{17}H_{12}ClN_5O$	339

Pharmacological examples

I_kB-kinase ELISA

The in-vitro assay for detecting and measuring inhibition activity against IκBα-kinase complex by candidate pharmacological agents employs a biotinylated polypeptide spanning both Ser^{32} and Ser^{36} of IκBα and a specific antibody binding only to the phosphorylated form of the polypeptide, being either monoclonal or polyclonal (such as the commercially-available anti-phospho-$serine^{32}$ IκBα antibodies from New England Biolabs, Beverly, MA, USA, cat. #9240). Once the antibody-phospho-polypeptide complex is formed, the complex can be detected by a variety of analytical methods utilizing such as radioactivity, luminescence, fluorescence or optical absorbance. For the use of the ELISA method, the complex can be immobilized either onto a biotin-binding plate (such as Neutravidin coated plate) and detected with a secondary antibody conjugated to HRP, or onto an antibody-binding plate (such as Protein-A coated plate) and detected with biotin-binding protein conjugated to HRP (such as Streptavidin-HRP). The level of activity can be correlated with a standard curve using synthetic phosphopeptides corresponding to the substrate polypeptide.

Experimental

IκBα kinase complex was prepared by first diluting 10 mL of HeLa S3 cell-extracts S100 fraction with 40 mL of 50 mM HEPES pH 7.5. Then, 40% ammonium sulfate was added and incubated on ice for 30 minutes. Precipitated pellet was redissolved with 5 mL of SEC buffer (50 mM HEPES pH 7.5, 1 mM DTT, 0.5 mM EDTA, 10 mM 2-glycerophosphate), clarified by centrifugation at 20,000 x g for 15 min., and filtration through a 0.22 µm filter unit. Sample was loaded onto a 320-mL Superose-6 FPLC column (Amersham Pharmacia Biotech AB, Uppsala, Sweden) equilibrated with SEC buffer operated at 2 mL/min flow rate at 4°C. Fractions spanning the 670-kDa molecular-weight marker were pooled for activation. Kinase-containing pool was then activated by incubating with 100 nM MEKK1Δ, 250 µM MgATP, 10 mM $MgCl_2$, 5 mM DTT, 10 mM 2-glycerophosphate, 2.5 µM Microcystin-LR, for 45 minutes at 37°C. Activated enzyme was stored at –80°C until further use. Per well of a 96-well plate, compounds at various concentrations in 2 µL DMSO were pre-incubated for 30 minutes at 25°C with 43 µL of activated enzyme diluted [1:25] with assay buffer (50 mM HEPES pH 7.5, 5 mM DTT, 10 mM $MgCl_2$, 10 mM 2-glycerophosphate, 2.5 µM Microcystin-LR). Five

microliters of peptide substrate (biotin-$(CH_2)_6$- DRHDSGLDSMKD-$CONH_2$) at 200 µM stock solution was added to each well and incubated for 1 hour before quenching with 150 µL of 50 mM HEPES pH 7.5, 0.1% BSA, 50 mM EDTA, plus [1:200] antibody. Quenched kinase reaction samples and phospho-peptide-calibration standards (biotin-$(CH_2)_6$- DRHDS[PO_3]GLDSMKD-$CONH_2$, serially diluted in assay buffer) at 100 µL per well were transferred to a Protein-A plate (Pierce Chemical Co., Rockford, IL, USA) and incubated for 2 hours. with shaking. Following 3 washes with PBS, 100 µL of 0.5 µg/mL Streptavidin conjugated with HRP (horseradish peroxidase) diluted with 50 mM HEPES/ 0.1% BSA, was added for 30 minutes. After 5 washes with PBS, 100 µL TMB substrate (Kirkegaard & Perry Laboratories, Gaithersburg, MD, USA) was added and color development was stopped by adding 100 µL of 0.18 M H_2SO_4. Absorbance signals were recorded at 450 nm. Calibration-curve standards were fitted by linear regression using a 4-parameter dose-response equation. Based on this standard curve, levels of kinase activity were calculated in order to determine inhibition activity of candidate pharmacological agents.

Table 3 which follows shows the results.

The compound according to example 121 shows a IC_{50} of 1.7.

Table 3: Kinase inhibition at a substance concentration of IC_{50} in µM

Example number	IkB-kinase IC_{50}	Example number	IkB-kinase IC_{50}	Example number	IkB-kinase IC_{50}	Example number	IkB-kinase IC_{50}
1	0.4	31	3.3	61	0.94	91	2.3
2	0.4	32	4.6	62	0.38	92	0.4
3	1	33	1.5	63	1.3	93	1.3
4	2.5	34	1	64	0.11	94	0.64
5	1	35	3.5	65	0.10	95	1.0
6	3	36	1.4	66	0.7	96	1.3
7	65	37	0.15	67	0.5	97	0.69
8	0.2	38	11	68	0.16	98	0.9
9	0.2	39	0.1	69	3.0	99	0.09
10	0.4	40	2	70	0.36	100	1.5
11	0.7	41	2.2	71	3.0	101	1.8
12	0.4	42	0.8	72	0.58	102	0.8
13	0.5	43	1	73	0.4	103	0.31
14	4	44	2	74	3.8	104	1.0
15	0.8	45	8.3	75	0.29	105	0.4
16	0.3	46	0.3	76	0.9	106	0.6
17	5	47	0.6	77	4.4	107	0.4
18	23	48	4	78	2.3	108	2.1
19	3	49	0.22	79	0.18	109	2.1
20	14	50	10	80	0.31	110	0.3
21	1.8	51	0.6	81	0.25	111	0.54
22	15	52	0.6	82	0.15	112	0.93
23	22	53	1.4	83	0.06	113	0.64
24	4.6	54	0.7	84	0.1	114	2.1
25	31	55	0.8	85	0.2	115	4.6
26	12	56	0.27	86	0.7	116	1.8
27	4.5	57	4.3	87	0.75	117	0.67
28	11	58	0.33	88	0.28	118	0.12
29	40	59	3.2	89	0.57	119	0.6
30	5.2	60	0.052	90	1.4	120	0.4

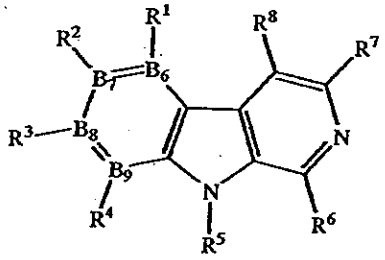
Mouse heterotopic cardiac transplant model

In the mouse heterotopic cardiac transplant model across full histocompatibility barriers (BALB/c->C57BL/6 or B6/129), graft survival is typically limited to 7.3 ± 0.4 days (mean ± SD, n0 allografts) (see for example in Hancock WW, Sayegh MH, Zheng XG, Peach R, Linsley PS, Turka LA. Costimulatory function and expression of CD40-ligand, CD80 and CD86 or in vascularized murine cardiac allograft rejection. Proc Natl Acad Sci (USA) 93, 1996, 13967-13972; and Hancock W W, Buelow R, Sayegh MH, Turka LA. Antibody-induced transplant arteriosclerosis is prevented by graft expression of anti-oxidant and anti-apoptotic genes. Nature Med 4, 1998, 1392-1396).

The effects of oral administration of the compounds according to examples 49 and 60 were tested using 25 mg/kg/day for 14 days, starting at transplantation in said animal model. Whereas grafts in animals receiving the carrier, methyl-cellulose, rejected by 7 days (6.7 ± 0.8), grafts in compound 49-treated mice survived around 15 days (15.3 ± 0.6), and grafts in those given compound 60 survived for 20 days (20 ± 1). Current immunosuppressive therapies used in transplantation have limited efficacy and/or considerable toxicity. Targeting of IkB-kinase with these agents significantly prolonged allograft survival without associated toxicity.

What is claimed is:

1. A compound of formula I



(I)

or a stereoisomeric form of a compound of the formula I or a physiologically tolerable salt of a compound of the formula I,

where B_6, B_7, B_8 and B_9 are ring atoms independently chosen from carbon atoms and nitrogen atoms, where B_6, B_7, B_8 and B_9 together comprise no more than two nitrogen atoms; wherein

in case a)

the substituents R^1, R^2 and R^3 may be independently chosen from:

1.1. hydrogen atom,

1.2. halogen,

1.3. -CN,

1.4. -COOH,

1.5. $-NO_2$,

1.6. $-NH_2$,

1.7. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from:

1.7.1 phenyl, which is unsubstituted or mono- to penta-substituted by substituents independently chosen from halogen or $-O-(C_1-C_4)$-alkyl,

1.7.2 halogen,

1.7.3 $-NH_2$,

1.7.4 -OH,

1.7.5 $-COOR^{16}$, wherein R^{16} is hydrogen atom or $-(C_1-C_{10})$-alkyl,

1.7.6 $-NO_2$,

1.7.7 -$S(O)_y$ -R^{14}, wherein y zero, 1 or 2, R^{14} is -(C_1 -C_{10})-alkyl, phenyl, which phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those defined under 1.7.1 to 1.7.11, amino or -$N(R^{13})_2$,

wherein R^{13} is independently of one another chosen from hydrogen atom, phenyl, -(C_1 -C_{10})-alkyl, -C(O)-(C_1 -C_7)-alkyl, -C(O)-phenyl, -C(O)-NH-(C_1 -C_7)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C_1 -C_7)-alkyl, -$S(O)_y$ -R^{14}, wherein R^{14} and y are as defined in 1.7.7,

and wherein the R^{13} alkyl or phenyl groups in each case are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, or R^{13} together with the nitrogen atom to which it is bonded may be independently chosen to form a heterocycle having 5 to 7 ring atoms,

1.7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta-substituted independently of one another as defined under 1.7.1 to 1.7.11,

1.7.9 a radical selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

1.7.10 -(C_3 -C_7)-cycloalkyl or

1.7.11 =O,

1.8. -$N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above,

1.9. -NH-C(O)-R, wherein R^{15} is

1.9.1 a radical selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

wherein said radical is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, by -CF_3, by benzyl or by -(C_1 -C_{10})-alkyl, wherein the -(C_1 -C_{10})-alkyl is mono to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

1.9.2 -(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above or by -O-(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

1.9.3 -(C_3 -C_7)-cycloalkyl,

1.9.4 -$N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above, or

1.9.5 phenyl, wherein phenyl is unsubstituted or mono- to penta-substituted by

substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, by -O-(C_1 -C_{10})-alkyl, by -CN, by -CF_3, by -(C_1 -C_{10})-alkyl, wherein alkyl is mono to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, or by two substituents of said phenyl which form a dioxolan ring,

1.10. -$S(O)_y$ -R^{14}, wherein R^{14} and y are as defined in 1.7.7 above,

1.11. -C(O)-R^{12}, wherein R^{12} is phenyl or -(C_1 -C_7)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

1.12. -C(O)-O-R^{12}, wherein R^{12} is as defined in 1.11 above,

1.13. -(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

1.14. -O-(C_1 -C_6)-alkyl-O-(C_1 -C_6)-alkyl,

1.15. -O-(C_0 -C_4)-alkyl-(C_3 -C_7)-cycloalkyl,

1.16. -(C_1 -C_4)-alkyl-N(R^{13})$_2$, wherein R^{13} is as defined in 1.7.7 above

1.17. -CF_3 or

1.18. -CF_2 -CF_3,

R^4 is

1. -(C_1 -C_{10})-alkyl, wherein alkyl is mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.10 above,

2. -CF_3,

3. -CF_2 -CF_3,

4. -CN,

5. -$S(O)_y$ -R^{14}, wherein R^{14} and y are as defined in 1.7.7 above,

6. -NH_2,

7. -O-(C_1 -C_{10})-alkyl, wherein alkyl is mono- to penta-substituted by substituents independently chosen from

7.1 phenyl, which is unsubstituted or mono- to penta-substituted by substituents independently chosen from halogen or -O-(C_1 -C_4)-alkyl,

7.2 halogen,

7.3 -NH_2,

7.4 -OH,

7.5 -$COOR^{16}$, wherein R^{16} is hydrogen atom or -(C_1 -C_{10})-alkyl,

7.6 -NO_2,

7.7 -$S(O)_y$ -R^{14}, wherein y is zero, 1 or 2, R^{14} is -(C_1 -C_{10})-alkyl, phenyl, which phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, amino or

wherein R^{13} is independently of one another chosen from hydrogen atom, phenyl, -(C_1 -C_{10})-alkyl, -C(O)-(C_1 -C_7)-alkyl, -C(O)-phenyl, -C(O)-NH-(C_1 -C_7)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C_1 -C_7)-alkyl, -$S(O)_y$ -R^{14}, wherein R^{14} and y are defined as in 7.7 above, and wherein the R^{13} alkyl or phenyl groups in each case are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, or

R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

7.9 a radical selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, isoxazolidine, thiophene, 2-isoxazoline, isothiazolidine, 2-isothiazoline, or thiomorpholine,

7.10 -(C_3 -C_7)-cycloalkyl or

7.11 =O,

8. -$N(R^{17})_2$, wherein R^{17} is independently of one another chosen from hydrogen atom, phenyl, -(C_1 -C_{10})-alkyl, -C(O)-phenyl, -C(O)-NH-(C_1 -C_7)-alkyl, -C(O)-(C_1 -C_{10})-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C_1 -C_7)-alkyl, -$S(O)_y$ -R^{14}, wherein R^{14} and y are as defined as in 7.7 above,

and wherein alkyl or phenyl in each case are unsubstituted or mono- to penta-substituted independently of one another as defined under 1.7.1 to 1.7.11 above, or

R^{17} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

9. -NH-C(O)-R^{15}, wherein R^{15} is

9.1 a radical selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

wherein said radical is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, $-CF_3$, benzyl or by $-(C_1-C_{10})$-alkyl, wherein alkyl is mono to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

9.2 $-(C_1-C_{10})$-alkyl, wherein alkyl is mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above or by $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

9.3 $-(C_3-C_7)$-cycloalkyl,

9.4 $-N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above provided that $-N(R^{13})_2$ is not $-NH_2$, or

9.5 phenyl, wherein phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, by $-O-(C_1-C_{10})$-alkyl, by -CN, by $-CF_3$, by $-(C_1-C_{10})$-alkyl, wherein alkyl is mono to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, or by two substituents of the phenyl radical which form a dioxolan ring,

10. $-C(O)-R^{12}$, wherein R^{12} is phenyl or $-(C_1-C_7)$-alkyl, wherein phenyl or alkyl are mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

11. $-C(O)-O-R^{12}$, wherein R^{12} is phenyl or $-(C_1-C_7)$-alkyl, wherein phenyl or alkyl are mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

12. $-O-(C_1-C_6)$-alkyl-$O-(C_1-C_6)$-alkyl,

13. $-O-(C_0-C_4)$-alkyl-(C_3-C_7)-cycloalkyl or

14. $-(C_1-C_4)$-alkyl-$N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above,

R^5 is

1. a hydrogen atom,

2. $-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.4 above,

3. $-C(O)-R^9$, wherein R^9 is

$-NH_2$, $-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.4, or $-N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above, or

4. $-S(O)_2-R^9$, wherein R^9 is as defined in 3 above, or

R^4 and R^5 together with the atom to which they are bonded form a heterocycle, or

R^3 and R^5 together with the atom to which they are bonded form a heterocycle containing an additional oxygen atom in the ring and

R^6, R^7 and R^8 independently of one another are chosen from hydrogen atom or methyl, or in case b)

the substituents R^1, R^2 and R^4 may be independently chosen as defined under 1.1 to 1.18 in case a) above,

R^3 is

1. $-CF_3$,

2. $-CF_2-CF_3$,

3. -CN,

4. -COOH,

5. $-NO_2$,

6. $-NH_2$,

7. -O-(C_1 -C_{10})-alkyl, wherein alkyl is mono- to penta substituted by substituents independently chosen from

7.1 phenyl, which is unsubstituted or mono- to penta-substituted by substituents independently chosen from halogen or -O-(C_1 -C_4)-alkyl,

7.2 halogen,

7.3 $-NH_2$,

7.4 -OH,

7.5 $-COOR^{16}$, wherein R^{16} is hydrogen atom or -(C_1 -C_{10})-alkyl,

7.6 $-NO_2$,

7.7 $-S(O)_y-R^{14}$, wherein y is zero, 1 or 2, R^{14} is -(C_1 -C_{10})-alkyl, phenyl, which phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, amino or

wherein R^{13} is independently of one another chosen from hydrogen atom, phenyl, -(C_1 -C_{10})-alkyl, -C(O)-(C_1 -C_7)-alkyl, -C(O)-phenyl, -C(O)-NH-(C_1 -C_7)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C_1 -C_7)-alkyl, $-S(O)_y-R^{14}$, wherein R^{14} and y are defined as in 7.7 above, and wherein the R^{13} alkyl or phenyl groups in each case are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined

under 1.7.1 to 1.7.11 above, or

R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta- by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

7.9 a radical selected from tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

7.10 -(C_3 -C_7)-cycloalkyl or

7.11 .dbd.O,

8. -$N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above,

9. -NH-C(O)-R^{15}, wherein R^{15} is

9.1 a radical selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

wherein said radical is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, -CF_3, benzyl or by -(C_1 -C_{10})-alkyl, wherein alkyl is mono to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

9.2 -(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above or by -O-(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

9.3 -(C_3 -C_7)-cycloalkyl,

9.4 -$N(R^{13})_2$, wherein R^{13} is as defined in 1.7.7 above, or

9.5 phenyl, wherein phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, by -O-(C_1 -C_{10})-alkyl, by -CN, by -CF_3, by -(C_1 -C_{10})-alkyl, wherein alkyl is mono to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above, or by two substituents of the phenyl radical which form a dioxolan ring,

10. -$S(O)_y$ -R^{14}, wherein R^{14} and y are as defined in 1.7.7 above,

11. -C(O)-R^{12}, wherein R^{12} is phenyl or -(C_1 -C_7)-alkyl, wherein phenyl or alkyl are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

12. -C(O)-O-R^{12}, wherein R^{12} is phenyl or -(C_1 -C_7)-alkyl, wherein phenyl or alkyl are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

13. -(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

14. -O-(C_1 -C_6)-alkyl-O-(C_1 -C_6)-alkyl,

15. -O-(C_0 -C_4)-alkyl-(C_3 -C_4)-cycloalkyl or

16. -(C_1 -C_4)-alkyl-N(R^{13})$_2$, wherein R^{13} is as defined in 1.7.7 above,

R^5 is as defined as R^5 in case a) above,

R^6, R^7 and R^8 independently of one another are chosen from hydrogen atom or methyl, with the following provisos for case b):

when R^6 is methyl, R^3 is not an O-(C_1 -C_{10})-alkyl monosubstituted by either an unsubstituted phenyl or a -COO-(C_1 -C_{10})-alkyl; and

when R^3 is an O-(C_1 -C_{10})-alkyl monosubstituted by a -(C_3 -C_7)-cycloalkyl, R^6 is hydrogen.

2. A compound of the formula I as claimed in claim 1, wherein in case a)

B_6, B_7, B_8, and B_9 are each a carbon atom,

R^1, R^2 and R^3 independently of one another are chosen from hydrogen atom, halogen, cyano, nitro, amino, -O-(C_1 -C_7)-alkyl, wherein alkyl is unsubstituted or substituted by phenyl, -CF_2 -CF_3, -CF_3, -N(R^{18})$_2$,

wherein R^{18} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -C_4)-alkyl or -C(O)-(C_1 -C_7)-alkyl, wherein alkyl, pyridyl or phenyl are unsubstituted or mono- to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

$S(O)_y$ -R^{14},

wherein y is zero, 1 or 2, and R^{14} is -(C_1 -C_{10})-alkyl, phenyl, which phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, amino or -N(R^{18})$_2$,

wherein R^{13} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -C_4)-alkyl or -C(O)-(C_1 -C_7)-alkyl, wherein each alkyl is unsubstituted or mono- to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to

1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms, or

-C(O)-O-R^{12}, wherein R^{12} is as defined as in 1.11 above,

R^4 is cyano, amino, -O-(C_1 -C_7)-alkyl, wherein alkyl is substituted by phenyl;

-CF_2 -CF_3, -CF_3, -N(R^{18})$_2$,

wherein R^{18} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -C_4)-alkyl or -C(O)-(C_1 -C_7)-alkyl, wherein each alkyl, pyridyl or phenyl are unsubstituted or mono- to tri-substituted independently of one another as defined under 1.7.1 to 1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

S(O)$_y$ -R^{14},

wherein y is zero, 1 or 2, and R^{14} is -(C_1 -C_{10})-alkyl, phenyl, which phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, amino or -N(R^{18})$_2$,

wherein R^{18} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -C_4)-alkyl or -C(O)-(C_1 -C_7)-alkyl, wherein each alkyl is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.7.1 to 1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms, or

-C(O)-O-R^{12}, wherein R^{12} is phenyl or -(C_1 -C_7)-alkyl, wherein said phenyl or alkyl are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

R^6, R^7 and R^8 independently of one another are chosen from hydrogen atom or methyl, and

R^5 is as defined as for case a) above.

3. A compound of the formula I as claimed in claim 1,

wherein in case b)

the substituents R^1, R^2 and R^4 independently of one another are hydrogen atom, halogen, cyano, nitro, amino, -O-(C_1 -C_7)-alkyl, wherein alkyl is unsubstituted or substituted by phenyl,

-CF_2 -CF_3, -CF_3, -N(R^{18})$_2$,

wherein R^{18} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -

(C_4)-alkyl or -C(O)-(C_1 -C_7)-alkyl, wherein each alkyl, pyridyl or phenyl are unsubstituted or mono- to tri-substituted independently of one another as defined under 1.7.1 to 1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

$S(O)_y$ -R^{14},

wherein y is zero, 1 or 2, and R^{14} is -(C_1 -C_{10})-alkyl, phenyl, which phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, amino or -$N(R^{18})_2$,

wherein R^{18} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -C_4)-alkyl or -C(O)-(C_1 -C_7)-alkyl, wherein each alkyl is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.7.1 to 1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms, or

-C(O)-O-R^{12}, wherein R^{12} is phenyl or -(C_1 -C_7)-alkyl, wherein said phenyl or alkyl are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

R^3 is cyano, nitro, amino, -O-(C_1 -C_7)-alkyl, wherein alkyl is substituted by phenyl, -CF_2 -CF_3, -CF_3, -$N(R^{18})_2$,

wherein R^{18} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -(C_4)-alkyl or -C(O)-(C_1 -C_7)-alkyl, wherein each alkyl, pyridyl or phenyl are unsubstituted or mono- to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

$S(O)_y$ -R^{14},

wherein y is zero, 1 or 2, and R^{14} is -(C_1 -C_{10})-alkyl, phenyl, which phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, amino or -$N(R^{18})_2$,

wherein R^{18} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -C_4)-alkyl or -C(O)-(C_1 -C_7)-alkyl, wherein each alkyl is unsubstituted or mono- to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11, or R^{18} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms, or

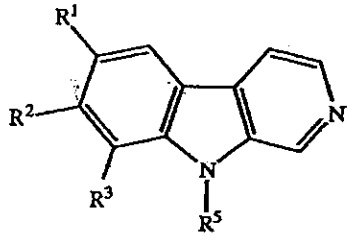
-C(O)-O-R^{12}, wherein R^{12} is phenyl or -(C_1 -C_7)-alkyl, wherein said phenyl or alkyl are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 above,

R^6, R^7 and R^8 independently of one another are chosen from hydrogen atom or methyl,

and

R^5 is as defined in claim 1.

4. A compound of formula II



(II)

or a stereoisomeric form of a compound of the formula II or a physiologically tolerable salt of a compound of the formula II, wherein;

R^1 and R^2 are independently of one another chosen from hydrogen atom, halogen, cyano, amino, -O-(C_1 -C_4)-alkyl, nitro, -CF_3, -CF_2 -CF_3, -$S(O)_y$ -R^{14},

wherein y is 1 or 2, R^{14} is amino, -(C_1 -C_7)-alkyl or phenyl, which phenyl is unsubstituted or mono- to tri-substituted as defined for substituents under 1.7.1 to 1.7.11 in claim 1,

-$N(R^{18})_2$, wherein R^{18} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl-C(O)-(C_1 -C_7)-alkyl, -C(O)-phenyl, C(O)-pyridyl, -C(O)-NH-(C_1 -C_4)-alkyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -C_4)-alkyl or -(C_1 -C_{10})-alkyl, wherein pyridyl, alkyl or phenyl are unsubstituted or mono- to tri-substituted independently of one another as defined under 1.7.1 to 1.7.11 in claim 1, or R^{18} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

R^3 is cyano, amino, -O-(C_1 -C_4)-alkyl, nitro, -CF_3, -CF_2 -CF_3, -$S(O)_y$ -R^{14}, wherein y is 1 or 2, R^{14} is amino, -(C_1 -C_7)-alkyl or phenyl, which phenyl is unsubstituted or mono- to tri-substituted as defined for substituents under 1.7.1 to 1.7.11 in claim 1,

-$N(R^{18})_2$, wherein R^{18} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl-C(O)-(C_1 -C_7)-alkyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-O-phenyl, -C(O)-NH-(C_1 -C_4)-alkyl, -C(O)-O-(C_1 -C_4)-alkyl or -(C_1 -C_{10})-alkyl, wherein pyridyl, alkyl or phenyl are unsubstituted or mono- to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.11 in claim 1, or R^{18} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms, and

R^5 is hydrogen atom, -(C_1 -C_{10})-alkyl,

wherein alkyl is unsubstituted or mono- to tri-substituted by substituents independently chosen from those as defined under 1.7.1 to 1.7.4 in claim 1,

-C(O)-R^9 or -$S(O)_2$ -R^9, wherein

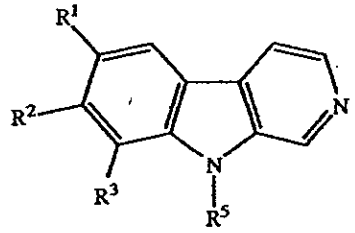
R^9 is -(C_1 -C_{10})-alkyl, -O-(C_1 -C_{10})-alkyl,

wherein alkyl is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.7.1 to 1.7.4 in claim 1, or

phenyl, which is unsubstituted or mono- to tri-substituted as defined under 1.7.1 to 1.7.11 in claim 1, or $-N(R^{18})_2$, wherein R^{18} is independently of one another chosen from hydrogen atom, $-(C_1-C_7)$-alkyl, $-C(O)-(C_1-C_7)$-alkyl, -C(O)-phenyl, C(O)-pyridyl, $-C(O)-NH-(C_1-C_4)$-alkyl, -C(O)-O-phenyl, $-C(O)-O-(C_1-C_4)$-alkyl or $-(C_1-C_{10})$-alkyl, wherein pyridyl, alkyl or phenyl are unsubstituted or mono- to tri-substituted independently of one another as defined under 1.7.1 in to 1.7.11 in claim 1, or R^{18} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms.

5. A compound of formula II

(II)



or a stereoisomeric form of a compound of the formula II or a physiologically tolerable salt of a compound of the formula II, wherein;

R^1 is bromo, $-CF_3$ or chloro,

R^2 is hydrogen atom or $O-(C_1-C_2)$-alkyl,

R^3 is $-N(R^{18})_2$, wherein R^{18} is independently of one another chosen from hydrogen atom, -C(O)-pyridyl, -C(O)-phenyl, $-(C_1-C_7)$-alkyl, $-C(O)-(C_1-C_4)$-alkyl or $-C(O)-O-(C_1-C_4)$-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri-substituted by substituents independently chosen from halogen or $-O-(C_1-C_2)$-alkyl, and

R^5 is hydrogen atom, methyl or $-S(O)_2-CH_3$.

6. A compound of the formula II as claimed in claim 5,

wherein

R^1 is chloro, R^3 is $-N-C(O)-CH_2-O-CH_3$, and R^2 and R^5 are each hydrogen atom, or

R^1 is chloro, R^3 is -N-C(O)-pyridyl, wherein pyridyl is unsubstituted or substituted by chloro, R^2 is hydrogen atom or $-O-CH_3$ and R^5 is hydrogen atom, or

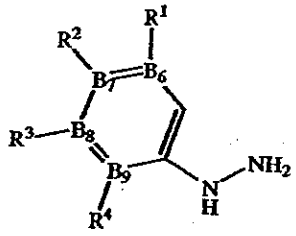
R^1 is chloro, R^3 is -N-C(O)-phenyl, wherein phenyl is mono- or di-substituted by fluoro and

R^2 and R^5 are each hydrogen atom.

7. A process for the preparation of a compound of the formula I as claimed in claim 1, which comprises

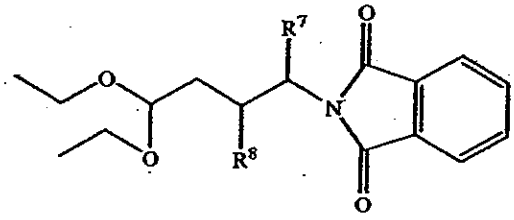
reacting a compound of formula III

(III)



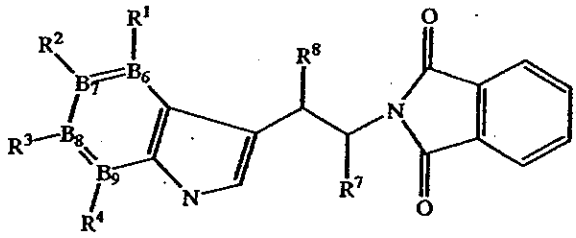
in which R^1, R^2, R^3, R^4, B_6, B_7, B_8 and B_9 are each as defined in formula I, with a compound of the formula IV,

(IV)



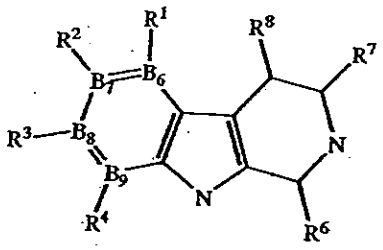
in the presence of a acid, to yield a compound of the formula V

(V)



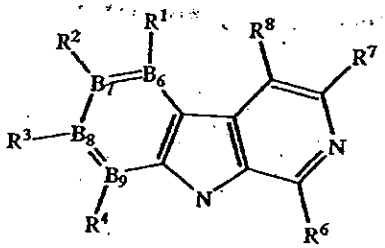
which is reacted with hydrazine hydrate and later with R^6 CHO or formaldehyde (R^6 is H) to give a compound of formula VI

(VI)



and then oxidizing formula VI to give a compound of the formula VII,

(VII)



where R^1 to R^4, R^6 to R^8 and B_6 to B_9 are as defined in formula I, a compound of formula (I).

8. A process according to claim 7, wherein a compound of the formula VII is reacted with a compound of the formula VIII

$Y\text{-}R^5$ (VIII)

where Y is halogen or -OH and R^5 is as defined in formula I, to give a compound of the formula I.

9. A process according to claim 7, which further comprises resolving a compound of the formula I formed by the process of claim 7, which on account of its chemical structure occurs in enantiomeric forms, into the pure enantiomers by salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds, separation of the diastereomers thus obtained, and removal of the chiral auxiliary groups.

10. A process according to claim 8, which further comprises resolving a compound of the formula I formed by the process of claim 8, which on account of its chemical structure occurs in enantiomeric forms, into the pure enantiomers by salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds, separation of the diastereomers thus obtained, and removal of the chiral auxiliary groups.

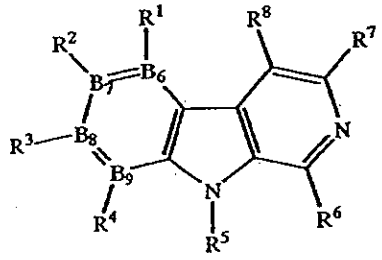
11. A process according to claim 7, which further comprises isolating a compound of the formula I prepared by the process of claim 7, either in free form or, in the case of the presence of acidic or basic groups, converting it into physiologically tolerable salts.

12. A process according to claim 8, which further comprises isolating a compound of the formula I prepared by the process of claim 8, either in free form or, in the case of the presence of acidic or basic groups, converting it into physiologically tolerable salt.

13. A process according to claim 9, which further comprises isolating a compound of the formula I prepared by process 9, either in free form or, in the case of the presence of acidic or basic groups, converting it into physiologically tolerable salts.

14. A composition which comprises an efficacious amount of at least one compound chosen from the compounds of formula I as claimed in claim 1, a physiologically tolerable salt of the compounds of the formula I or an optionally stereoisomeric form of the compounds of the formula I, together with at least one pharmaceutically suitable and physiologically tolerable excipient, additive, active compound or auxiliary.

15. A method for the production of a pharmaceutical for the prophylaxis or therapy of disorders in whose course an increased activity of I_k B kinase is involved, comprising bringing into a suitable administration form at least one compound chosen from a compound of formula I,



(I)

a stereoisomeric form of a compound of formula I or a physiologically tolerable salt of a compound of formula I, together with a pharmaceutically suitable and physiologically tolerable excipient,

wherein B_6, B_7, B_8 and B_9 are ring atoms independently chosen from carbon atoms and nitrogen atoms and wherein B_6, B_7, B_8 and B_9 together are no more than two nitrogen atoms at the same time;

where the substituents R^1, R^2, R^3, R^4 and R^8 may be independently chosen from

1. hydrogen atom,

2. halogen,

3. -OH,

4. -CN,

5. sulfo,

6. $-NO_2$,

7. $-NH_2$,

8. alkoxy,

9. substituted amino,

10. -NH-C(O)-R^{15}, wherein R^{15} is a heterocycle having 5 to 7 ring atoms, an alkyl, an aryl, a substituted aryl or a substituted alkyl,

11. -COOH,

12. -O-R^{10}, wherein R^{10} is alkyl, substituted alkyl or aryl,

13. -C(O)-R^{12}, wherein R^{12} is alkyl, substituted alkyl or aryl,

14. -C(O)-O-R^{12}, wherein R^{12} is alkyl, substituted alkyl or aryl,

15. aryl,

16. -O-aryl,

17. substituted aryl,

18. -O-substituted aryl,

19. alkyl,

20. substituted alkyl,

21. $-CF_3$ or

22. $-CF_2-CF_3$,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,

R^5 is

1. hydrogen atom,

2. alkyl,

3. alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,

4. $-C(O)-R^9$ or

5. $-S(O)_2-R^9$, in which

R^9 is

a) alkyl,

b) alkyl radical, substituted at one or more positions by one or more of the radicals, halogen, amino or hydroxyl,

c) aryl,

d) aryl radical, substituted at one or more positions by one or more of the radicals, halogen, amino, or hydroxyl,

e) $-NH_2$,

f) alkoxy or

g) substituted amino, and

R^6 and R^7 may be independently chosen from

1. hydrogen atom,

2. halogen,

3. -OH,

4. methyl,

5. $-O-(C_1-C_{10})$-alkyl, wherein alkyl is unsubstituted or mono- to tri-substituted by substituents independently chosen from

5.1 aryl,

5.2 halogen,

5.3 -NO_2,

5.4 sulfo,

5.5 -COOH,

5.6 -NH_2,

5.7 -O-(C_1 -C_4)-alkyl or

5.8 -OH, or
6. -$N(R^{13})_2$, wherein R^{13} is independently of one another chosen from hydrogen atom, aryl, -C(O)-(C_1 -C_4)-alkyl or substituted aryl or alkyl,

wherein said -C(O)-(C_1 -C_4)-alkyl is unsubstituted or mono- or tri-substituted independently of one another as defined under 5.1 to 5.8, or
R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms.

16. The method as claimed in claim 15,

wherein

B_6, B_7, B_8, and B_9 are each a carbon atom,

R^1, R^2, R^3, R^4 and R^8 are independently chosen from

1. hydrogen atom,

2. halogen,

3. -CN,

4. -COOH,

5. -NO_2,

6. -NH_2,

7. -O-(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from

7.1 phenyl, which is unsubstituted or mono- to penta-substituted by substituents independently chosen from halogen or -O-(C_1 -C_4)-alkyl,

7.2 halogen,

7.3 $-NH_2$,

7.4 -OH,

7.5 $-COOR^{16}$, wherein R^{16} is hydogen atom or $-(C_1-C_{10})$-alkyl,

7.6 $-NO_2$,

7.7 $-S(O)_y-R^{14}$, wherein y is zero, 1 or 2, R^{14} is $-(C_1-C_{10})$-alkyl, phenyl, which phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.11, amino or $-N(R^{13})_2$,

wherein R^{13} is independently of one another chosen from hydrogen atom, phenyl, $-(C_1-C_{10})$-alkyl, $-C(O)-(C_1-C_7)$-alkyl, -C(O)-phenyl, $-C(O)-NH-(C_1-C_7)$-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, $-C(O)-O-(C_1-C_7)$-alkyl, $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined immediately above,

and wherein the R^{13} alkyl or phenyl groups in each case are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 above, or

R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 above,

7.9 a radical selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

7.10 $-(C_3-C_7)$-cycloalkyl or

7.11 =O,

8. $-N(R^{13})_2$, wherein R^{13} is as defined in 7.7 above,

9. $-NH-C(O)-R^{15}$, wherein R^{15} is

9.1 a radical selected from pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene or thiomorpholine,

wherein said radical is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 above, $-CF_3$, benzyl or by $-(C_1-C_{10})$-alkyl, wherein alkyl is mono to tri-substituted independently of one another as defined under 7.1 to 7.11 above,

9.2 -(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 above or by -O-(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 above,

9.3 -(C_3 -C_7)-cycloalkyl,

9.4 -$N(R^{13})_2$, wherein R^{13} is as defined in 7.7 above, or

9.5 phenyl, wherein phenyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 above, by -O-(C_1 -C_{10})-alkyl, by -CN, by -CF_3, by -(C_1 -C_{10})-alkyl, wherein alkyl is mono to tri-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 above, or by two substituents of the phenyl radical which form a dioxolan ring,

10. -$S(O)_y$ -R^{14}, wherein R^{14} and y are as defined in 7.7 above,

11. -C(O)-R^{12}, wherein R^{12} is phenyl or -(C_1 -C_7)-alkyl, wherein phenyl or alkyl are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 above,

12. -C(O)-O-R^{12}, wherein R^{12} is phenyl or -(C_1 -C_7)-alkyl, wherein phenyl or alkyl are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 above,

13. -(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 above,

14. -O-(C_1 -C_6)-alkyl-O-(C_1 -C_6)-alkyl,

15. -O-(C_0 -C_4)-alkyl-(C_3 -C_7)-cycloalkyl,

16. -(C_1 -C_4)-alkyl-$N(R^{13})_2$, wherein R^{13} is as defined in 7.7 above

17. -CF_3 or

18. -CF_2 -CF_3,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom,

R^5 is

1. hydrogen atom,

2. -(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.4 above,

3. -C(O)-R^9, wherein R^9 is

-NH_2, -(C_1 -C_{10})-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.4, or -$N(R^{13})_2$, wherein R^{13} is as defined in 7.7 above, or

4. $-S(O)_2-R^9$, wherein R^9 is as defined in 3 above,

or R^4 and R^5 together with the atom to which they are bonded form a heterocycle,

or R^3 and R^5 together with the atom to which they are bonded form a heterocycle containing an additional oxygen atom in the ring and

R^6 and R^7 independently of one another are chosen from hydrogen atom or methyl.

17. The method as claimed in claim 16,

wherein
B_6, B_7, B_8, and B_9 are each a carbon atom,
R^1, R^2, R^3 and R^4 independently of one another are hydrogen atom, halogen, cyano, nitro, amino, -O-(C_1 -C_7)-alkyl, phenyl, -O-phenyl, $-CF_2-CF_3$, $-CF_3$, $N(R^3)_2$,

wherein R^{13} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl, phenyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-phenyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -C_4)-alkyl, -C(O)-(C_1 -C_7)-alkyl or -(C_1 -C_{10})-alkyl, wherein alkyl, pyridyl or phenyl are unsubstituted or mono- to tri-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 of claim 16, or R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

$-S(O)_y-R^{14}$,
wherein y is zero, 1 or 2, and R^{14} is -(C_1 -C_{10})-alkyl, phenyl, which phenyl is unsubstituted or mono- to penta-substituted as defined for substituents under 7.1 to 7.11 of claim 16, amino or $-N(R^{13})_2$,

wherein R^{13} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl-C(O)-(C_1 -C_7)-alkyl, -C(O)-phenyl, C(O)-pyridyl, -C(O)-NH-(C_1 -C_4)-alkyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -C_4)-alkyl or -(C_1 -C_{10})-alkyl, wherein each alkyl is unsubstituted or mono- to tri-substituted independently of one another as defined under 7.1 to 7.11 of claim 16, or R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms, or

-C(O)-O-R^{12}, wherein R is phenyl or -(C_1 -C_7)-alkyl, wherein said phenyl or alkyl are unsubstituted or mono- to penta-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 of claim 16,

R^6, R^7 and R^8 independently of one another are hydrogen atom, methyl, amino, $-N(R^{13})_2$, wherein R^{13} is independently of one another chosen from

hydrogen atom, -(C_1 -C_7)-alkyl-C(O)-(C_1 -C_7)-alkyl, -C(O)-phenyl, C(O)-pyridyl, -C(O)-NH-(C_1 -C_4)-alkyl, -C(O)-O-phenyl, -C(O)-O-(C_1 -C_4)-alkyl or -(C_1 -C_{10})-alkyl, wherein pyridyl, alkyl or phenyl are unsubstituted or mono- to tri-substituted independently of one another as defined under 7.1 to 7.11 of claim 16, or

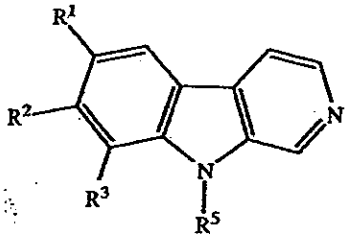
R^{13} together with nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

provided that at least one of R^1, R^2, R^3, R^4 and R^8 is not a hydrogen atom, and R^5 is as defined in claim 16.

18. A method for the production of a pharmaceutical for the prophylaxis or therapy of disorders in whose course an increased activity of I_k B kinase is involved, comprising

bringing into suitable administration form at least one compound chosen from a compound of formula II,

(II)



a stereoisomeric form of a compound of the formula II, or a physiologically tolerable salt of a compound of the formula II, together with a pharmaceutically suitable and physiologically tolerable excipient,

wherein, R^1, R^2 and R^3 are independently chosen from hydrogen atom, halogen, cyano, amino, -O-(C_1 -C_4)-alkyl, nitro, -CF_3, -CF_2 -CF_3, -$S(O)_y$ -R^{14}, wherein y is 1 or 2,

R^{14} is amino, -(C_1 -C_7)-alkyl, phenyl, which is unsubstituted or mono- to tri-substituted by substituents independently chosen from those as defined 7.1 to 7.9 of claim 16, or -$N(R^{13})_2$,

wherein R^{13} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl-C(O)-(C_1 -C_7)-alkyl, -C(O)-phenyl, -C(O)-O-phenyl, -C(O)-pyridyl, -C(O)-NH-(C_1 -C_4)-alkyl, -C(O)-O-(C_1 -C_4)-alkyl, or -(C_1 -C_{10})-alkyl, wherein pyridyl, alkyl or phenyl are unsubstituted or mono- to tri-substituted with substituents independently chosen from those as defined under 7.1 to 7.11 of claim 16, or R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms,

provided that at least one of R^1, R^2 and R^3 is not a hydrogen atom, and

R^5 is hydrogen atom, -(C_1 -C_{10})-alkyl,

wherein alkyl is unsubstituted or mono- to tri-substituted by substituents independently chosen from those as defined under 7.1 to 7.4 of claim 16, -C(O)-R^9 or -$S(O)_2$ -R^9, wherein

R^9 is -(C_1 -C_{10})-alkyl, -O-(C_1 -C_{10})-alkyl,

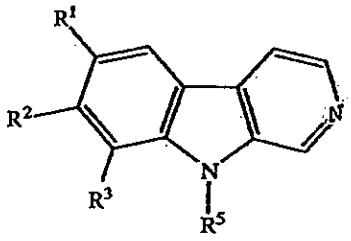
wherein alkyl is unsubstituted or mono- to tri-substituted by substituents independently chosen from those as defined under 7.1 to 7.4 of claim 16, phenyl, which is unsubstituted or mono- to tri-substituted by substituents independently chosen from those as defined under 7.1 to 7.11 of claim 16, or

wherein R^{13} is independently of one another chosen from hydrogen atom, -(C_1 -C_7)-alkyl-C(O)-(C_1 -C_7)-alkyl, -C(O)-phenyl, -C(O)-O-phenyl, -C(O)-pyridyl, -C(O)-NH-(C_1 -C_4)-alkyl, -C(O)-O-(C_1 -C_4)-alkyl, or -(C_1 -C_{10})-alkyl, wherein pyridyl, alkyl or phenyl are unsubstituted or mono- to tri-substituted with substituents independently chosen from those as defined under 7.1 to 7.11 of claim 16, or R^{13} together with the nitrogen atom to which it is bonded form a heterocycle having 5 to 7 ring atoms.

19. A method for the production of a compound for the prophylaxis or therapy of disorders in whose course an increased activity of I_k B kinase is involved, comprising

bringing into a suitable administration form at least one compound chosen from a compound of formula II,

(II)



wherein R^1, R^2 and R^3 are independently chosen from hydrogen atom, halogen, cyano, amino, -O-(C_1 -C_4)-alkyl, nitro, -CF_3 or

wherein R^{13} is independently of one another chosen from hydrogen atom, -(C_1 -C_4)-alkyl, -C(O)-(C_1 -C_7)-alkyl, -C(O)-pyridyl, -C(O)-phenyl or -C(O)-O-(C_1 -C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri-substituted by substituents independently chosen from halogen or -O-(C_1 -C_4)-alkyl, and

R^5 is hydrogen atom, -C(O)-OH_3 -, methyl, -S(O)$_2$ -CH_3, -C(O)-morpholinyl, -CH_2 -CH_2 -OH or -CH_2 -C(O)-NH_2,
provided that no more than two of R^1, R^2, R^3 and R^5 are a hydrogen atom.

20. The method as claimed in

claim 19, wherein

R^1 is bromo, -CF_3 or chloro, R^2 is hydrogen atom or O-(C_1 -C_2)-alkyl, R^3 is hydrogen atom, bromo, chloro or -N(R^{13})$_2$,

wherein R^{13} is independently of one another chosen from hydrogen atom, -C(O)-phenyl, -(C_1 -C_7)-alkyl, -C(O)-(C_1 -C_4)-alkyl or -C(O)-O-(C_1 -C_4)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to tri-substituted by substituents independently chosen from halogen or -O-(C_1 -C_2)-alkyl, and

R^5 is hydrogen atom, -C(O)-OH_3 -, methyl or -S(O)$_2$ -CH_3,

provided that no more than two of R^1, R^2, R^3 and R^5 are a hydrogen atom.

21. The method as claimed in claim 19, wherein

R^1 is chloro, R^3 is -N-C(O)-CH_2 -O-CH_3, and R^2 and R^5 are each hydrogen atom, or

R^1 is chloro, R^3 is -N-C(O)-pyridyl, wherein pyridyl is unsubstituted or substituted by chloro, R^2 is hydrogen atom or -O-OH_3 and R^5 is hydrogen atom, or

R^1 is chloro, R^3 is -N-C(O)-phenyl, wherein phenyl is mono- or di-substituted by fluoro and

R^2 and R^5 are each hydrogen atom, or

R^1 and R^3 are each chloro, R^2 is -C(O)-CH_3 and R^5 is hydrogen atom, or

R^1 and R^3 are each chloro, R^2 is -C(O)-CH_2 -CH_3 and R^5 is hydrogen atom.

22. The use of a therapeutically effective amount of at least one compound chosen from a compound of formula I as set forth in claim 1, a stereoisomeric form of a compound of the formula I, or a physiologically tolerable salt of a compound of the formula I in the manufacture of a medicament for treating a patient experiencing at least one disorder involving an increased activity of I_kB kinase.

23. The use as claimed in claim 22, wherein the at least one disorder is joint inflammation, acute synovitis, tuberculosis, atherosclerosis, muscle degeneration, cachexia, Reiter's syndrome, endotoxaemia, sepsis, septic shock, endotoxic shock, gram negative sepsis, gout, toxic shock syndrome, chronic pulmonary inflammatory diseases, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, carcinoses, leukemia, sarcomas, lymph node tumors, skin carcinoses, lymphoma, apoptosis, graft versus host reaction, allograft rejection, leprosy, infections, acquired immune deficiency syndrome (AIDS); AIDS related complex, cachexia secondary to infection or malignancy; cachexia secondary to acquired immune deficiency syndrome or to cancer; keloid and scar tissue formation; pyresis; diabetes; inflammatory bowel diseases; diseases of or injury to the brain in which over- expression of TNFα has been implicated, psoriasis, Alzheimer's disease, carcinomatous disorders, cardiac infarct, chronic obstructive pulmonary disease and acute respiratory distress syndrome.

24. The use as claimed in claim 22, wherein the disorder is a inflammation disorder chosen from arthritis and arthritic conditions.

25. The use as claimed in claim 24, wherein the disorder is arthritis or arthritic conditions chosen from rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis, and osteoarthritis.

26. The use of claim 22, wherein the disorder is chronic pulmonary inflammatory diseases chosen from asthma and adult respiratory distress syndrome.

27. The use of claim 22, wherein the disorder is an infection chosen from viral infections, parasitic infections, and yeast and fungal infections.

28. The use of claim 27, wherein the disorder is a viral infection chosen from HIV, cytomegalovirus, influenza, adenovirus and the Herpes group of viruses.

29. The use of claim 22, wherein the disorder is malaria.

30. The use of claim 29, wherein the malaria is cerebral malaria.

31. The use of claim 22, wherein the disorder is a yeast infection, fungal infection, or fever and myalgias due to infection.

32. The use of claim 22, wherein disorder is an inflammatory bowel disease chosen from Crohn's disease and ulcerative colitis.

33. The use of claim 22, wherein the disorder is a disease of or injury to the brain chosen from multiple sclerosis or head trauma.

34. The use of a therapeutically effective amount of at least one compound chosen from a compound of formula II as set forth in claim 4, a stereoisomeric form of a compound of the formula II, or a physiologically tolerable salt of a compound of the formula II in the manufacture of a medicament for treating a patient experiencing at least one disorder, wherein the at least one disorder is asthma, osteoarthritis, rheumatoid arthritis, Alzheimer's disease, carcinomatous disorders and cardiac infarct.

35. The process according to claim 9, wherein the chiral enantiomerically pure compounds are amino acids.

36. The process according to claim 10, wherein the chiral enantiomerically pure compounds are amino acids.

37. The use of claim 23, wherein the disorder is a carcinomatous disorder and the at least one compound effects potentiation of the cytotoxic therapies used to treat the carcinomatous disorder.

38. The use of claim 31, wherein the fungal infection is fungal meningitis.