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(54) Title: PHARMACEUTICAL COMBINATION COMPOSITION COMPRISING AT LEAST ONE PKC INHIBITOR AND AT LEAST ONE JAK3 KINASE INHIBITOR FOR TREATING AUTOIMMUNE DISORDERS

(57) Abrégé/Abstract:
The present invention relates to a pharmaceutical combination comprising at least one PKC inhibitor, in particular indolylmaleimide derivatives, and at least one JAK3 kinase inhibitor and the uses of such a combination e.g. in autoimmune diseases, e.g. in preventing or treating type I diabetes mellitus and disorders associated therewith, or in transplantation.

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(54) Title: PHARMACEUTICAL COMBINATION COMPOSITION COMPRISING AT LEAST ONE PKC INHIBITOR AND AT LEAST ONE JAK3 KINASE INHIBITOR FOR TREATING AUTOIMMUNE DISORDERS

(57) Abstract: The present invention relates to a pharmaceutical combination comprising at least one PKC inhibitor, in particular indolylmaleimide derivatives, and at least one JAK3 kinase inhibitor and the uses of such a combination e.g. in autoimmune diseases, e.g. in preventing or treating type I diabetes mellitus and disorders associated therewith, or in transplantation.

PHARMACEUTICAL COMBINATION COMPOSITION COMPRISING AT LEAST ONE PKC INHIBITOR AND AT LEAST ONE JAK3 KINASE INHIBITOR FOR TREATING AUTOIMMUNE DISORDERS

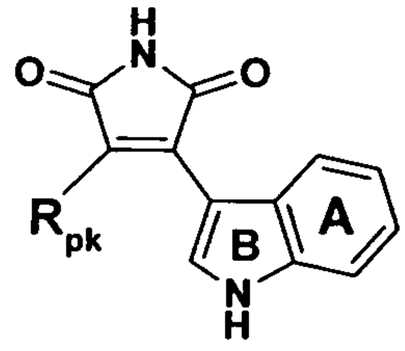
The present invention relates to a pharmaceutical combination comprising at least one PKC inhibitor, in particular indolylmaleimide derivatives, and at least one JAK3 kinase inhibitor and the uses of such a combination e.g. in autoimmune diseases, e.g. in preventing or treating type I diabetes mellitus and disorders associated therewith, or in transplantation.

The present invention further relates to a pharmaceutical combination comprising at least one and at least one JAK3 kinase inhibitor and the uses of such a combination e.g. in autoimmune diseases, e.g. in preventing or treating type I diabetes mellitus and disorders associated therewith, or in transplantation.

In spite of numerous treatment options for organ transplant and autoimmune disease patients, there remains a need for effective and safe immunosuppressive agents and a need for their preferential use in combination therapy.

It has now been found that a combination comprising at least one PKC inhibitor and a Janus Kinase 3 (JAK3) kinase inhibitor, e.g. as defined below, has a beneficial effect on autoimmune diseases, e.g. type I diabetes and the disorders associated therewith, or graft rejection.

The PKC inhibitors of the invention may be staurosporine analogues or maleimide derivatives. For example, they may be of formula I

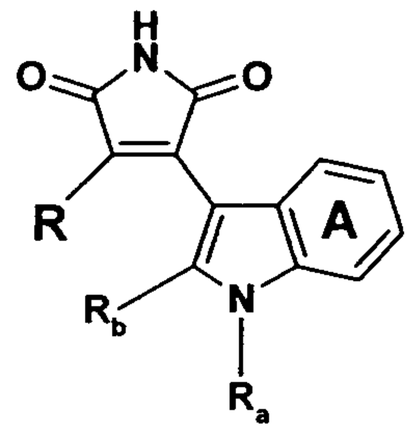


I

wherein R_{pk} is an aromatic cycle, e.g. an aromatic heterocycle, optionally fused to another cycle, e.g. another aromatic cycle, optionally an aromatic heterocycle; R_{pk} and the fused cycle being optionally substituted; and the cycles A and B being optionally substituted.

Examples of appropriate PKC inhibitors are, for example:

- Compounds as disclosed in EP1337527A1, and EP 1490355A1, e.g. a compound of formula II



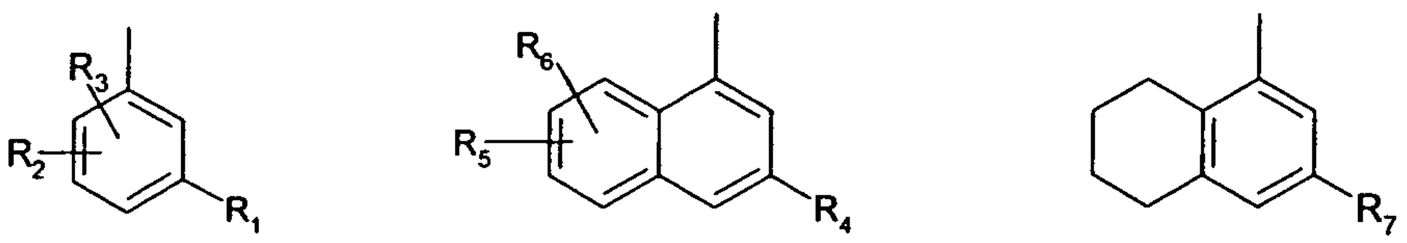
(II)

wherein

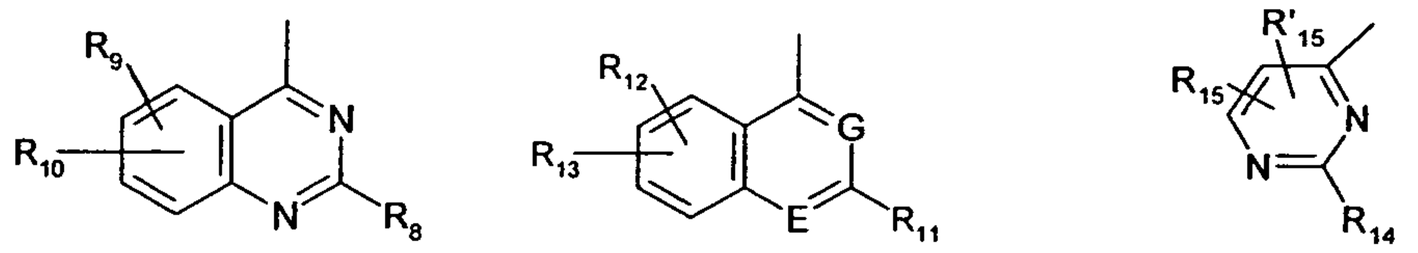
R_a is H; C_{1-4}alkyl; or C_{1-4}alkyl substituted by OH, NH_2, NHC_{1-4}alkyl or $N(di\text{-}C_{1-4}alkyl)_2$;

R_b is H; or C_{1-4}alkyl; and

R is a radical of formula (a), (b), (c), (d), (e) or (f)



(a) (b) (c)



(d) (e) (f)

wherein

each of R_1, R_4, R_7, R_8 , R_{11} and R_{14} is OH; SH; a heterocyclic residue; $NR_{16}R_{17}$ wherein each of R_{16} and R_{17}, independently, is H or C_{1-4}alkyl or R_{16} and R_{17} form together with the nitrogen atom to which they are bound a heterocyclic residue; or a radical of formula α

$$-X-R_c-Y \qquad (\alpha)$$

wherein X is a direct bond, O, S or NR_{18} wherein R_{18} is H or C_{1-4}alkyl,

R_c is C_{1-4}alkylene or C_{1-4}alkylene wherein one CH_2 is replaced by CR_xR_y wherein one of R_x and R_y is H and the other is CH_3, each of R_x and R_y is CH_3 or R_x and R_y form together $-CH_2-CH_2-$, and

Y is bound to the terminal carbon atom and is selected from OH, a heterocyclic residue and $-NR_{19}R_{20}$ wherein each of R_{19} and R_{20} independently is H, C_{3-6}cycloalkyl, C_{3-}

$_6$cycloalkyl-C_{1-4}alkyl, aryl-C_{1-4}alkyl or C_{1-4}alkyl optionally substituted on the terminal carbon atom by OH, or R_{19} and R_{20} form together with the nitrogen atom to which they are bound a heterocyclic residue;

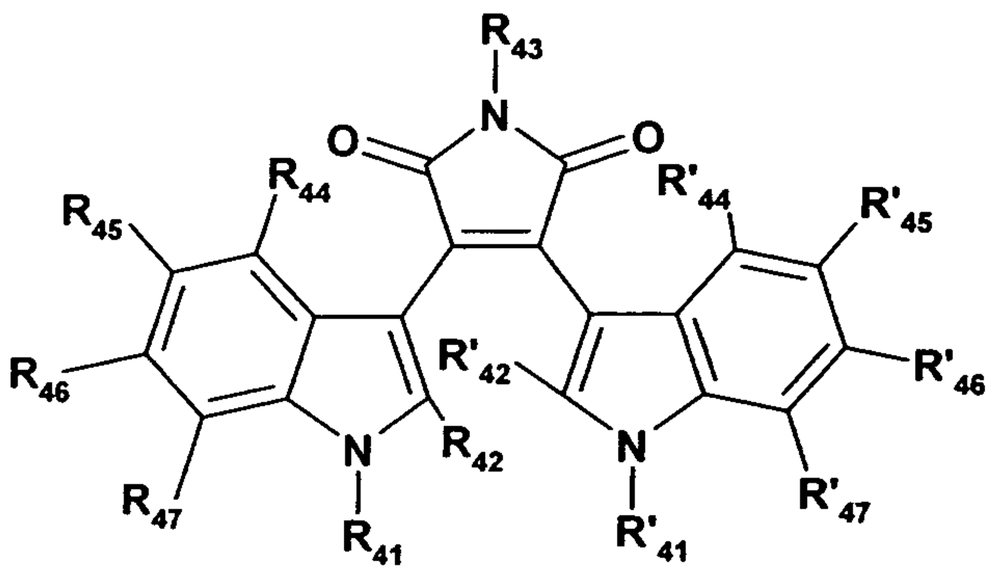
each of R_2, R_3, R_5, R_6, R_9, R_{10}, R_{12}, R_{13}, R_{15} and R'_{15}, independently, is H, halogen, C_{1-4}alkyl, CF_3, OH, SH, NH_2, C_{1-4}alkoxy, C_{1-4}alkylthio, NHC_{1-4}alkyl, $N(di\text{-}C_{1-4}alkyl)_2$ or CN;

either E is –N= and G is –CH= or E is –CH= and G is –N=; and

ring A is optionally substituted,

or a pharmaceutically acceptable salt or hydrate thereof.

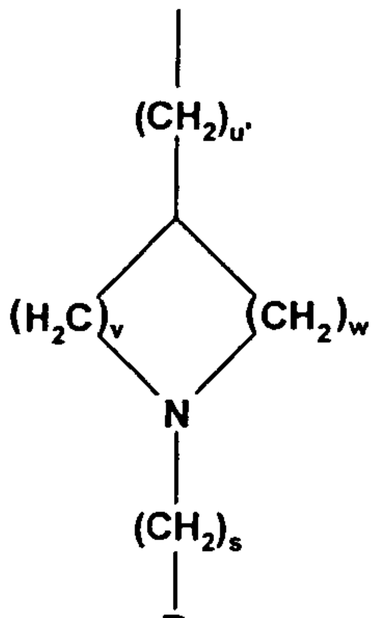
- Compounds of formula (III)



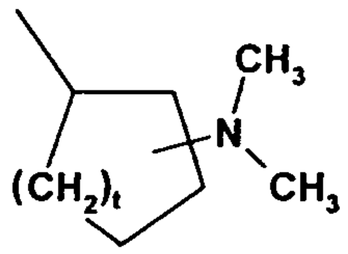
(III)

wherein

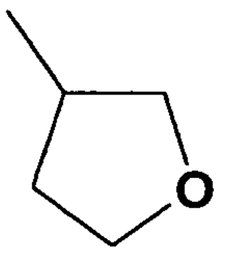
R_{41} is a group of formula (g), (h) or (i)



(g)



(h)



(i)

wherein each of v and w independently is 1, 2, 3, or 4;

s is 0, 1, 2 or 3;

t is 1 or 2;

u is 0 or 1; and

R_{412} is hydrogen, alkyl, haloalkyl, cycloalkyl, acetyl, aryl, --CH(aryl)$_2$, amino, mono-alkylamino, dialkylamino, guanidino, —C(=N(alkoxycarbonyl))NH(alkyoxycarbonyl), amidino, hydroxy, carboxy, alkoxycarbonyl or heterocyclyl;

R'_{41} is hydrogen, C_{1-4}alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl,

each of R_{42} and R'_{42}, independently, is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_3alkylthio, S(O)C_1–C_3alkyl, CF_3;

R_{43} is hydrogen or CH_3CO—; and

each of R_{44}, R'_{44}, R_{45}, R'_{45}, R_{46}, R'_{46}, R_{47} and R'_{47}, independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy, --COO(C_1–C_3alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_3alkylthio, or S(O)C_1–C_3alkyl,

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

The compounds of formula (I), (II) and (III) may be synthesized as known in the art, e.g. as described in US6,645,970 or EP1490355A1 (for compounds of formula II), EP1490355A1 (for compounds of formula II), US 5,545,636 (for compounds of formula III).

The PKC inhibitors of the invention may inhibit several isoforms of the PKC, in particular they may selectively inhibit specific PKC isoforms, i.e. be selective PKC inhibitors, i.e. isozyme-selective PKC inhibitors. Preferably, the PKC inhibitors of the invention are able to selectively inhibit PKC isoforms which are selected from the classical PKC isoforms (α, β_1, β_2, γ) and novel PKC isoforms (ε,η, δ, θ), more preferably selected from the α, β (β_1 and β_2 isoforms) and θ PKC isoforms. Preferred PKC inhibitors of the invention are able to selectively inhibit the α, β, and optionally θ, isoforms of PKC.

For example, the PKC inhibitor of the invention may possess a selectivity for one or more PKC isoforms, e.g. PKC alpha or PKC alpha, beta and optionally theta, over the other PKC isoforms of at least 20 fold, e.g. 100, 500, 1000 or 2000 fold.

The PKC inhibition activity of the PKC inhibitors of the invention may be determined in an Allogeneic Mixed Lymphocyte Reaction (MLR) assay. MLR assay can be done according to known methods, e.g. mouse of human MLR assay, e.g. as disclosed in EP1337527A1, the content regarding the MLR assay being incorporated herein by reference.

In a preferred embodiment, the PKC inhibitors of the invention show an IC_{50} value, e.g. for the α and β, and optionally θ, PKC isoforms, of 1 μM or less, preferably 10 nM or less in the hereinabove mentioned assay.

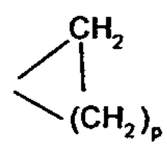
In formula II, any alkyl or alkyl moiety in e.g. alkoxy may be linear or branched. Halogen may be F, Cl, Br or I, preferably F or Cl. Any aryl may be phenyl or naphthyl, preferably phenyl.

By heterocyclic residue as R_{pk}, R_1, R_4, R_7, R_8, R_{11}, R_{14} or Y or formed, respectively, by $NR_{16}R_{17}$ or $NR_{19}R_{20}$, is meant a three to eight, preferably five to eight, membered saturated, unsaturated or aromatic heterocyclic ring comprising 1 or 2 heteroatoms, preferably selected from N, O and S, and optionally substituted.

Suitable examples of heterocyclic residue as R_1, R_4, R_7, R_8, R_{11}, R_{14} or Y or formed, respectively, by $NR_{16}R_{17}$ or $NR_{19}R_{20}$, include e.g. pyridyl, e.g. 3- or 4-pyridyl, piperidyl, e.g. piperidin-1-yl, 3- or 4-piperidyl, homopiperidyl, piperazinyl, e.g. 1-piperazinyl, homopiperazinyl, morpholin-4-yl, imidazolyl, imidazolidinyl, pyrrolyl or pyrrolidinyl, optionally substituted, e.g. mono- or polysubstituted.

Suitable examples of heterocyclic residue as R_{11} include e.g. 4,7-diaza-spiro[2.5]oct-7-yl.

When the heterocyclic residue is substituted, this may be on one or more ring carbon atoms and/or on a ring nitrogen atom when present. Examples of a substituent on a ring carbon atom include e.g. C_{1-4}alkyl e.g. CH_3;

C_{3-6}cycloalkyl e.g. cyclopropyl, optionally further substituted by C_{1-4}alkyl;  wherein p is 1,2 or 3, preferably 1; CF_3; halogen; OH; NH_2; $-CH_2-NH_2$; $-CH_2-OH$; piperidin-1-yl; or pyrrolidinyl. Examples of a substituent on a ring nitrogen atom are e.g. C_{1-6}alkyl; acyl, e.g. R'_x-CO wherein R'_x is H, C_{1-6}alkyl or phenyl optionally substituted by C_{1-4}alkyl, C_{1-4}alkoxy or amino, e.g formyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-4}alkyl; phenyl; phenyl-C_{1-4}alkyl e.g. benzyl; a heterocyclic residue, e.g. as disclosed above, e.g. an aromatic heterocyclic residue comprising 1 or 2 nitrogen atoms; or a residue of formula β

$$-R_{21}-Y' \qquad (\beta)$$

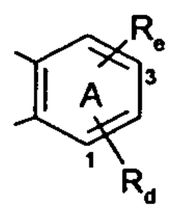
wherein R_{21} is C_{1-4}alkylene or C_{2-4}alkylene interrupted by O and Y' is OH, NH_2, $NH(C_{1-4}alkyl)$ or $N(C_{1-4}alkyl)_2$.

In formula II C_{2-4}alkylene interrupted by O may be e.g. $-CH_2-CH_2-O-CH_2-CH_2-$.

In formula II, when the substituent on a cyclic nitrogen is a heterocyclic residue, it may be a five or six membered saturated, unsaturated or aromatic heterocyclic ring comprising 1 or 2 heteroatoms, preferably selected from N, O and S. Examples include e.g. 3- or 4-pyridyl, piperidyl, e.g. piperidin-1-yl, 3- or 4-piperidyl, homopiperidyl, piperazinyl, homopiperazinyl, pyrimidinyl, morpholin-4-yl, imidazolyl, imidazolidinyl, pyrrolyl or pyrrolidinyl,

In formula II, when R_a is substituted C_{1-4}alkyl, the substituent is preferably on the terminal carbon atom.

When ring A is substituted, it may be mono- or polysubstituted, preferably monosubstituted, the substituent(s) being selected from the group consisting of e.g. halogen, OH, C_{1-4}alkoxy, e.g. OCH_3, C_{1-4}alkyl, e.g. CH_3, NO_2, CF_3, NH_2, NHC_{1-4}alkyl, N(di-C_{1-4}alkyl)$_2$ and CN. For example, ring A may be a residue of formula



wherein

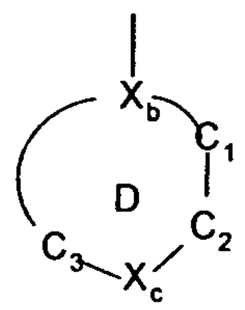
R_d is H; C_{1-4}alkyl; or halogen; and

R_e is OH; NO_2; NH_2; NHC_{1-4}alkyl; or N(di-C_{1-4}alkyl)$_2$.

Preferably R_d is in position 1; preferably R_e is in position 3.

When R_c has a CH_2 replaced by CR_xR_y, it is preferably the CH_2 bearing Y.

Examples of heterocyclic residue as R_1, R_4, R_7, R_8, R_{11}, R_{14} or Y or formed, respectively, by $NR_{16}R_{17}$ or $NR_{19}R_{20}$, include e.g. a residue of formula (γ)



wherein

the ring D is a 5, 6 or 7 membered saturated, unsaturated or aromatic ring;

X_b is –N-, -C= or –CH-;

X_c is -N=, -NR_f-, -CR_f'= or –CHR_f'- wherein R_f is a substituent as indicated above for a ring nitrogen atom, and R_f' is a substituent as indicated above for a ring carbon atom;

the bond between C_1 and C_2 is either saturated or unsaturated;

each of C_1 and C_2, independently, is a carbon atom which is optionally substituted by one or two substituents selected among those indicated above for a ring carbon atom; and

the line between C_3 and X_b and between C_1 and X_b, respectively, represents the number of carbon atoms as required to obtain a 5, 6 or 7 membered ring D.

A preferred residue of formula (γ) is one wherein the ring D forms a 1,4-piperazinyl ring optionally C- and/or N-substituted as indicated.

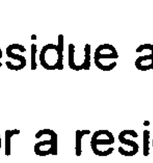
Representative examples of a residue of formula (γ) are e.g. 3- or 4- pyridyl; piperidin-1-yl; 1-N-(C_{1-4}alkyl)- or –(ω-hydroxy-C_{1-4}alkyl)-3-piperidyl; morpholin-4-yl; imidazolyl; pyrrolidinyl; 1-piperazinyl; 2-C_{1-4}alkyl- or –C_{3-6}cycloalkyl-1-piperazinyl ;3-C_{1-4}alkyl- or –C_{3-6}cycloalkyl-1-piperazinyl; 2,2- or 3,5- or 2,5- or 2,6-di(C_{1-4}alkyl)-1-piperazinyl; 3,4,5-tri-(C_{1-4}alkyl)-1-piperazinyl; 4-N-(C_{1-4}alkyl)- or -(ω-hydroxy-C_{1-4}alkyl)- or –(ω–dimethylamino-C_{1-4}alkyl)-1-piperazinyl; 4-N-pyridin-4-yl-1-piperazinyl; 4-N-phenyl- or –C_{3-6}cycloalkyl-1-piperazinyl; 4-N-(C_{1-4}alkyl)- or -(ω-hydroxy-C_{1-4}alkyl)-3-C_{1-4}alkyl- or –3,3–di(C_{1-4}alkyl)-1-piperazinyl; 4-N-(1-C_{1-4}alkyl-C_{3-6}cycloalkyl)-1-piperazinyl; 4-N-formyl-1-piperazinyl; 4-N-pyrimidin-2-yl-1-piperazinyl; 4,7-diaza-spiro[2.5]oct-7-yl or 4-N-C_{1-4}alkyl-1-homopiperazinyl.

The compounds of formulae I and II may exist in free form or in salt form, e.g. addition salts with e.g. organic or inorganic acids, for example, hydrochloric acid, acetic acid, when R_1, R_4, R_7, R_8, R_{11} or R_{14} and/or R_2, R_3, R_5, R_6, R_9, R_{10}, R_{12}, R_{13} or R_{15} comprises an optionally substituted amino group or a heterocyclic residue which can form acid addition salts.

It will be appreciated that the compounds of formula I, formula II and formula III may exist in the form of optical isomers, racemates or diastereoisomers. For example, a ring carbon atom bearing a substituent in the heterocyclic residue as R_1, R_4, R_7, R_8, R_{11}, R_{14} or Y or formed, respectively, by $NR_{16}R_{17}$ or $NR_{19}R_{20}$, is asymmetric and may have the D- or L-configuration. It is to be understood that the present invention embraces all enantiomers and their mixtures. Similar considerations apply in relation to starting materials exhibiting asymetric carbon atoms as mentioned.

In the compounds of formula II, the following significances are preferred individually or in any sub-combination:

1. R_a is H or CH_3;
2. R_b is H;
3. Ring A is unsubstituted; or is substituted by methyl in position 7;
4. Preferred heterocyclic residue as formed by $NR_{16}R_{17}$ is e.g. piperazin-1-yl optionally N-substituted, e.g. by C_{1-4}alkyl, ω-hydroxy-C_{1-4}alkyl, ω-dimethylamino-C_{1-4}alkyl, C_{5-}

$_6$cycloalkyl, C_{1-4}alkyl-C_{5-6}cycloalkyl, an aromatic heterocyclic residue comprising 1 or 2 nitrogen atoms, e.g. pyridyl or pyrimidin-2-yl, or a residue of formula β as defined above and/or optionally C-substituted, e.g. by CH_3 e.g. in positions 2, and/or 3 and/or 5 and/or 6 and/or 2,2 or 3,3 or by  , e.g. in position 2 or 3; piperidin-1-yl optionally C-substituted, e.g. in position 4, by NH_2, $-CH_2-NH_2$ or piperidin-1-yl, or in position 3, e.g. by OH or NH_2; or pyrrolidinyl optionally C-substituted in position 3 by OH or NH_2;

5. R_{18} is H or CH_3;
6. R_c is C_{1-4}alkylene or C_{1-4}alkylene wherein the terminal CH_2 is replaced by CR_xR_y whereinR$_x$ and R_y form together $-CH_2-CH_2-$;
7. X is O;
8. The radical of formula (α) is $-O-CH_2-CH_2-Y$;
9. Each of R_{19} and R_{20} is H, C_{1-4}alkyl, e.g. methyl, C_{1-4}alkyl substituted on the terminal carbon atom by OH, e.g. $-CH_2-CH_2-OH$, or cyclopropyl;
10. Preferred heterocyclic residue as formed by $NR_{19}R_{20}$ is e.g. piperazin-1-yl optionally N-substituted by C_{1-4}alkyl or a residue of formula β; piperidin-1-yl; 1-(C_{1-4}alkyl)-piperidin-3-yl; 3- or 4-pyridyl; imidazolyl; pyrrolidinyl; or morpholin-4-yl;
11. Each of R_1, R_4, R_7, R_8, R_{11} or R_{14}, independently, is 1-N-methyl-piperidin-4-yl; 4-methyl-piperazin-1-yl; 4-methyl-1-homopiperazinyl; 4-(2-hydroxyethyl)-piperazin-1-yl; or $-X'-C_{1,\ 2\ or\ 3}$-alkylene-$NR_{19}R_{20}$ wherein X' is a direct bond, O or NH;
12. In the residue of formula (a) either each of R_2 and R_3 is H or one of R_2 and R_3 is H and the other is F, Cl, CH_3, OH, OCH_3 or CF_3;
13. In the residue of formula (a) R_2 is OH;
14. In the residue of formula (b) either each of R_5 and R_6 is H or one of R_5 and R_6 is H and the other is F, Cl, CH_3, OCH_3 or CF_3;
15. In the residue of formula (b) R_4 is a radical of formula (α) or $NR_{16}R_{17}$;
16. In the residue of formula (d) either each of R_9 and R_{10} is H or one of R_9 and R_{10} is H and the other is F, Cl, CH_3, OCH_3 or CF_3; preferably R_{10} is H and R_9 is in position 5, 6, 7 or 8, preferably in position 6;
17. In the residue of formula (d), each of R_9 and R_{10} is H, R_8 is optionally substituted piperazin, e.g. R_8 is 4-methyl-piperazin-1-yl
18. In the residue of formula (e) each of R_{12} and R_{13} is H;
19. In the residue of formula (e) one of R_{12} and R_{13} is H and the other is F, Cl, CH_3, OCH_3 or CF_3;

when E is –N= and G is –CH=, preferably R_{13} is H and R_{12} is in position 6 or 7;

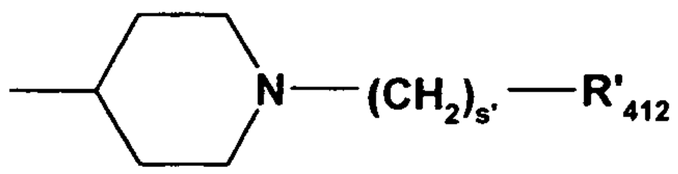
when E is –CH= and G is –N=, preferably R_{13} is H and R_{12} is in position 7;

20. In the residue of formula (e), each of R_{12} and R_{13} is H; E is –CH= and G is –N=, R_{11} is 4,7-diaza-spiro [2.5] oct-7-yl; or piperazin-1-yl substituted in position 3 by methyl or ethyl and optionally in position 4 by methyl,
21. In the residue of formula (f) R_{15} is H, CH_3 or Cl, e.g. in position 5 or 6;
22. In the residue of formula (f) R'_{15} is H or CH_3, e.g. in position 5, preferably H;
23. R is a radical of formula (d), (e) or (f).

In the compounds of formula III, the following significances are preferred:

each of R_{44}, R'_{44}, R_{45}, R'_{45}, R_{46}, R'_{46}, R_{47} and R'_{47} is hydrogen;

R_{41} is



wherein either s' is 0 and R'_{12} is hydrogen or C_{1-4}alkyl; or s' is 1 and R'_{412} is pyridyl, preferably 2-pyridyl, and

$R_{41'}$ is H; or C_{1-4}alkyl.

Preferred compounds of formula II are 3-(*1.H.*-indol-3-yl)-4-[2-(4-methyl-piperazin-1-yl)-quinazolin-4-yl]-pyrrole-2,5-dione (referred to hereinafter as Compound A), 3-(*1.H.*-indol-3-yl)-4-[2-(piperazin-1-yl)-quinazolin-4-yl]-pyrrole-2,5-dione (referred to hereinafter as Compound B) , 3-[3-(4,7-Diaza-spiro[2.5]oct-7-yl)-isoquinolin-1-yl]-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione (Compound C), in free form or in a pharmaceutically acceptable salt form, e.g. the acetate salt thereof.

Preferred compounds of formula II are 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione (Compound D), 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione (Compound E), or a pharmaceutically acceptable salt, hydrate or solvate thereof.

JAK3 is an enzyme which is primarily expressed in T and B cells and plays a critical role in T cell development and function. JAK3 kinase inhibitors are e.g. compounds having an IC_{50} value < 5 μM, preferably < 1 μM, more preferably < 0.1 μM in the following assays:

Interleukin-2 (IL-2) dependent proliferation assays with CTL/L and HT-2 cells

The IL-2 dependent mouse T cell lines CTL/L and HT-2 are cultured in RPMI 1640 (Gibco 52400-025) supplemented with 10% Fetal Clone I (HyClone), 50μM 2-mercaptoethanol (31350-010), 50μg/ml gentamycine (Gibco 15750-037), 1mM sodium pyruvate (Gibco 11360-039), non-essential amino acids (Gibco 11140-035; 100x) and 250U/ml mouse IL-2 (supernatant of X63-Ag8 transfected cells containing 50'000 U/ml mouse IL-2 according to Genzyme standard). Cultures are split twice a week 1:40.
Before use the cells are washed twice with culture medium without mouse IL-2. The proliferation assay is performed with 4000 CTL/L cells/well or 2500 HT-2 cells/well in flat-bottom 96-well tissue culture plates containing appropriate dilutions of test compounds in culture medium with 50U/ml mouse IL-2. CTL/L cultures are incubated at 37°C for 24 h and HT-2 cultures are incubated for 48 h. After addition of 1μCi ^{3}H-thymidine and a further overnight incubation cells are harvested onto fibre filters and radioactivity is counted.

Interleukin-2 dependent proliferation of human peripheral blood mononuclear cells

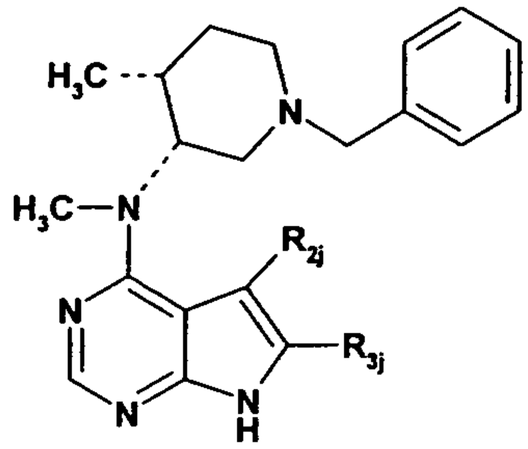
Human peripheral blood mononuclear cells are isolated on Ficoll from buffy coats with unknown HLA type (Blutspendezentrum, Kantonsspital, Basel, Switzerland). Cells are kept at 2×10^7 cells/ml (90% FCS, 10% DMSO) in cryotubes (Nunc) in liquid nitrogen until use.

The cells are incubated for four days at 37°C in a humidified CO_2 (7%) incubator in costar flasks at the concentration of 7×10^5 cells/ml in culture medium containing RPMI 1640 (Gibco, Pacely, England) supplemented with Na-pyruvate (1 mM; Gibco), MEM nonessential amino acids and vitamins (Gibco), 2-mercaptoethanol (50 μM), L-glutamine (2 mM), gentamicin and penicillin/streptomycin (100 μg/ml; Gibco), bacto asparagine (20 □g/ml; Difco), human insulin (5 □g/ml; Sigma), human transferrin (40 □g/ml; Sigma), selected fetal calf serum (10%, Hyclone Laboratories, Logan, UT) and 100 μg/ml phytohemagglutinine. Cells are washed twice in RPMI 1640 medium containing 10% FCS and incubated for 2 hours. After centrifugation the cells are taken up in the culture medium mentioned above (without phytohemagglutinine) containing interleukin-2 (Chiron 200 U/ml), distributed in triplicates into flat-bottomed 96-well tissue culture plates (Costar #3596) at a concentration of 5×10^4 cells/0.2 ml in the presence of appropriate concentrations of test compounds and

incubated at 37°C for 72 hours. ^{3}H-thymidine (1 μCi/0.2 ml) was added for the last 16 hours of culture. Subsequently cells are harvested and counted on a scintillation counter.

Suitable JAK3 kinase inhibitors include e.g.

- Compounds as disclosed in USP 2003/0073719A1, e.g. a compound of formula IV



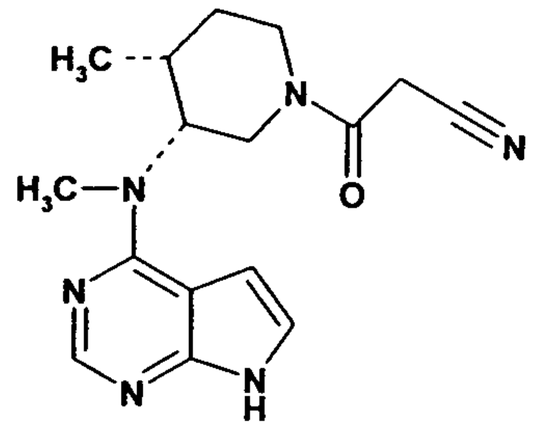
IV

wherein

each of R_{2j} and R_{3j} independently is selected from the group consisting of H, amino, halogen, OH, nitro, carboxy, C_{2-6}alkenyl, C_{2-6}alkynyl, CF_3, trifluoromethoxy, C_{1-6}alkyl, C_{1-6} alkoxy, C_{3-6}cycloalkyl wherein the alkyl, alkoxy or cycloalkyl groups are optionally substituted by one to three groups selected from halogen, OH, carboxy, amino, C_{1-6}alkylthio, C_{1-6} alkylamino, $(C_{1-6}$ alkyl$)_2$amino, C_{5-9}heteroaryl, C_{2-9}heterocycloalkyl, C_{3-9}cycloalkyl or C_{6-10}aryl; or each of R_{2j} and R_{3j} independently is C_{3-10}cycloalkyl, C_{3-10}cycloalkoxy, C_{1-6}alkylamino, $(C_{1-6}$ alkyl$)_2$amino, C_{6-10}arylamino, C_{1-6}alkylthio, C_{6-10}arylthio, C_{1-6}alkylsulfinyl, C_{6-10}arylsulfinyl, C_{1-6}alkylsulfonyl, C_{6-10}arylsulfonyl, C_{1-6}acyl, C_{1-6}alkoxy-CO-NH-, C_{1-6}alkylamino-CO-, C_{5-9}heteroaryl, C_{2-9} heterocycloalkyl or C_{6-10}aryl wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halogeno, C_{1-6}alkyl, C_{1-6}alkyl-CO-NH-, C_{1-6}alkoxy-CO-NH-, C_{1-6}alkyl-CO-NH-C_{1-6}alkyl, C_{1-6}alkoxy-CO-NH—C_{1-6}alkyl, C_{1-6}alkoxy-CO-NH—C_{1-6} alkoxy, carboxy, carboxy-C_{1-6}alkyl, carboxy-C_{1-6}alkoxy, benzyloxycarbonyl-C_{1-6}alkoxy, C_{1-6} alkoxycarbonyl-C_{1-6}alkoxy, C_{6-10}aryl, amino, aminoC_{1-6}alkyl, C_{2-7}alkoxycarbonylamino, C_{6-10} aryl-C_{2-7}alkoxycarbonylamino, C_{1-6}alkylamino, $(C_{1-6}$alkyl$)_2$amino, C_{1-6}alkylamino-C_{1-6}alkyl, $(C_{1-6}$alkyl$)_2$amino-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, carboxy, carboxy-C_{1-6}alkyl, C_{2-7}alkoxycarbonyl, C_{2-7}alkoxycarbonyl-C_{1-6}alkyl, C_{1-6}alkoxy-CO-NH-, C_{1-6}alkyl-CO-NH-, cyano, C_{5-9} hetero-cycloalkyl, amino-CO-NH-, C_{1-6}alkylamino-CO-NH-, $(C_{1-6}$alkyl$)_2$amino-CO-NH-, C_{6-10} arylamino-CO-NH-, C_{5-9}heteroarylamino-CO-NH-, C_{1-6}alkylamino-CO-NH—C_{1-6}alkyl, $(C_{1-6}$ alkyl$)_2$amino-CO-NH—C_{1-6}alkyl, C_{6-10}arylamino-CO-NH—C_{1-6}alkyl, C_{5-9}heteroarylamino-CO--NH—C_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonylaminoC_{1-6}alkyl, C_{6-10} arylsulfonyl, C_{6-10}arylsulfonylamino, C_{6-10}arylsulfonylamino-C_{1-6}alkyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonylamino-C_{1-6}alkyl, C_{5-9}heteroaryl or C_{2-9}heterocycloalkyl; for example methyl-

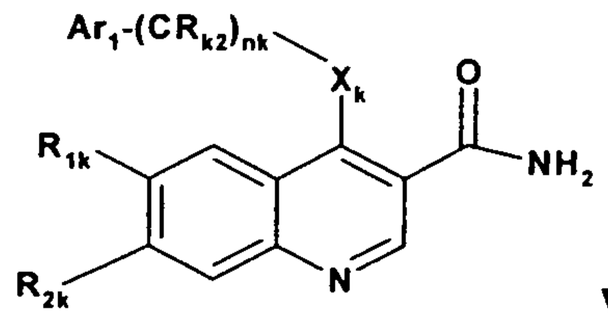
[(3R,4R)-4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine; (3R,4R)-)-4-methyl-3-[methyl-(7H-pyrrolo[2- ,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester; 3,3,3-trifluoro-1-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin- -4-yl)-amino]-piperidin-1-yl}-propan-1-one; (3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide; {(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-- yl)-amino]-piperidine-1-carbonyl}-amino)-acetic acid ethyl ester; 3-{(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile; 3,3,3-trifluoro-1-{(3R,4R)-4-methyl-3-[- methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one; 1-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-y- l)-amino]piperidin-1-yl}-but-3-yn-1-one; 1-{(3R,4R)-3-[(5-chloro-7H-pyrrol- o[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one; 1-{(3R,4R)-3-[(5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-- 4-methyl-piperidin-1-yl}-propan-1-one; (3R,4R)-N-cyano-4-methyl-3-[methyl-- (7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamidine; or (3R,4R)-N-cyano-4,N',N'-trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamidine;

- Compounds as disclosed in WO 01/042246, e.g. a compound of formula IVb



IVb

- Compounds as disclosed in WO 02/092571, e.g. a compound of formula V



V

wherein

Ar_1 is selected from phenyl, tetrahydronaphthenyl, indolyl, pyrazolyl, dihydroindenyl, 1-oxo-2,3-dihydroindenyl or indazolyl, each of which can be optionally substituted by one or more groups selected from halogen, hydroxy, cyano, C_{1-8}alkoxy, CO_2R_{8k}, $CONR_{9k}R_{10k}$, C_{1-8}alkyl-O-C_{1-8}alkyl, C_{1-8}alkyl-NR_{8k}-C_{1-8}alkyl, C_{1-8}alkyl-$CONR_8$-C_{1-8}alkyl,

C_{1-8}alkyl-$CONR_{9k}R_{10k}$, $NR_{8k}COC_{1-8}$alkyl, C_{1-8}thioalkyl, C_{1-8}alkyl (itself optionally substituted by one or more OH or cyano or fluorine) or C_{1-8}alkoxy;

X_k is NR_{3k} or O; n_k is 0 or 1;

each R_k group independently is hydrogen or C_{1-8}alkyl ;

each of R_{1k} and R_{2k} independently is selected from H, halogen, nitro, cyano, C_{1-8}alkyl, C_{1-8}alkoxy, OH, aryl, $Y_k(CR_{11k2})_{pk}NR_{4k}R_{5k}$, $Y_k(CR_{11k2})_{pk}CONR_{4k}R_{5k}Y_k(CR_{11k2})_{pk}CO_2R_{6k}$, $Y_k(CR_{11k2})_{pk}OR_{6k}$; $Y_k(C\ R_{11k2})_{pk}\ R_{6k}$; or R_{1k} and R_{2k} are linked together as –OCHO- or -OCH_2CH_2O- ;

each R_{11k} independently is H,C_{1-8}alkyl, hydroxy or halogen; p_k is 0, 1,2,3,4 or 5;

R_{3k} is H or C_{1-8}alkyl;

Y_k is oxygen, CH_2 or $NR_{7k}R_{3k}$ is hydrogen or C_{1-8}alkyl ;

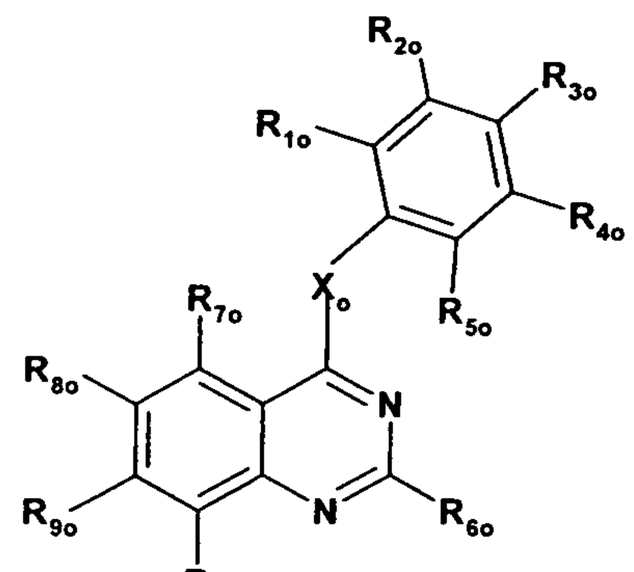
each of R_{4k} and R_{5k} independently is H, C_{1-8}alkyl or R_{4k} and R_{5k} together with the nitrogen atom to which they are attached form a 4-to 7-membered saturated or aromatic heterocyclic ring system optionally containing a further O, S or NR_{6k}, or one of R_{4k} and R_{5k} is H or C_{1-8} alkyl and the other is a 5-or 6-membered heterocyclic ring system optionally containing a further O, S or N atom;

R_{6k} is H, C_{1-8}alkyl, phenyl or benzyl;

R_{7k} is H orC_{1-8}alkyl ;

R_{8k} is H or C_{1-8}alkyl; each of R_{9k} and R_{10} independently is hydrogen or C_{1-8}alkyl;

- Compounds as disclosed in US 2002/0055514A1, e.g. a compound of formula VI



VI

wherein

X_o is NH, NR_{11o}, S, O CH_2 or $R_{11o}CH$;

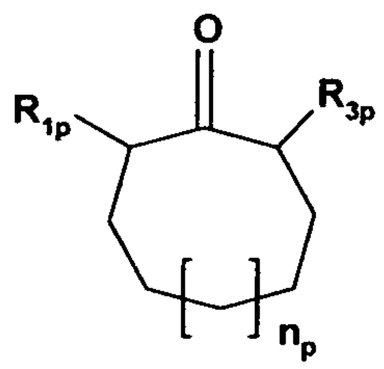
R_{11o} is H, C_{1-4}alkyl or C_{1-4}alkanoyl;

each of R_{1o} to R_{8o}, independently, is H, halogen, OH, mercapto, amino, nitro, C_{1-4}alkyl, C_{1-4}alkoxy or C_{1-4}alkylthio; wherein 2 of R_{1o}-R_{5o} together with the phenyl ring to which they are

attached may optionally form a fused ring, for example, forming a naphthyl or a tetrahydronaphthyl ring; and further wherein the ring formed by the two adjacent groups of R_{1o}-R_{5o} may optionally be substituted by 1, 2, 3 or 4 halogen, hydroxy, mercapto, amino, nitro, C_{1-4}alkyl, C_{1-4}alkoxy or C_{1-4}alkylthio; and provided that at least one of R_{2o}-R_{5o} is OH, and

each of R_{9o} and R_{10o} independently is H, halogen, C_{1-4}alkyl, C_{1-4}alkoxy or C_{1-4}alkanoyl; or R_{9o} and R_{10o} together are methylenedioxy;

- Compounds as disclosed in WO 04/052359, e.g. a compound of formula VII



VII

wherein n_p is 1,2,3,4 or 5;

R_{1p} is H, CH_3 or $CH_2N(CH_3)_2$; and

R_{3p} is $CH_2N(CH_3)_2$

in free form or in a pharmaceutically acceptable salt form.

The compounds of formulae IV to VII may exist in free or salt form. Examples of pharmaceutically acceptable salts of the compounds of the formulae IV to VI include salts with inorganic acids, such as hydrochloride, salts with organic acids, such as acetate or citric acid, or, when appropriate, salts with metals such as sodium or potassium, salts with amines, such as triethylamine and salts with dibasic amino acids, such as lysine.

When the compounds of formulae IV to VII have one or more asymmetric centers in the molecule, the present invention is to be understood as embracing the various optical isomers, as well as racemates, diastereoisomers and mixtures thereof are embraced. When the compounds of formulae IV to VII comprise a double bond, the compounds may exist as cis or trans configurations or as mixtures thereof.

In formula IV C_{6-10}aryl is phenyl or naphthyl. C_{2-9}heterocycloalkyl may be e.g. pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, pyranyl, thiopyranyl, aziridinyl, oxiranyl, methylenedioxy, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, piperidinyl, morpholinyl, piperazinyl, etc. Such a group will be attached either by a C or N atom. C_{2-9}heteroaryl may be e.g. furyl, thienyl, thiazolyl, pyrazolyl, isothizolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxadiazolyl,

thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, benzoxazolyl, benzothiazolyl, benzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzoxazinyl, etc.. Such a group will be attached either by a C or N atom.

Preferred JAK3 kinase inhibitors include e.g. N-benzyl-3,4-dihydroxy-benzylidene-cyanoacetamide α-cyano-(3,4-dihydroxy)-]N-benzylcinnamamide (Tyrphostin AG 490), prodigiosin 25-C (PNU156804), [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline] (WHI-P131), [4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline] (WHI-P154), [4-(3',5'-dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline] WHI-P97, and 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile, in free form or in a pharmaceutically acceptable salt form, e.g. mono-citrate, or a compound of formula IVb, in free form or in a pharmaceutically acceptable salt form, e.g. mono-citrate (also called CP-690,550) or a compound of formula VII.

In each case where citations of patent applications are given above, the subject matter relating to the compounds is hereby incorporated into the present application by reference. Comprised are likewise the pharmaceutically acceptable salts thereof, the corresponding racemates, diastereoisomers, enantiomers, tautomers as well as the corresponding crystal modifications of above disclosed compounds where present, e.g. solvates, hydrates and polymorphs, which are disclosed therein. The compounds used as active ingredients in the combinations of the invention can be prepared and administered as described in the cited documents, respectively. Also within the scope of this invention is the combination of more than two separate active ingredients as set forth above, i.e. a pharmaceutical combination within the scope of this invention could include three active ingredients or more.

In accordance with the particular findings of the present invention, there is provided

1. A pharmaceutical combination comprising:

   a) at least one PKC inhibitor, and

   b) at least one JAK3 kinase inhibitor.

2. A method for treating or preventing an autoimmune disease or disorder, or cell, tissue or organ graft rejection in a subject in need thereof, comprising co-administration to said subject, e.g. concomitantly or in sequence, of a therapeutically effective amount of at least one PKC inhibitor, and preferably at least one JAK3 kinase inhibitor, e.g. as disclosed above.

Examples of autoimmune diseases include e.g. sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, obstructive airways disease, incluading conditions such as asthma, intrinsic asthma, extrinsic asthma, dust asthma, particularly chronic or inveterate asthma (for example late asthma and airway hyperreponsiveness), bronchitis, including bronchial asthma, infantile asthma, allergic rheumatoid arthritis, systemic lupus erythematosus, nephrotic syndrome lupus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes mellitus and complications associated therewith, type II adult onset diabetes mellitus, uveitis, nephrotic syndrome, steroid dependent and steroid-resistant nephrosis, palmoplantar pustulosis, allergic encephalomyelitis, glomerulonephritis, psoriasis, psoriatic arthritis, atopic eczema (atopic dermatitis), contact dermatitis and further eczematous dermatitises, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, acne, alopecia areata, eosinophilic fasciitis, atherosclerosis, conjunctivitis, keratoconjunctivitis, keratitis, vernal conjunctivitis, uveitis associated with Behcet's disease, herpetic keratitis, conical cornea, dystorphia epithelialis corneae, keratoleukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' ophthalmopathy, severe intraocular inflammation, inflammation of mucosa or blood vessels such as leukotriene B4-mediated diseases, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel disease, inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis), necrotizing enterocolitis, renal diseases including interstitial nephritis, Goodpasture's syndrome hemolytic uremic syndrome and diabetic nephropathy, nervous diseases selected from multiple myositis, Guillain-Barre syndrome, Meniere's disease and radiculopathy, collagen disease including scleroderma, Wegener's granuloma and Sjogren' syndrome, chronic autoimmune liver diseases including autoimmune hepatitis, primary biliary cirrhosis and sclerosing cholangitis), partial liver resection, acute liver necrosis (e.g. necrosis caused by toxins, viral hepatitis, shock or anoxia), B-virus hepatitis, non-A/non-B hepatitis and cirrhosis, fulminant hepatitis, pustular psoriasis, Behcet's disease, active chronic hepatitis, Evans syndrome, pollinosis, idiopathic hypoparathyroidism, Addison disease, autoimmune atrophic gastritis, lupoid hepatitis, tubulointerstitial nephritis, membranous nephritis, amyotrophic lateral sclerosis or rheumatic fever.

By graft rejection is meant acute or chronic rejection of cells, tissue or solid organ allo- or xenografts of e.g. pancreatic islets, stem cells, bone marrow, skin, muscle, corneal tissue, neuronal tissue, heart, lung, combined heart-lung, kidney, liver, bowel, pancreas, trachea or

oesophagus, or graft-versus-host diseases. Chronic rejection may also be named graft vessel diseases or graft vasculopathies.

3. A pharmaceutical combination as defined under 1) above, e.g. in the form of a kit which may further comprise instructions for the administration, e.g. for use in a method as defined under 2) above.

4. A pharmaceutical combination as defined under 1) above for use in the preparation of a medicament for use in a method as defined under 2) above.

Utility of the combination of the invention in a method as hereinabove specified, may be demonstrated in animal test methods as well as in clinic, for example in accordance with the methods hereinafter described.

A. Rat Heart transplantation

The strain combination used: Male Lewis (RT^1 haplotype) and BN (RT^1 haplotype). The animals are anaesthetised using inhalational isofluorane. Following heparinisation of the donor rat through the abdominal inferior vena cava with simultaneous exsanguination via the aorta, the chest is opened and the heart rapidly cooled. The aorta is ligated and divided distal to the first branch and the brachiocephalic trunk is divided at the first bifurcation. The left pulmonary artery is ligated and divided and the right side divided but left open. All other vessels are dissected free, ligated and divided and the donor heart is removed into iced saline.

The recipient is prepared by dissection and cross-clamping of the infra-renal abdominal aorta and vena cava. The graft is implanted with end-to-side anastomoses, using 10/0 monofilament suture, between the donor brachiocephalic trunk and the recipient aorta and the donor right pulmonary artery to the recipient vena cava. The clamps are removed, the graft tethered retroabdominally, the abdominal contents washed with warm saline and the animal is closed and allowed to recover under a heating lamp. Graft survival is monitored by daily palpation of the beating donor heart through the abdominal wall. Rejection is considered to be complete when heart beat stops. Increases of graft survival are obtained in animals treated with a combination according to the invention, e.g. a combination of Compound A, e.g. in acetate salt form, and the compound CP-690,550 in the mono-citrate salt form, each component of the combination being administered orally at a daily dose of 0.1 to 50 mg/kg. Thus Compound A in the acetate form, when administered at a dose of 1 to 30 mg/kg/day, and CP-690,550 mono-citrate, when administered at an EC_{50} (drug

concentration in blood at which 50% of the animals maintain their graft for >28 days) of 60 ng/ml, significantly increase the graft survival.

B. Combined Treatment

Suitable clinical studies are, for example, open label, dose escalation studies in patients with psoriasis or multiple sclerosis. Such studies prove in particular the synergism of the active ingredients of the combination of the invention. The beneficial effects on psoriasis or multiple sclerosis can be determined directly through the results of these studies which are known as such to a person skilled in the art. Such studies are, in particular, suitable to compare the effects of a monotherapy using the active ingredients and a combination of the invention. Preferably, the dose of agent (a) is escalated until the Maximum Tolerated Dosage is reached, and agent (b) is administered with a fixed dose. Alternatively, the agent (a) is administered in a fixed dose and the dose of agent (b) is escalated. Each patient receives doses of the agent (a) either daily or intermittent. The efficacy of the treatment can be determined in such studies, e.g., after 12, 18 or 24 weeks by evaluation of symptom scores every 6 weeks.

Alternatively, a placebo-controlled, double blind study can be used in order to prove the benefits of the combination of the invention mentioned herein, e.g. in transplantation of an organ, tissue or cells, e.g. Langerhans islet cells.

The administration of a pharmaceutical combination of the invention results not only in a beneficial effect, e.g. a synergistic therapeutic effect, e.g. with regard to alleviating, delaying progression of or inhibiting the symptoms, but also in further surprising beneficial effects, e.g. fewer side-effects, an improved quality of life or a decreased morbidity, compared with a monotherapy applying only one of the pharmaceutically active ingredients used in the combination of the invention.

A further benefit is that lower doses of the active ingredients of the combination of the invention can be used, for example, that the dosages need not only often be smaller but are also applied less frequently, which may diminish the incidence or severity of side-effects. This is in accordance with the desires and requirements of the patients to be treated.

The terms “co-administration” or “combined administration” or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

It is one objective of this invention to provide a pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against graft rejection or autoimmune diseases or disorders associated therewith comprising a combination of the invention. In this composition, agent a) and agent (b) may be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination.

The pharmaceutical compositions for separate administration of agent a) and agent b) or for the administration in a fixed combination, i.e. a single galenical composition comprising at least two combination partners a) and b), according to the invention may be prepared in a manner known per se and are those suitable for enteral, e.g. oral, and parenteral administration to mammals (warm-blooded animals), including humans, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone, e.g. as indicated above, or in combination with one or more pharmaceutically acceptable carriers or diluents, especially suitable for enteral or parenteral application.

Suitable pharmaceutical compositions contain, for example, from about 0.1 % to about 99.9%, preferably from about 1 % to about 60 %, of the active ingredient(s). Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets, tablets, capsules or suppositories, or ampoules. If not indicated otherwise, these are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of a combination partner contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can be reached by administration of a plurality of dosage units.

In particular, a therapeutically effective amount of each of the combination partner of the combination of the invention may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination. For example, the method of preventing or treating graft rejection or autoimmune diseases according to the invention may comprise (i) administration of the first agent a) in free or pharmaceutically acceptable salt form and (ii) administration of an agent b) in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, e.g. in daily or intermittently dosages corresponding to the amounts described herein. The individual

combination partners of the combination of the invention may be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Furthermore, the term administering also encompasses the use of a pro-drug of a combination partner that convert *in vivo* to the combination partner as such. The instant invention is therefore to be understood as embracing all such regimens of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

The effective dosage of each of the combination partners employed in the combination of the invention may vary depending on the particular compound or pharmaceutical composition employed, the mode of administration, the condition being treated, the severity of the condition being treated. Thus, the dosage regimen of the combination of the invention is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the single active ingredients required to alleviate, counter or arrest the progress of the condition. Optimal precision in achieving concentration of the active ingredients within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites.

Daily dosages for agent a) or b) or will, of course, vary depending on a variety of factors, for example the compound chosen, the particular condition to be treated and the desired effect. In general, however, satisfactory results are achieved on administration of agent a) at daily dosage rates of the order of about 0.1 to about 100 mg/kg per day, as a single dose or in divided doses. The PKC inhibitor, e.g. a compound of formulae I to III, e.g. Compound A, B, C, D or E, may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. An indicated daily dosage for oral administration in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 2000 mg active ingredient, e.g. Compound A, B, C, D or E, conveniently administered, for example, in divided doses up to four times a day or in retard form.

Agent b), e.g. CP-690,550 or a compound of formula XVII, may be administered to a human in a daily dosage range of 0.5 to 1000 mg. Suitable unit dosage forms for oral administration comprise from ca. 0.1 to 500 mg active ingredient, together with one or more pharmaceutically acceptable diluents or carriers therefor.

The administration of a pharmaceutical combination of the invention results not only in a beneficial effect, e.g. a synergistic therapeutic effect, e.g. with regard to inhibiting graft rejection in transplanted patients or slowing down or arresting autoimmune disorders, but also in further surprising beneficial effects, e.g. less side-effects, an improved quality of life or a decreased morbidity, compared to a monotherapy applying only one of the pharmaceutically active ingredients used in the combination of the invention.
A further benefit is that lower doses of the active ingredients of the combination of the invention can be used, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side-effects. This is in accordance with the desires and requirements of the patients to be treated.

A preferred combination is the combination of compound A, B, C, D or E, preferably compound A, even more preferably compound A in form of acetate salt, with CP-690,555 monocitrate.

CLAIMS:

1. A pharmaceutical combination comprising:

a) at least one PKC inhibitor, and

b) at least one JAK3 kinase inhibitor.

2. A pharmaceutical combination according to claim 1 wherein agent a) is a PKC inhibitor selected from a compound of formulae I and II as hereinabove described, a pharmaceutically acceptable salt or hydrate thereof, a compound of formula III as hereinabove described, a pharmaceutically acceptable salt, hydrate or solvate thereof.

3. A pharmaceutical combination according to claim 1 or 2 wherein agent b) is a JAK3 kinase inhibitor having an IC_{50} value < 5 μM in the IL-2 dependent proliferation assay with CTL/L and HT-2 cells and in the IL-2 dependent proliferation assay of human peripheral blood mononuclear cells.

4. A pharmaceutical combination according to claim 1 wherein agent b) is selected from a compound of formulae IV to VII as hereinabove described, or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical combination according to claim 1 wherein the agent a) is 3-(*1.H.*-indol-3-yl)-4-[2-(4-methyl-piperazin-1-yl)-quinazolin-4-yl]-pyrrole-2,5-dione; 3-(*1.H.*-indol-3-yl)-4-[2-(piperazin-1-yl)-quinazolin-4-yl]-pyrrole-2,5-dione; or 3-[3-(4,7-Diaza-spiro[2.5]oct-7-yl)-isoquinolin-1-yl]-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione, in free form or in a pharmaceutically acceptable salt form or in hydrate form; 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or a pharmaceutically acceptable salt, hydrate or solvate thereof; preferably wherein the agent a) is the acetate salt of 3-(*1.H.*-indol-3-yl)-4-[2-(4-methyl-piperazin-1-yl)-quinazolin-4-yl]-pyrrole-2,5-dione.

6. A pharmaceutical combination according to claim 1 or 5 wherein the JAK3 kinase inhibitor b) is 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile or a compound or formula XVII as defined in claim 5, in free form or in a pharmaceutically acceptable salt form.

7. A pharmaceutical combination according to claim 1 or 5 wherein the JAK3 kinase inhibitor b) is CP-690,550 in free form or in a pharmaceutically acceptable salt form.

8. A pharmaceutical combination according to claim 1 for use in a method for treating or preventing an autoimmune disease or disorder, or cell, tissue or organ graft rejection.

9. A pharmaceutical combination according to claim 1 for use in the preparation of a medicament or a kit for treating or preventing an autoimmune disease or disorder, or cell, tissue or organ graft rejection.

10. A method for treating or preventing an autoimmune disease or disorder, or cell, tissue or organ graft rejection in a subject in need thereof, comprising co-administration to said subject, e.g. concomitantly or in sequence, of a therapeutically effective amount of at least one PKC inhibitor and at least one JAK3 kinase inhibitor.