



(11) **EP 1 443 927 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention
of the grant of the patent:
10.01.2007 Bulletin 2007/02

(21) Application number: **02789471.6**

(22) Date of filing: **06.11.2002**

(51) Int Cl.:
A61K 31/4439 ^(2006.01) **A61P 35/00** ^(2006.01)

(86) International application number:
PCT/US2002/035645

(87) International publication number:
WO 2003/039545 (15.05.2003 Gazette 2003/20)

(54) **CARBOLINE DERIVATIVES AS INHIBITORS OF IKB IN THE TREATMENT OF MULTIPLE MYELOMA**

CARBOLINE DERIVATE ALS IKB-INHIBITOREN ZUR BEHANDLUNG DES MULTIPLEN MYELOMAS

DERIVES DE CARBOLINE EN TANT QU'INHIBITEURS D'IKB DANS LE CADRE DU TRAITEMENT DU MYELOME MULTIPLE

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
IE IT LI LU MC NL PT SE SK TR**

(30) Priority: **07.11.2001 US 344911 P**

(43) Date of publication of application:
11.08.2004 Bulletin 2004/33

(73) Proprietor: **MILLENNIUM PHARMACEUTICALS,
INC.
Cambridge,
Massachusetts 02139 (US)**

(72) Inventors:
• **ADAMS, Julian
Brooklin, MA 02146 (US)**
• **ANDERSON, Kenneth C
Wellesley, MA 02482 (US)**

(74) Representative: **Hall, Robert Leonard
Harrison Goddard Foote
Fountain Precinct
Balm Green
Sheffield S1 2JA (GB)**

(56) References cited:
**WO-A-01/68648 WO-A-99/65449
DE-A- 19 807 993 DE-A- 19 951 360
GB-A- 2 303 627**

- **KOBAYASHI J ET AL: "EUDISTOMINS A D G H I
J M N O P AND Q BROMO-BETA CARBOLINES
HYDROXY BETA CARBOLINE PYRROLYL-BETA
CARBOLINE AND 1 PYRROLINYL BETA
CARBOLINES FROM THE ANTI VIRAL
CARIBBEAN TUNICATE EUDISTOMA-
OLIVACEUM" JOURNAL OF THE AMERICAN
CHEMICAL SOCIETY, vol. 106, no. 5, 1984, pages
1526-1528, XP002234219 ISSN: 0002-7863**
- **RINEHART K L JR ET AL: "EUDISTOMINS C E K
AND L POTENT ANTI VIRAL COMPOUNDS
CONTAINING A NOVEL OXATHIA ZEPINE RING
FROM THE CARIBBEAN TUNICATE
EUDISTOMA-OLIVACEUM" JOURNAL OF THE
AMERICAN CHEMICAL SOCIETY, vol. 106, no. 5,
1984, pages 1524-1526, XP002234220 ISSN:
0002-7863**

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 443 927 B1

Description

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to the treatment of cancer. In particular, the invention relates to the use of inhibitors I κ B kinase to inhibit the growth of a cancer cell and for the treatment of multiple myeloma.

Background of the Invention

[0002] The transcription factor NF- κ B is a member of the Rel protein family, and is typically a heterodimer composed of p50 and p65 subunits. NF- κ B is constitutively present in the cytosol, and is inactivated by its association with one of the I κ B family of inhibitors. Palombella *et al.*, WO 95/25533, teaches that the ubiquitin-proteasome pathway plays an essential role in the regulation of NF- κ B activity, being responsible both for processing of p105 to p50 and for the degradation of the inhibitor protein I κ B α . Chen *et al.*, *Cell* 84:853 (1996), teaches that prior to degradation, I κ B α undergoes selective phosphorylation at serine residues 32 and 36 by the multisubunit I κ B kinase complex (IKK). Once phosphorylated, I κ B is targeted for ubiquitination and degradation by the 26S proteasome, allowing translocation of NF- κ B into the nucleus, where it binds to specific DNA sequences in the promoters of target genes and stimulates their transcription.

[0003] Ritzeler *et al.*, WO 01/68648, discloses a series of beta-carboline compounds with I κ B kinase inhibitory activity. Rinehart *et al.*, U.S. Patent No. 4,631,149, discloses beta-carboline compounds useful as antiviral, antibacterial, and antitumor agents.

[0004] The protein products of genes under the regulatory control of NF- κ B include cytokines, chemokines, cell adhesion molecules, and proteins mediating cellular growth and control. Importantly, many of these proinflammatory proteins also are able to act, either in an autocrine or paracrine fashion, to further stimulate NF- κ B activation. In addition, NF- κ B plays an important role in the growth of normal and malignant cells. Baldwin, *J. Clin. Invest.*, 107:241 (2001), teaches that NF- κ B promotes cell growth by upregulating cyclin D transcription, with associated hyperphosphorylation of Rb, G1 to S-phase transition, and inhibition of apoptosis. Bargou *et al.*, *J. Clin. Invest.*, 100:2961 (1997), teaches that NF- κ B is constitutively activated in Hodgkin's disease, and inhibition of NF- κ B blocks growth of these lymphoma cells. Furthermore, Mayo *et al.*, *Science* 278:1812 (1997), teaches that inhibition of NF- κ B via expression of the super-repressor of I κ B α induces apoptosis in cells expressing the oncogenic allele of H-Ras.

[0005] Read *et al.*, *Immunity* 2:493-506 (1995), teaches that proteasome-mediated activation of NF- κ B is required for expression of cell adhesion molecules, such as E-selectin, ICAM-1, and VCAM-1. Zetter, *Seminars in Cancer Biology* 4:219-229 (1993), teaches that cell adhesion molecules are involved in tumor metastasis and angiogenesis *in vivo*, by directing the adhesion and extravasation of tumor cells to and from the vasculature to distant tissue sites within the body. Moreover, Beg and Baltimore, *Science* 274:782 (1996), teaches that NF- κ B is an anti-apoptotic controlling factor, and that inhibition of NF- κ B activation makes cells more sensitive to environmental stress and cytotoxic agents.

[0006] Multiple myeloma is a B-cell malignancy of the plasma cells. It represents the second most common hematological malignancy, with non-Hodgkin's lymphoma being the most common. The annual incidence in the United States (US) is about four per 100,000, and rates in northern Europe are similar to the US. Greenlee *et al.*, *CA Cancer J Clin* 50:7-33 (2000) discloses that approximately 13,600 cases of multiple myeloma are diagnosed each year with ~11,200 deaths per year due to the disease, representing ~2% of all cancer deaths. Multiple myeloma is one of only three cancer types to show increased mortality rates for both men and women (increases of 5.6 and 3.8%, respectively) during the period 1991-1995.

[0007] Multiple myeloma results from the clonal proliferation of plasma cells arising in the lymph nodes and "homing" to the bone marrow where these cells localize and proliferate. The disease is characterized by marrow plasma cell tumors and overproduction of a patient-specific intact monoclonal immunoglobulin heavy and/or light chain (paraprotein or M-protein). Plasma cell tumors produce immunoglobulin G (IgG) in about 53% of myeloma patients and immunoglobulin A (IgA) in about 25%; 40% of these IgG and IgA patients also have Bence Jones proteinuria. Light chain myeloma is found in 15 to 20% of patients; their plasma cells secrete only free monoclonal light chains (κ or λ Bence Jones protein), and serum M-components are usually absent on electrophoresis. Immunoglobulin D (IgD) myeloma accounts for about 1% of cases. Only a few cases of immunoglobulin E (IgE) myeloma have been reported. The production of an easily detectable paraprotein in the blood and/or urine is a convenient marker for the tumor burden in most of these patients.

[0008] Multiple myeloma, unless successfully treated, leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), anemia, renal failure, and, less commonly, neurological complications and hyperviscosity. Anderson *et al.*, *Semin. Hematol.* 36:3 (1999), teaches that patients may initially respond to cytotoxic chemotherapy and/or steroids, but they ultimately suffer from resistant disease. This cancer remains incurable. Raje and Anderson, *New Eng J Med* 341:

1606-1609 (1999) states that the five-year survival rate for patients with multiple myeloma has remained at 29% "for more than four decades".

[0009] Vidriales MB and Anderson KC, *Molec. Med. Today* 2(1):425-431 (1996), suggests that there are complex controls on the growth of the myeloma tumor cell mass in the bone marrow, with influences from the microenvironment of the bone marrow and the production of cytokines by the malignant cell and bone marrow stromal cells. IL-6 is a critical growth factor for the myeloma cell and also inhibits apoptosis in myeloma cells. Chauhan *et al.*, *Blood*, 87:1104 (1996), teaches that adhesion of myeloma cells to the bone marrow stromal cells (BMSCs) induces NF- κ B dependent upregulation of IL-6 transcription and perpetuates further myeloma cell proliferation. Furthermore, Hideshima *et al.*, *Oncogene* 20: 4519 (2001), teaches that multiple myeloma cells secrete TNF α , which induces activation of I κ B-NF- κ B in BMSCs, and thereby directly upregulates IL-6 transcription and secretion in BMSCs. The reference also teaches that TNF α -induced I κ B-NF- κ B activation results in upregulation of ICAM-1 (CD54) and VCAM-1 (CD106) expression on both MM cells and BMSCs, resulting in an increase in MM-BMSC binding. Consistent with the role for NF- κ B in multiple myeloma suggested by these references, Feinman R *et al.*, *Blood* 93:3044 (1999) teaches that elevated levels of NF- κ B activity are found in relapsing multiple myeloma.

[0010] DE 198 07 993 A1, discloses that diseases mediated by tumor necrosis factor- α (TNF- α) can be treated using beta -carboline derivatives (I), i.e. harmine or its derivatives.

[0011] DE 199 51360 A1, discloses compounds which are suitable for the production of medicaments for the prophylaxis and treatment of disease states, the course of which involves increased NF κ B activity. The compounds are specific I κ B-kinase inhibitors.

[0012] WO 99/ 65449, discloses pharmaceutical compositions of salicylanilide inhibitors of transcription factor NF-kappa B, and methods for treating diseases in which activation of NF- kappa B is implicated.

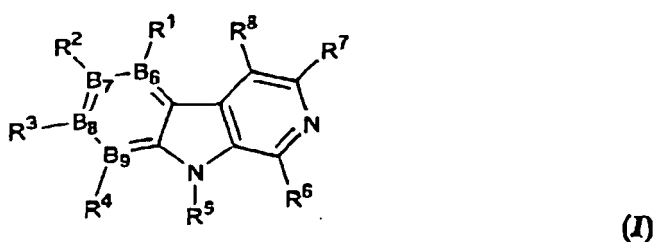
[0013] GB 2 303 627 A, discloses a novel platinum complex of the beta-carboline alkaloid (harmine) and its use for treating malignant tumors in animals.

[0014] Thus, there remains a need to identify inhibitors of NF- κ B that are effective for the treatment of multiple myeloma.

BRIEF SUMMARY OF THE INVENTION

[0015] The present inventors have discovered that specific inhibition of I κ B kinase (IKK) inhibits cancer cell growth, inhibits the NF- κ B-mediated upregulation of adhesion molecule expression on cancer cells, and inhibits intercellular adhesion. Furthermore, inhibition of IKK blocks the protective effect of IL-6 against drug-induced apoptosis.

[0016] In a first aspect therefore, the invention provides the use of an inhibitor of I κ B kinase as described herein in the manufacture of a medicament for the treatment of multiple myeloma. In a first embodiment, the inhibitor of I κ B kinase is a compound of formula (I)



or a stereoisomer or physiologically tolerable salt thereof, wherein:

B₆, B₇, B₈, and B₉ are independently selected from the group consisting of carbon atom and nitrogen atom, where a total of no more than two of B₆, B₇, B₈, and B₉ are nitrogen atoms; and in case a):

the substituents R¹, R² and R³ independently of one another are

- 1.1. hydrogen atom,
- 1.2. halogen,
- 1.3. -CN,
- 1.4. -COOH,

1.5. -NO₂,

1.6. -NH₂,

1.7. -O-(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of

1.7.1 phenyl, which is unsubstituted or mono- to pentasubstituted by halogen or -O-(C₁-C₄)-alkyl,

1.7.2 halogen,

1.7.3 -NH₂,

1.7.4 -OH,

1.7.5 -COOR¹⁶, wherein R¹⁶ is hydrogen atom or -(C₁-C₁₀)-alkyl,

1.7.6 -NO₂,

1.7.7 -S(O)_y-R¹⁴, wherein y is zero, 1 or 2, and R¹⁴ is -(C₁-C₁₀)-alkyl, phenyl, which is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, amino or -N(R¹³)₂,

wherein each R¹³ independently is hydrogen atom, phenyl, -(C₁-C₁₀)-alkyl, -C(O)-(C₁-C₇)-alkyl, -C(O)-phenyl, -C(O)-NH-(C₁-C₇)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C₁-C₇)-alkyl, or -S(O)_y-R¹⁴, wherein R¹⁴ and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, or

the two R¹³ groups, together with the nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms,

1.7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11,

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

1.7.10 -(C₃-C₇)-cycloalkyl or

1.7.11 =O,

1.8. -N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above,

1.9. -NH-C(O)-R¹⁵, wherein R¹⁵ is

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

wherein said radical is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -CF₃, benzyl, and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

1.9.2 -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above and -O-(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

1.9.3 $-(C_3-C_7)\text{-cycloalkyl}$,

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 with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, $-O-(C_1-C_{10})\text{-alkyl}$, $-\text{CN}$, $-\text{CF}_3$, and $-(C_1-C_{10})\text{-alkyl}$, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, or two substituents of the phenyl radical together form a dioxolane 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 $-(C_1-C_7)\text{-alkyl}$, wherein alkyl or phenyl are unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents 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. $-(C_1-C_{10})\text{-alkyl}$, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

1.14. $-O-(C_1-C_6)\text{-alkyl}-O-(C_1-C_6)\text{-alkyl}$,

1.15. $-O-(C_0-C_4)\text{-alkyl}-(C_3-C_7)\text{-cycloalkyl}$,

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

1.17. $-\text{CF}_3$ or

1.18. $-\text{CF}_2-\text{CF}_3$;

R^4 is

1. $-(C_1-C_{10})\text{-alkyl}$, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

2. $-\text{CF}_3$,

3. $-\text{CF}_2-\text{CF}_3$,

4. $-\text{CN}$,

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

6. $-\text{NH}_2$,

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

7.1 phenyl, which is unsubstituted or mono- to pentasubstituted by halogen or $-O-(C_1-C_4)\text{-alkyl}$,

7.2 halogen,

7.3 $-\text{NH}_2$,

7.4 $-\text{OH}$,

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

7.6 -NO₂,

7.7 -S(O)_y-R¹⁴, wherein y is zero, 1 or 2, R¹⁴ is -(C₁-C₁₀)-alkyl, phenyl, which is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, amino, and -N(R¹³)₂, wherein each R¹³ independently is hydrogen atom, phenyl, -(C₁-C₁₀)-alkyl, -C(O)-(C₁-C₇)-alkyl, -C(O)-phenyl, -C(O)-NH-(C₁-C₇)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C₁-C₇)-alkyl, or -S(O)_y-R¹⁴, wherein R¹⁴ and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, or the two R¹³ groups, together with the nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms,

7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

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

7.10 -(C₃-C₇)-cycloalkyl or

7.11 =O,

8. -N(R¹⁷)₂, wherein each R¹⁷ independently is hydrogen atom, phenyl, -(C₁-C₁₀)-alkyl, -C(O)-(C₁-C₇)-alkyl, -C(O)-phenyl, -C(O)-NH-(C₁-C₇)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C₁-C₇)-alkyl, or -S(O)_y-R¹⁴, wherein R¹⁴ and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, or the two R¹⁷ groups, together with the nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms,

9. -NH-C(O)-R¹⁵, wherein R¹⁵ is

9.1 a radical selected from the group consisting of pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene, and thiomorpholine, wherein said radical is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -CF₃, benzyl and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

9.2 -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -O-(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

9.3 -(C₃-C₇)-cycloalkyl,

9.4 -N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above provided that -N(R¹³)₂ is not -NH₂, or

9.5 phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -O-(C₁-C₁₀)-alkyl, -CN, -CF₃, and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, or two substituents of the phenyl radical form a dioxolane ring,

10. -C(O)-R¹², wherein R¹² is phenyl or -(C₁-C₇)-alkyl, wherein alkyl or phenyl are mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

11. -C(O)-O-R¹², wherein R¹² is as defined in 10. above,

12. -O-(C₁-C₆)-alkyl-O-(C₁-C₆)-alkyl,

13. -O-(C₀-C₄)-alkyl-(C₃-C₇)-cycloalkyl, or

14. -(C₁-C₄)-alkyl-N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above;

R⁵ is

1. a hydrogen atom,

2. -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.4 above,

3. -C(O)-R⁹, wherein R⁹ is

-NH₂, -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under 7.1 to 7.4, or -N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above, or

4. -S(O)₂-R⁹, wherein R⁹ is as defined in 3. above; or

R⁴ and R⁵, together with the atom to which they are bonded form a heterocycle; or

R³ and R⁵, together with the atom to which they are bonded form a heterocycle containing an additional oxygen atom in the ring; and

R⁶, R⁷ and R⁸, independently of one another are hydrogen atom or methyl; or

in case b):

the substituents R¹, R² and R⁴ independently of one another are as defined under 1.1 to 1.18 in case a) above;

R³ is

1. -CF₃,

2. -CF₂-CF₃,

3. -CN,

4. -COOH,

5. -NO₂,

6. -NH₂,

7. -O-(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta substituted independently of one another by

7.1 phenyl, which is unsubstituted or mono- to pentasubstituted by halogen or -O-(C₁-C₄)-alkyl,

7.2 halogen,

7.3 -NH₂,

7.4 -OH,

7.5 -COOR¹⁶, wherein R¹⁶ is hydrogen atom or -(C₁-C₁₀)-alkyl,

7.6 -NO₂,

7.7 -S(O)_y-R¹⁴, wherein y is zero, 1 or 2, R¹⁴ is -(C₁-C₁₀)-alkyl, phenyl, which is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of

substituents defined under 1.7.1 to 1.7.11, amino, and -N(R¹³)₂,
 wherein each R¹³ independently is hydrogen atom, phenyl, -(C₁-C₁₀)-alkyl, -C(O)-(C₁-C₇)-alkyl, -C(O)-phenyl, -C(O)-NH-(C₁-C₇)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C₁-C₇)-alkyl, or -S(O)_y-R¹⁴,
 wherein R¹⁴ and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined under

1.7.1 to 1.7.11, or
 the two R¹³ groups, together with the nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms,

7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

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

7.10 -(C₃-C₇)-cycloalkyl, or

7.11 =O,

8. -N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above,

9. -NH-C(O)-R¹⁵, wherein R¹⁵ is

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

wherein said radical is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -CF₃, benzyl, and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

9.2 -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, and -O-(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

9.3 -(C₃-C₇)-cycloalkyl,

9.4 -N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above, or

9.5 phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -O-(C₁-C₁₀)-alkyl, -CN, -CF₃, and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, or two substituents of the phenyl radical form a dioxolane ring,

10. -S(O)_y-R¹⁴, wherein R¹⁴ and y are as defined in 1.7.7 above,

11. -C(O)-R¹², wherein R¹² is phenyl or -(C₁-C₇)-alkyl, wherein alkyl or phenyl are unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

12. -C(O)-O-R¹², wherein R¹² is as defined in 11. above,

13. -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

14. -O-(C₁-C₆)-alkyl-O-(C₁-C₆)-alkyl,

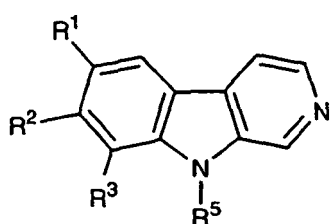
15. -O-(C₀-C₄)-alkyl-(C₃-C₇)-cycloalkyl, or

16. -(C₁-C₄)-alkyl-N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above;

R⁵ is as defined as R⁵ in case a) above; and

R⁶, R⁷ and R⁸ independently of one another are hydrogen atom or methyl.

[0017] In a second embodiment, the inhibitor of IκB kinase is a compound of formula (II)



(II)

or a stereoisomer or physiologically tolerable salt thereof, wherein:

R¹ and R² are independently of one another hydrogen atom, halogen, cyano, amino, -O-(C₁-C₄)-alkyl, nitro, -CF₃, -CF₂-CF₃, -S(O)_y-R¹⁴, or -N(R¹⁸)₂, wherein

y is 1 or 2;

R¹⁴ is amino, -(C₁-C₇)-alkyl, or phenyl, wherein the alkyl or phenyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I);

each R¹⁸ independently is hydrogen atom, -(C₁-C₇)-alkyl-C(O)-(C₁-C₇)-alkyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-(C₁-C₄)-alkyl, -C(O)-O-phenyl, -C(O)-O-(C₁-C₄)-alkyl or -(C₁-C₁₀)-alkyl, wherein pyridyl or phenyl in each case is unsubstituted or mono- to trisubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I), -CF₃, benzyl, and -(C₁-C₁₀)-alkyl, and wherein alkyl in each case is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I); or

the two R¹⁸ groups, together with nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms;

R³ is cyano, amino, -O-(C₁-C₄)-alkyl, nitro, -CF₃, -CF₂-CF₃, -S(O)_y-R¹⁴, or -N(R¹⁸)₂, wherein

y is 1 or 2;

R¹⁴ is amino, -(C₁-C₇)-alkyl, or phenyl, wherein the alkyl or phenyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I);

each R¹⁸ independently is hydrogen atom, -(C₁-C₇)-alkyl-C(O)-(C₁-C₇)-alkyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-(C₁-C₄)-alkyl, -C(O)-O-phenyl, -C(O)-O-(C₁-C₄)-alkyl or -(C₁-C₁₀)-alkyl, wherein pyridyl or phenyl in each

case is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I), -CF₃, benzyl, and -(C₁-C₁₀) alkyl, and wherein alkyl in each case is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I); or

the two R¹⁸ groups, together with nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms; and

R⁵ is hydrogen atom, -(C₁-C₁₀)-alkyl, -C(O)-R⁹, or -S(O)₂-R⁹, wherein

R⁹ is -(C₁-C₁₀)-alkyl, -O-(C₁-C₁₀)-alkyl, or phenyl;

alkyl, in each instance, is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.4 for the compounds of formula (I); and

phenyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I), and -N(R¹⁸)₂, wherein R¹⁸ is as defined above.

BRIEF DESCRIPTION OF THE FIGURES

[0018]

Figure 1 is an immunoblot showing the effect of compound 1 on phosphorylation and degradation of IκBα. (A) MM.1S cells were pre-treated with compound 1 (10 μM for 90 min), and then stimulated by TNFα (5 ng/mL for 0-20 min). (B) MM.1S cells were pre-treated with 0.125-40 μM compound 1 for 90 min before stimulation by TNFα (5 ng/mL for 5 min). (C) Patient MM cells were pre-treated with compound 1 (10 μM for 90 min), and then stimulated by TNFα (5 ng/mL for 0-10 min). The cells were lysed, electrophoresed, and then immunoblotted with anti-phospho IκBα and anti-IκBα Abs. The results show that compound 1 blocks phosphorylation and degradation of IκBα triggered by TNFα.

Figure 2 shows the results of electrophoretic mobility shift assay (EMSA) analysis of the effect of compound 1 on NF-κB activation. MM.1S cells were pre-treated with compound 1 (10 μM for 90 min), and then stimulated by TNFα (5 ng/mL for 0-20 min). Nuclear extracts of the cells were subjected to EMSA. PS-341 served as a positive control for the inhibition of NF-κB activation, as described in Hideshima *et al.*, *Cancer Res.* 61:3071 (2001). These results show that compound 1 blocks NF-κB activation triggered by TNFα.

Figure 3 is a graphical representation of an assay to determine the effect of compound 1 (A) and PS-341 (B) on DNA synthesis in multiple myeloma (MM) cell lines. MM.1S (●), U266 (▲), and RPMI8226 (■) cells were cultured in the presence of compound 1 (1.5-5.0 μM) or PS-341 (0.00001-10 μM) for 48 h. DNA synthesis was assessed by [³H]-TdR uptake.

Figure 4 shows the effect of compound 1 on cell cycle profile. U266 cells were cultured in the presence of compound 1 (10 μM for 24, 36, and 48 h), harvested, stained with PI, and analyzed for cell cycle profile by flow cytometry. These results show that compound 1 induced G1 growth arrest,

Figure 5 is an immunoblot showing the effect of compound 1 on phosphorylation of p42/44 MAPK or STAT3. MM.1S cells were pre-treated with compound 1 (10 μM for 90 min) or PS-341 (5 μM for 60 min) and then stimulated by IL-6 (50 ng/mL for 5 min). The cells were harvested, lysed, electrophoresed, and immunoblotted with anti-phospho-STAT3, phospho-p42/44 MAPK, and p42/44 MAPK Abs. These results show that compound 1 does not affect phosphorylation of p42/44 MAPK or STAT3 in MM.1S cells.

Figure 6 shows the effect of dexamethasone (Dex) on IκBα protein expression and NF-κB activation. (A) MM.1S cells were cultured in the presence of Dex (1 μM for 0-36 h), in the presence or absence of IL-6. The cells were harvested, lysed, electrophoresed, and immunoblotted with anti-phospho-IκBα Abs. (B) MM.1S cells were cultured with either DMSO control or Dex (1 μM for 18 h), stimulated by TNFα (5 ng/mL) or IL-6 (50 ng/mL), and nuclear extracts were subjected to EMSA to assess NF-κB activation. (C) MM.1S cells were pre-treated with either DMSO

control or Dex (1 μ M for 18 h), and then incubated in the presence of compound 1 (2.5-10 μ M for 90 min). The cells were harvested, and nuclear extracts were subjected to EMSA to assess NF- κ B activation.

Figure 7 is an immunoblot showing the effect of Dex, compound 1, PS-341 and/or IL-6 on TNF α -induced phosphorylation of I κ B α . MM.1S cells were cultured in the presence of Dex (1 μ M for 18 h), IL-6 (50 ng/mL for 18 h), PS-341 (5 μ M for 60 min) or compound 1 (10 μ M for 90 min), and then stimulated by TNF α (5 ng/mL for 5 min). The cells were harvested, lysed, electrophoresed, and then immunoblotted with anti-phospho-I κ B α and anti-I κ B α Abs. These results show that IL-6 does not affect I κ B α phosphorylation triggered by TNF α .

Figure 8 is a graphical representation of the effect of compound 1 on cell growth. (A) MM.1S cells were cultured with DMSO control ($\square$), or with 1.5 μ M ($\boxminus$), 3 μ M ($\boxplus$), 6 μ M ($\boxtimes$), 12.5 μ M ($\boxdot$), 25 μ M ($\boxtimes$), and 50 μ M ($\blacksquare$) compound 1, in the absence or presence of 0.01 and 0.1 μ M Dex for 48 h. (B) MM.1S cells were cultured with DMSO control ($\square$), or with 1.5 μ M ($\boxdot$), 3 μ M ($\boxplus$), 6 μ M ($\boxtimes$), or 12.5 μ M ($\blacksquare$) compound 1, in the absence or presence of 0.5, 5, and 50 ng/mL IL-6 for 48 h. (C) MM.1S cells were cultured with DMSO control ($\square$), or 0.4 μ M ($\boxtimes$), 2 μ M ($\boxdot$), or 10 μ M ($\blacksquare$) compound 1 in the presence of Dex (0.1 μ M) and/or IL-6 (50 ng/mL) for 48 h. DNA synthesis was assessed by [3 H]-TdR uptake. These results show that compound 1 inhibits growth and blocks the protective effect of IL-6 against Dex-induced growth inhibition.

Figure 9 is a graphical representation of the effect of compound 1 on cell growth in cells treated with the immunomodulatory derivative IMiD3 in the presence or absence of IL-6. (A) MM.1S cells were cultured for 48 h with DMSO control ($\square$), or with 25 μ M ($\boxminus$), 50 μ M ($\boxplus$), or 100 μ M ($\blacksquare$) thalidomide (Thal), in the presence or absence of compound 1 (10 μ M) and with or without IL-6 (50 ng/mL). (B) MM.1S cells were cultured for 48 h with DMSO control ($\square$), or with 0.25 μ M ($\boxminus$), 0.5 μ M ($\boxplus$), or 1 μ M ($\blacksquare$) IMiD3, in the presence or absence of compound 1 (10 μ M) and with or without IL-6 (50 ng/mL). DNA synthesis was assessed by [3 H]-TdR uptake, these results show that compound 1 overcomes the protective effect of IL-6 against IMiD3.

Figure 10 shows the effect of compound 1 on TNF α -induced ICAM-1 expression on MM cells. MM.1S and RPMI8226 cells were cultured for 24 h with DMSO control ($\square$), TNF α (5 ng/mL) alone ($\square$), or TNF α + compound 1 ($\square$). The cells were harvested, stained with isotype control (...) or FITC-conjugated anti-ICAM-1 Ab, and analyzed using flow cytometry. These results show that compound 1 inhibits TNF α -induced ICAM-1 expression on MM cells.

Figure 11 shows that TNF α induces apoptosis in MM.1S cells treated with compound 1. MM.1S cells were cultured for 48 h with 0.2 and 1 ng/mL TNF α , in the absence ($\square$) or presence of 2.5 μ M ($\boxplus$), 5 μ M ($\boxtimes$), 10 μ M ($\blacksquare$) compound 1. Cell viability was assessed by MTT assay.

Figure 12 shows that compound 1 inhibits paracrine MM cell growth and IL-6 secretion in BMSCs triggered by MM cell adherence. BMSCs, BMSCs with MM.1S cells, or MM.1S cells alone were cultured for 48 h, in the presence of DMSO control ($\square$), or with 0.4 μ M ($\boxtimes$), 2 μ M ($\boxdot$), or 10 μ M ($\blacksquare$) compound 1. (A) IL-6 level was measured in culture supernatants by ELISA, and (B) DNA synthesis was assessed by [3 H]-TdR uptake.

DETAILED DESCRIPTION OF THE INVENTION

[0019] The invention relates to the use of an inhibitor of I κ B kinase as herein described in the manufacture of a medicament for the treatment of multiple myeloma.

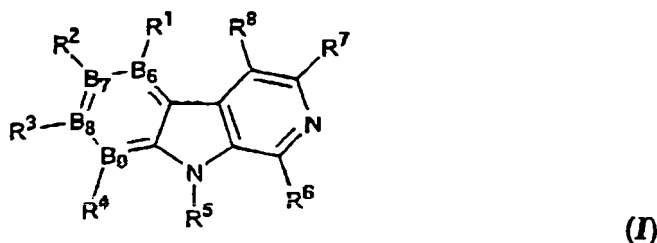
[0020] The issued patents and published scientific literature referred to herein establishes knowledge that is available to those with skill in the art. All patents, patent applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure will prevail.

[0021] In a first aspect, the invention provides the use of an inhibitor of I κ B kinase (IKK) in the manufacture of a medicament for the treatment of multiple myeloma. Preferably, such inhibition is specific, *i.e.*, the IKK inhibitor reduces the ability of IKK to phosphorylate I κ B α at a concentration that is lower than the concentration of the inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for IKK inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological

effect. The concentration of inhibitor required for IKK inhibitory activity can be determined by any assay suitable for measuring IKK activity, including the assays described in the Examples. The concentration of inhibitor required to produce an unrelated biological effect can be determined by subjecting the inhibitor to a panel of enzymatic, receptor binding, and/or pharmacological assays.

[0022] Some preferred IKK inhibitors are beta-carboline compounds, including those described in Rizeler *et al.*, WO 01/68648, including all compounds, formulae, and synthetic procedures disclosed therein.

[0023] In some embodiments, therefore, the use according to this aspect of the invention comprises use of an IkB kinase inhibitor of formula (I)



or a stereoisomer or physiologically tolerable salt thereof, wherein:

B₆, B₇, B₈, and B₉ are independently selected from the group consisting of carbon atom and nitrogen atom, where a total of no more than two of B₆, B₇, B₈, and B₉ are nitrogen atoms; and

in case a):

the substituents R¹, R² and R³ independently of one another are

1.1. hydrogen atom,

1.2. halogen,

1.3. -CN,

1.4. -COOH,

1.5. -NO₂,

1.6. -NH₂,

1.7. -O-(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of

1.7.1 phenyl, which is unsubstituted or mono- to pentasubstituted by halogen or -O-(C₁-C₄)-alkyl,

1.7.2 halogen,

1.7.3 -NH₂,

1.7.4 -OH,

1.7.5 -COOR¹⁶, wherein R¹⁶ is hydrogen atom or -(C₁-C₁₀)-alkyl,

1.7.6 -NO₂,

1.7.7 -S(O)_y-R¹⁴, wherein y is zero, 1 or 2, and R¹⁴ is -(C₁-C₁₀)-alkyl, phenyl, which is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined

under 1.7.1 to 1.7.11, amino or $-N(R^{13})_2$,

wherein each R^{13} independently is 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, or $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono-

to pentasubstituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, or

the two R^{13} groups, together with the nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms,

1.7.8 $-O$ -phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11,

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

wherein said radical is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, $-CF_3$, benzyl, and $-(C_1-C_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents 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 with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above and $-O-(C_1-C_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents 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 with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, $-O-(C_1-C_{10})$ -alkyl, $-CN$, $-CF_3$, and $-(C_1-C_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, or two substituents of the phenyl radical together form a dioxolane 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 with a substituent or substituents independently selected from the group of substituents 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 pentasubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

1.14. -O-(C₁-C₆)-alkyl-O-(C₁-C₆)-alkyl,

1.15. -O-(C₀-C₄)-alkyl-(C₃-C₇)-cycloalkyl,

1.16. -(C₁-C₄)-alkyl-N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above

1.17. -CF₃ or

1.18. -CF₂-CF₃;

R⁴ is

1. -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

2. -CF₃,

3. -CF₂-CF₃,

4. -CN,

5. -S(O)_y-R¹⁴, wherein R¹⁴ and y are as defined in 1.7.7 above,

6. -NH₂,

7. -O-(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted independently of one another by

7.1 phenyl, which is unsubstituted or mono- to pentasubstituted by halogen or -O-(C₁-C₄)-alkyl,

7.2 halogen,

7.3 -NH₂,

7.4 -OH,

7.5 -COOR¹⁶, wherein R¹⁶ is hydrogen atom or -(C₁-C₁₀)-alkyl,

7.6 -NO₂,

7.7 -S(O)_y-R¹⁴, wherein y is zero, 1 or 2, R¹⁴ is -(C₁-C₁₀)-alkyl, phenyl, which is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, amino, and -N(R¹³)₂,

wherein each R¹³ independently is hydrogen atom, phenyl, -(C₁-C₁₀)-alkyl, -C(O)-(C₁-C₇)-alkyl, -C(O)-phenyl, -C(O)-NH-(C₁-C₇)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C₁-C₇)-alkyl, or -S(O)_y-R¹⁴, wherein R¹⁴ and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, or

the two R¹³ groups, together with the nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms,

7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

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

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

7.11 $=O$,

8. $-N(R^{17})_2$, wherein each R^{17} independently is 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, or $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, or the two R^{17} groups, together with the nitrogen atom to which they are 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 the group consisting of pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene, and thiomorpholine, wherein said radical is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, $-CF_3$, benzyl and $-(C_1-C_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents 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 with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, $-O-(C_1-C_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents 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 with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, $-O-(C_1-C_{10})$ -alkyl, $-CN$, $-CF_3$, and $-(C_1-C_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, or two substituents of the phenyl radical form a dioxolane 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 with a substituent or substituents independently selected from the group of substituents 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 pentasubstituted with a substituent or substituents independently selected from the group 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 with a substituent or substituents independently selected from the group 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 R^1 , R^2 and R^4 independently of one another are 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 unsubstituted or mono- to penta substituted independently of one another by

7.1 phenyl, which is unsubstituted or mono- to pentasubstituted 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 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 is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11, amino, and $-N(R^{13})_2$,

wherein each R^{13} independently is 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, or $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, or

the two R^{13} groups, together with the nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms,

7.8 $-O$ -phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

7.9 a radical selected from the group consisting of pyrrolidine, tetrahydropyridine, piperidine, piperazine,

imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene, and 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 radical selected from the group consisting of pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene, and thiomorpholine,

wherein said radical is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, $-CF_3$, benzyl, and $-(C_1-C_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents 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 with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, and $-O-(C_1-C_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents 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 with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, $-O-(C_1-C_{10})$ -alkyl, $-CN$, $-CF_3$, and $-(C_1-C_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, or two substituents of the phenyl radical form a dioxolane 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 with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 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 pentasubstituted with a substituent or substituents independently selected from the group of substituents 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; and

R^6 , R^7 and R^8 independently of one another are hydrogen atom or methyl, in the manufacture of a medicament for the treatment of multiple myeloma.

[0024] In some embodiments, the BKK inhibitors of formula (I) are compounds of case a), wherein:

B₆, B₇, B₈, and B₉ are each a carbon atom; and

R⁴ is -NH-C(O)-R¹⁵, wherein R¹⁵ is as defined under 9.1 to 9.5 above.

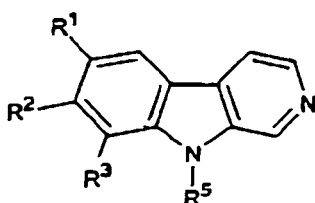
[0025] In some preferred embodiments, R¹⁵ is:

a radical selected from the group consisting of pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene, and thiomorpholine,

wherein said radical is unsubstituted or mono- to penta-substituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -CF₃, benzyl, and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above; or

phenyl, wherein phenyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -O-(C₁-C₁₀)-alkyl, -CN, -CF₃, and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, or two substituents of the phenyl radical form a dioxolane ring.

[0026] In some embodiments, the use according to this aspect of the invention comprises the use of an IκB kinase inhibitor of formula (II)



(II)

or a stereoisomer or physiologically tolerable salt thereof, wherein:

R¹ and R² are independently of one another hydrogen atom, halogen, cyano, amino, -O-(C₁-C₄)-alkyl, nitro, -CF₃, -CF₂-CF₃, -S(O)_y-R¹⁴, or -N(R¹⁸)₂, wherein

y is 1 or 2;

R¹⁴ is amino, -(C₁-C₇)-alkyl, or phenyl, wherein the alkyl or phenyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I);

each R¹⁸ independently is hydrogen atom, -(C₁-C₇)-alkyl-C(O)-(C₁-C₇)-alkyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-(C₁-C₄)-alkyl, -C(O)-O-phenyl, -C(O)-O-(C₁-C₄)-alkyl or -(C₁-C₁₀)-alkyl, wherein pyridyl or phenyl in each case is unsubstituted or mono- to trisubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I), -CF₃, benzyl, and -(C₁-C₁₀)-alkyl, and wherein alkyl in each case is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I); or

the two R¹⁸ groups, together with nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms;

R³ is cyano, amino, -O-(C₁-C₄)-alkyl, nitro, -CF₃, -CF₂-CF₃, -S(O)_y-R¹⁴, or -N(R¹⁸)₂, wherein

y is 1 or 2;

R¹⁴ is amino, -(C₁-C₇)-alkyl, or phenyl, wherein the alkyl or phenyl is unsubstituted or mono- to tri- substituted with

a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I);

each R¹⁸ independently is hydrogen atom, -(C₁-C₇)-alkyl-C(O)-(C₁-C₇)-alkyl, -C(O)-phenyl, -C(O)-pyridyl, -C(O)-NH-(C₁-C₄)-alkyl, -C(O)-O-phenyl, -C(O)-O-(C₁-C₄)-alkyl or -(C₁-C₁₀)-alkyl, wherein pyridyl or phenyl in each case is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I), -CF₃, benzyl, and -(C₁-C₁₀)-alkyl, and wherein alkyl in each case is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I); or

the two R¹⁸ groups, together with nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms; and

R⁵ is hydrogen atom, -(C₁-C₁₀)-alkyl, -C(O)-R⁹, or -S(O)₂-R⁹, wherein

R⁹ is -(C₁-C₁₀)-alkyl, -O-(C₁-C₁₀)-alkyl, or phenyl;

alkyl, in each instance, is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.4 for the compounds of formula (I); and

phenyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 for the compounds of formula (I), and -N(R¹⁸)₂, wherein R¹⁸ is as defined above, in the manufacture of a medicament for the treatment of multiple myeloma.

[0027] In some embodiments, the IKK inhibitor is a compound of formula (II) as described above wherein:

R¹ is bromo, -CF₃ or chloro;

R² is hydrogen atom or O-(C₁-C₂)-alkyl;

R³ is -N(R¹⁸)₂, wherein each R¹⁸ independently is hydrogen atom, -N-C(O)-pyridyl, -C(O)-phenyl, -(C₁-C₇)-alkyl, -C(O)-(C₁-C₄)-alkyl or -C(O)-O-(C₁-C₄)-alkyl, wherein alkyl or phenyl, in each instance, is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group consisting of halogen and -O-(C₁-C₂)-alkyl; and

R⁵ is hydrogen atom, methyl or -S(O)₂-CH₃.

[0028] In various other embodiments, the IKK inhibitor is a compound of formula (II), wherein:

R¹ is chloro, R³ is -H-C(O)-CH₂-O-CH₃, and R² and R⁵ are each hydrogen atom; or

R¹ is chloro, R³ is -N-C(O)-pyridyl, wherein pyridyl is unsubstituted or substituted by chloro, R² is hydrogen atom or -O-CH₃, and R⁵ is hydrogen atom; or

R¹ is chloro, R³ is -N-C(O)-phenyl, wherein phenyl is mono- or disubstituted by fluoro, and R² and R⁵ are each hydrogen atom.

[0029] In some particularly preferred embodiments, the IKK inhibitor is selected from the group consisting of N-(6-Chloro-9H-carbolin-8-yl)-nicotinamide, including the bismesylate salt, bistrifluoroacetate salt and bishydrochloride salt thereof, N-(6-Chloro-9H-carbolin-8-yl)-3,4-difluoro-benzamide, including the hydrochloride salt thereof, N-(6-chloro-7-methoxy-9H-carbolin-8-yl)-nicotinamide, including the bistrifluoroacetate salt and bishydrochloride salt thereof, and 6-Chloro-N-(6-chloro-9H-carbolin-8-yl)-nicotinamide.

[0030] In one particularly preferred embodiment, the use according to this aspect of the invention comprises the use of N-(6-chloro-9H-β-carbolin-8-yl)-nicotinamide or a stereoisomer or physiologically tolerable salt thereof.

[0031] The IκB kinase inhibitors of formula (I) or formula (II) preferably are synthesized as described in Rizeler *et al.*, WO 01/68648. The preparation of physiologically tolerable salts of compounds of formula (I) or formula (II) capable of salt formation, including their stereoisomeric forms, can be carried out according to methods known in the art. 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.

[0032] 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 cyclopropyl, cyclobutyl, cyclohexyl or cycloheptyl.

[0033] The term "alkoxy" by itself or as part on another substituent, unless otherwise stated means -O-alkyl or -O-substituted alkyl.

[0034] The term "heterocycle having 5 to 7 ring atoms" refers to 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 such heterocycles having 5 to 7 ring atoms include, without limitation, pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene and thiomorpholine.

[0035] Unless otherwise stated, the term "aryl", whether by itself or as part of another substituent, refers to an organic radical derived from an aromatic molecule by removal of one atom; nonlimiting examples of such aryl groups include phenyl, pyridyl, thiazolyl, morpholinyl and naphthyl.

[0036] 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.

[0037] 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.

[0038] The term "substituted amino" refers to $-N(R^{13})_2$ wherein R^{13} at each occurrence is independently selected from the group consisting of 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.

[0039] 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.

[0040] The term "halogen" is understood as meaning fluorine, chlorine, bromine or iodine.

[0041] The term " $-(C_1-C_n)$ -alkyl" is understood as meaning a hydrocarbon radical, the carbon chain of which is linear or branched and contains 1 to n carbon atoms.

[0042] For purposes of the invention, the term "cancer cell" refers to multiple myeloma cells. In some embodiments, the cancer cell is grown in cell culture, including primary cultures and immortalized cell lines. In some other embodiments, the cancer cell is in an animal, preferably a mammal. As used herein, the term "mammal" includes, without limitation rats, mice, dogs, pigs, rabbits, non-human primates, and humans.

[0043] The I κ B kinase inhibitor can be administered by any pharmaceutically acceptable route, including, without limitation, parenteral (including intravenous, subcutaneous, and intramuscular), oral, sublingual, transdermal, topical, intranasal, intratracheal, intrarectal, intraocular, and vaginal. For the treatment of an adult patient weighing approximately 70 kg, depending on the efficacy of the compound according to formula (I) or formula (II), 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.

[0044] Both monotherapy and combination therapy regimens are contemplated within the scope of this invention. For purposes of the invention, the term "monotherapy" refers to treatment with an I κ B kinase inhibitor, without concurrent treatment with another antitumor agent. For purposes of the invention, the term "combination therapy" refers to concurrent therapy with an I κ B kinase inhibitor and another antitumor agent. The term "concurrent" is intended to encompass simultaneous, sequential, and alternating treatments.

[0045] In some embodiments, the antitumor agent is selected from the group consisting of cytotoxic chemotherapy, radiotherapy or immunotherapy. Nonlimiting examples of cytotoxic agents suitable for use in combination with I κ B kinase inhibitors include gemcitabine, irinotecan, 5-fluorouracil, taxanes such as taxol or taxotere, platinum agents such as cisplatin or carboplatin, anthracyclins such as doxorubicin, mitoxantrone, and DoxilTM, alkylating agents such as melphalan and cyclophosphamide, fludarabine, and dexamethasone.

[0046] In some other embodiments, the I κ B kinase inhibitor is administered with another agent that inhibits the activity of NF- κ B, including, without limitation, proteasome inhibitors. Examples of proteasome inhibitors suitable for use in

combination with an I κ B kinase inhibitor include, but are not limited to, those disclosed in Adams *et al.*, U.S. Patent No. 5,780,454 (1998), U.S. Patent No. 6,066,730 (2000), and U.S. Patent No. 6,083,903 (2000). One such proteasome inhibitor is N-pyrazinecarbonyl-L-phenylalanine-L-leucineboronic acid.

EXAMPLES

Example 1: Materials and Methods

MM derived cell lines and patient MM cells

[0047] Dex-sensitive (MM.1S) human MM cell line was kindly provided by Dr. Steven Rosen (Northwestern University, Chicago, IL). RPMI8226 and U266 human MM cells were obtained from American Type Culture Collection (Rockville, MD). All MM cell lines cultured in RPMI-1640 containing 10% fetal bovine serum (FBS, Sigma Chemical Co., St. Louis, MO), 2 μ M L-glutamine, 100 U/mL penicillin (Pen) and 100 μ g/mL streptomycin (Strep) (GIBCO, Grand Island, NY). Patient MM cells were purified from patient BM aspirates using RosetteSep separation system (StemCell Technologies, Vancouver, Canada). The purity of MM cells was confirmed by flow cytometry using PE-conjugated anti-CD138 antibody (Beckton Dickinson Co.).

BMSC cultures

[0048] BM specimens were obtained from patients with MM. Mononuclear cells (MNCs) separated by Ficoll-Hipaque density sedimentation were used to establish long-term BM cultures, as previously described (Uchiyama *et al.*, *Blood* 82:3712-3720 (1993)). When an adherent cell monolayer had developed, cells were harvested in Hank's Buffered Saline Solution (HBSS) containing 0.25% trypsin and 0.02% EDTA, washed, and collected by centrifugation.

Inhibitors

[0049] The proteasome inhibitor PS-341 and the I κ B α kinase (IKK) inhibitor compound 1 (Millennium Pharmaceuticals, Cambridge, MA) were dissolved in DMSO and stored at -20 °C until use. PS-341 and compound 1 were diluted in culture medium immediately before use, and PS-341 and compound 1 control media contained <0.1% DMSO. MAPK kinase (MEK) inhibitor PD98059 was purchased from Cell Signaling (Beverly, MA).

DNA synthesis

[0050] Proliferation was measured as previously described (Hideshima *et al.*, *Blood* 96:2943 (2000)). MM cells (3 x 10⁴ cells/well) were incubated in 96-well culture plates (Costar, Cambridge, MA) in the presence of media, PS-341, compound 1 and/or Dex or recombinant human IL-6 (Genetics Institute, Cambridge, MA) for 48 h at 37°C. DNA synthesis was measured by [³H]-thymidine ([³H]-TdR, NEN Products, Boston, MA) uptake. Cells were pulsed with [³H]TdR (0.5 μ Ci/well) during the last 8 h of 48 h cultures. All experiments were performed in triplicate.

Growth inhibition assay

[0051] The inhibitory effect of PS-341 and compound 1 on MM growth was assessed by measuring 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrasodium bromide (MTT) dye absorbance of the cells. Cells from 48 h cultures were pulsed with 10 μ L of 5 mg/mL MTT to each well for the last 4 h of 48 h cultures, followed by 100 μ L isopropanol containing 0.04N HCl. Absorbance was measured at 570 nm using a spectrophotometer (Molecular Devices Corp., Sunnyvale CA).

Immunoblotting

[0052] MM cells were cultured with PS-341 or compound 1; harvested; washed; and lysed using lysis buffer: 50 mM Tris-HCl (pH 7.4), 150 mM NaCl, 1% NP-40, 5 mM EDTA, 5 mM NaF, 2 mM Na₃VO₄, 1 mM PMSF, 5 μ g/mL leupeptin, and 5 μ g/mL aprotinin. For detection of phospho-I κ B α , I κ B α , phospho-MAPK, phospho-STAT3, ERK2 or alpha-tubulin, cell lysates were subjected SDS-PAGE, transferred to PVDF membrane (Bio-Rad Laboratories, Hercules, CA), and immunoblotted with anti-phospho-I κ B α , -I κ B α , -phospho-MAPK, or -phospho-STAT3 Abs (Cell Signaling, Beverly, MA), and anti-alpha-tubulin (Sigma) Abs.

Electrophoretic mobility shift analysis

[0053] Electrophoretic mobility shift analyses (EMSA) were carried out as in previous studies (Hideshima *et al.*, *Oncogene* 20:4519 (2001); Hideshima *et al.*, *Cancer Res.* 61:3071 (2001)). Briefly, MM.1S cells were pre-incubated with PS-341 (5 μ M for 1 h) and compound **1** (10 μ M for 90 min) before stimulation with TNF α (5 ng/mL) for 10 or 20 min. Cells were then pelleted, resuspended in 400 μ L of hypotonic lysis buffer (20 mM HEPES, pH 7.9, 10 mM KCl, 1 mM EDTA, 0.2% Triton X-100, 1 mM Na₃VO₄, 5 mM NaF, 1 mM PMSF, 5 μ g/mL leupeptin, 5 μ g/mL aprotinin), and kept on ice for 20 min. After centrifugation (14000g for 5 min) at 4 °C, the nuclear pellet was extracted with 100 μ L hypertonic lysis buffer (20 mM HEPES, pH 7.9, 400 mM NaCl, 1 mM EDTA, 1 mM Na₃VO₄, 5 mM NaF, 1 mM PMSF, 5 μ g/mL leupeptin, 5 μ g/mL aprotinin) on ice for 20 min. After centrifugation (14000g for 5 min) at 4 °C, the supernatant was collected as nuclear extract. Doublestranded NF- κ B consensus oligonucleotide probe (5'-GGGGACTTTCCC-3', Santa Cruz Biotech.) was end-labeled with [³²P]ATP (50 μ Ci at 222 TBq/mM; NEN, Boston, MA). Binding reactions containing 1 ng of oligonucleotide and 5 μ g of nuclear protein were conducted at room temperature for 20 min in a total volume of 10 μ L of binding buffer (10 mM Tris-HCl, pH 7.5, 50 mM NaCl, 1 mM MgCl₂, 0.5 mM EDTA, 0.5 mM DTT, 4% glycerol (v/v), and 0.5 μ g poly (dI-dC) (Pharmacia, Peapack, NJ). For supershift analysis, 1 μ g of anti-p65 NF- κ B Ab was added 5 min before the reaction mixtures, immediately after addition of radiolabeled probe. The samples were loaded onto a 4% polyacrylamide gel, transferred to Whatman paper (Whatman International, Maidstone, U.K.), and visualized by autoradiography.

Flow cytometric analysis

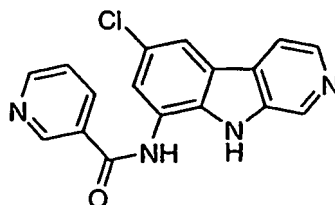
[0054] For cell cycle analysis, MM cells cultured for 24-48 h in compound **1** (10 μ M), Dex (1 μ M), IL-6 (20 ng/mL), or control media were harvested, washed with phosphate-buffered saline (PBS), fixed with 70% ethanol, and treated with 10 μ g/mL of RNase (Roche Diagnostics Corp., Indianapolis, IN). Cells were then stained with propidium iodide (PI, Sigma) (5 μ g/mL). For detection of ICAM-1 expression, MM cells cultured in TNF α (5 ng/mL) in the presence or absence of compound **1** (10 μ M) were harvested, washed with PBS, and stained with mouse IgG isotype control or FITC-conjugated mouse anti-human CD54 Ab. Both cell cycle profile and ICAM-1 expression were determined using an Epics (Coulter Immunology, Hialeah, FL) flow cytometer, as in prior studies (Hideshima *et al.*, *Oncogene* 20:4519 (2001)).

Effect of compound **1** on paracrine MM cell growth in the BM

[0055] To evaluate growth stimulation and signaling in MM cells adherent to BMSCs, 3 x 10⁴ MM.1S cells were cultured in BMSC coated 96-well plates for 48 h, in the presence or absence of compound **1**. DNA synthesis was measured as described above. The DuoSet ELISA (R&D System) was used to measure IL-6 in supernatants of 48 h cultures of BMSCs with or without MM.1S cells, in the presence or absence of compound **1**.

Statistical analysis

[0056] Statistical significance of differences observed in drug-treated versus control cultures was determined using the Student's t-test. The minimal level of significance was $P < 0.05$.

Example 2: Synthesis of N-(6-chloro-9H- β -carbolm-8-yl)-nicotinamide (compound **1)****[0057]**

[0058] To a solution of norharman (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 K₂CO₃ (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-carboline.

[0059] 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 NaHCO₃ (50 mL) and stirred at RT for 12 h.

[0060] 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 NaHCO₃ (150 mL) and EtOAc (100 mL). The aqueous phase was extracted (2 times) and the combined organic solutions dried (brine; NaSO₄) and concentrated to give 484 mg of 9-amino-7-chloro- β -carboline.

[0061] 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 nicotiny 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 3: Compound 1 inhibits I κ B kinase activity

Isolation of the I κ B kinase complex

[0062] The I κ B 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 $\times$ g for 15 min, and filtered through a 0.22 μ m 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.

Activation of the I κ B kinase complex

[0063] The kinase-containing pool was activated by incubation with 100 nM MEKK1 Δ , 250 μ M MgATP, 10 mM MgCl₂, 5 mM DTT, 10 mM 2-glycerophosphate, and 2.5 μ M Microcystin-LR for 45 min at 37°C. Activated enzyme was stored at -80 °C until further use.

Assay of I κ B kinase activity

[0064] Per well of a 96-well plate, compounds at various concentrations in 2 μ L DMSO were pre-incubated for 30 min at 25 °C with 43 μ L of activated enzyme diluted [1:25] with assay buffer (50 mM HEPES pH 7.5, 5 mM DTT, 10 mM MgCl₂, 10 mM 2-glycerophosphate, 2.5 μ M Microcystin-LR). Five microliters of peptide substrate (biotin-(CH₂)₆-DRH-DSGLDSMKD-CONH₂) at 200 μ M stock solution was added to each well and incubated for 1 hour before quenching with 150 μ L 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-(CH₂)₆-DRHDS[PO₃]GLDSMKD-CONH₂, serially diluted in assay buffer) at 100 μ L 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 μ L of 0.5 μ g/mL streptavidin conjugated with horseradish peroxidase (HRP) diluted with 50 mM HEPES / 0.1% BSA, was added for 30 minutes. After 5 washes with PBS, 100 μ L TMB substrate (Kirkegaard & Perry Laboratories, Gaithersburg, MD, USA) was added and color development was stopped by adding 100 μ L of 0.18 M H₂SO₄. 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. The inhibitor compound 1 exhibits an IC₅₀ of 0.052 μ M in this assay.

Example 4: Compound 1 inhibits I κ B α phosphorylation in MM.1S cells and patient MM cells

[0065] Inhibition of I κ B α phosphorylation by compound 1 was assayed in MM.1S and patient MM cells triggered by TNF α . As seen in Figure 1A, serine phosphorylation and degradation of I κ B α were significantly induced after 5 and 10 min TNF α treatment of cells in DMSO control media, whereas phosphorylation and degradation of I κ B α were completely blocked by compound 1 pre-treatment of MM.1S cells. To study the dose-dependent effect of compound 1, MM.1S cells were pre-treated with 1.25-40 μ M compound 1 for 90 min, and then stimulated by TNF α (5 ng/mL). As can be seen in

Figure 1B, phosphorylation of I κ B α was completely inhibited by $\geq 5 \mu\text{M}$ compound **1**. As in MM.1S cells, compound **1** also inhibited phosphorylation and degradation of I κ B α triggered by TNF α in patient MM cells (Figure 1C). These results demonstrate a time and a dose dependent inhibitory effect of compound **1** on phosphorylation and degradation of I κ B α .

Example 5: Compound **1** Inhibits NF- κ B activation in MM.1S cells

[0066] Since NF- κ B activation requires phosphorylation, ubiquitination, and degradation of I κ B α , we next examined whether compound **1** could inhibit NF- κ B activation, assessed by EMSA. MM.1S cells pre-treated with either DMSO control media or compound **1** ($10 \mu\text{M}$ for 90 min) were stimulated by TNF α (5 ng/mL for 0-20 min). As can be seen in Figure 2, NF- κ B activation was completely inhibited by compound **1** pre-treatment. PS-341 served as positive control for inhibition of NF- κ B activation, as previously reported (Hideshima *et al.*, *Oncogene* 20:4519 (2001); Hideshima *et al.*, *Cancer Res.* 61:3071 (2001)).

Example 6: Compound **1** decreases viability of MM cell lines

[0067] To study the direct effect of compound **1** on MM cells, [^3H]-TdR uptake was measured in MM.1S, U266, and RPMI8226 cell lines cultured for 48h in the presence of compound **1** ($1.5\text{-}50 \mu\text{M}$). Twenty% to 50% inhibition in proliferation was observed at dose $> 12.5 \mu\text{M}$ compound **1** (Figure 3A). In contrast, PS-341 completely inhibited [^3H]-TdR uptake in all cell lines tested at IC $_{50}$ of 0.02-0.005 (Figure 3B). These results indicate that complete blockade of NF- κ B activation cannot achieve $> 50\%$ inhibition of DNA synthesis in MM cell lines, and that complete inhibition by PS-341 is mediated through inhibition of another signaling pathway, such as p42/44 MAPK (Ogata *et al.*, *J. Immunol.* 159:2212 (1997)).

[0068] Cell cycle profile, assessed by PI staining, was also examined in these MM cell lines. Interestingly, compound **1** induced G1 growth arrest, but not apoptosis, in U266 cells (Figure 4). Similar results were observed in RPMI8226 cells (data not shown). These data show that NF- κ B blockade induces G1 growth arrest in MM cells.

Example 7: Compound **1** does not affect phosphorylation of p42/44 MAPK or STAT3 in MM.1S cells

[0069] As can be seen in Figure 5, IL-6 induces phosphorylation of both p42/44 MAPK and STAT3 in MM.1S cells, and the MEK1 inhibitor PD98059 selectively inhibits p42/44 MAPK phosphorylation. PS-341 also inhibits p42/44 MAPK phosphorylation; however, compound **1** does not inhibit either p42/44 MAPK or STAT3 phosphorylation. Phosphorylation of Akt triggered by IL-6 was also unaffected by compound **1** pre-treatment (data not shown). These results indicate that compound **1** specifically blocks NF- κ B, without affecting other known signaling pathways in MM.1S cells triggered by IL-6.

Example 8: Dex upregulates I κ B α protein and enhances the inhibitory effect of compound **1** on NF- κ B activation in MM.1S cells

[0070] MM.1S cells were cultured in the presence of Dex ($1 \mu\text{M}$ for 0-36 h), and expression of I κ B α protein was assessed by Western blotting. As can be seen in Figure 6A, Dex significantly induces I κ B α expression, and IL-6 partially blocks Dex-induced upregulation of I κ B α . NF- κ B activation was next examined in the presence of Dex, with or without IL-6. TNF α induced activation of NF- κ B in MM.1S cells is abrogated by pre-treatment with Dex (Figure 6B). compound **1** also inhibits NF- κ B activation triggered by TNF α in MM.1S cells in a dose-dependent fashion, and pre-treatment with Dex enhances the inhibitory effect of compound **1** (Figure 6C). These results suggest that Dex inhibits NF- κ B activation via upregulation of I κ B α , with related G1 growth arrest and apoptosis.

[0071] The effect of Dex, compound **1**, PS-341 and/or IL-6 on TNF α induced phosphorylation of I κ B α in MM.1S cells was next examined. As can be seen in Figure 7, Dex, PS-341 and/or IL-6 does not inhibit TNF α -induced phosphorylation of I κ B α ; moreover, PS-341 enhances phosphorylation of I κ B α , due to inhibition of proteasome activity and accumulation of I κ B α . In contrast compound **1**, in the presence or absence of IL-6, inhibits phosphorylation of I κ B α . Dex inhibits TNF α -induced degradation of I κ B α , whereas IL-6 blocks this effect. Both PS-341 and compound **1** inhibit degradation of I κ B α , in the presence or absence of IL-6.

Example 9: Growth inhibitory effect of compound **1** in the presence of Dex and/or IL-6 in MM

[0072] As can be seen in Figure 8A, Dex inhibited IL-6 induced proliferation of MM.1S cells, but compound **1** did not enhance its effect. Importantly, both constitutive and IL-6 induced DNA synthesis in MM.1S cells was abrogated in the presence of compound **1** in a dose dependent fashion (Figure 8B). Furthermore, the protective effect of IL-6 on Dex-induced growth inhibition was also abrogated by compound **1** (Figure 8C). These data suggest that promotion of cell growth and survival by IL-6 is mediated, at least in part, via NF- κ B signaling pathway.

[0073] Thalidomide (Thal) and its immunomodulatory derivative (IMiD3) previously have been reported to inhibit MM.

1S cell growth and that IL-6 abrogates this IMiD effect (Hideshima *et al. Blood* 96:2943 (2000)). Therefore, the effect of compound **1** on DNA synthesis of MM.1S cells treated with Thal and IMiD3 was studied in the presence or absence of IL-6. As can be seen in Figure 9, IMiD3 significantly ($p < 0.001$) inhibited DNA synthesis in MM.1S cell in a dose dependent fashion (0.25-1 μ M). IL-6 (20 ng/mL) overcomes the effect of IMiD3; importantly, however, compound **1** neutralized the inhibitory effect of IL-6 against IMiD3. These studies suggest that NF- κ B blockade can overcome resistance to Thal/IMiDs.

Example 10: Compound 1 Inhibits TNF α -induced ICAM-1 expression on MM cells

[0074] TNF α has been shown to induce ICAM-1 and VCAM-1 expression on both BMSCs and MM cells, and the proteasome inhibitor PS-341 blocks induction of these molecules (Hideshima *et al., Cancer Res.* 61:3071 (2001)). Since PS-341 is not a specific NF- κ B inhibitor, it cannot be concluded from these studies that TNF α -induced upregulation of ICAM-1 and VCAM-1 is mediated through NF- κ B. However, as can be seen in Figure 10, compound **1** also inhibits TNF α -induced upregulation of ICAM-1 expression on MM.1S and RPMI8226 cells. This result strongly suggests that upregulation of ICAM-1 by TNF α is mediated via activation of NF- κ B.

Example 11: TNF α and compound 1 triggers apoptosis in MM.1S cells

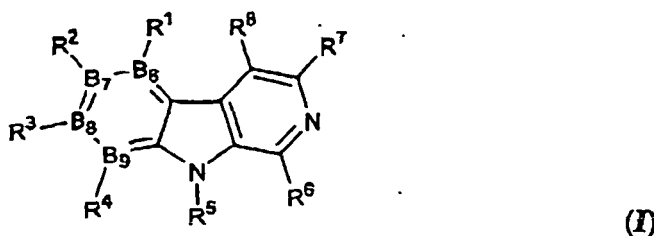
[0075] TNF α induces modest proliferation, but not apoptosis, in MM.1S cells (Hideshima *et al., Oncogene* 20:4519 (2001)). To test the hypothesis that TNF α would induce apoptosis in MM.1S cells when NF- κ B activation is blocked by compound **1**, MM.1S cells were cultured with TNF α , in the presence or absence of compound **1**. As can be see in Figure 11, TNF α treatment does not affect viability of MM.1S cells, assessed by MTT assay; however, in the presence of compound **1**, viability of the cells was significantly decreased ($p < 0.001$). For example, TNF α (1 ng/mL) induced 60% growth inhibition of MM.1S cells the presence of 10 μ M compound **1**. This effect on MM.1S viability is also confirmed by trypan blue exclusion (data not shown). These studies suggest that NF- κ B mediates protection of MM.1S cells against TNF α -induced apoptosis.

Example 12: Effect of compound 1 on paracrine MM cell growth and IL-6 secretion

[0076] To study the role of NF- κ B activation in regulating IL-6 transcription and secretion, as well as related paracrine MM cell growth in the BM milieu, MM.1S cells were cultured with or without BMSCs, in the presence or absence of compound **1**. As can be seen in Fig 12A, compound **1** blocks constitutive secretion of IL-6 in BMSCs in a dose dependent fashion. Importantly, adhesion of MM.1S cells to BMSCs triggers increased IL-6 secretion (1.6 fold, $p < 0.01$), and compound **1** also blocks this response in a dose dependent fashion. Adherence of MM1S cells to BMSCs also triggers increased MM1S cell growth (1.9 fold), and compound **1** similarly inhibits this augmentation in a dose dependent fashion (Figure 12B). These data confirm the hypothesis that induction of IL-6 secretion from BMSCs triggered by MM cell adhesion is mediated through NF- κ B (Chauhan *et al., Blood* 87:1104 (1996)), and show that compound **1** can abrogate this effect.

Claims

1. Use of an inhibitor of I κ B kinase of formula (I)



or a stereoisomer or physiologically tolerable salt thereof wherein:

B₆, B₇, B₈, and B₉ are independently selected from the group consisting of carbon atom and nitrogen atom, where a total of no more than two of B₆, B₇, B₈, and B₉ are nitrogen atoms; and

in case a):

the substituents R¹, R² and R³ independently of one another are

- 1.1. hydrogen atom,
- 1.2 halogen,
- 1.3. -CN,
- 1.4. -COOH,
- 1.5. -NO₂,
- 1.6. -NH₂,
- 1.7. -O-(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of

1.71 phenyl, which is unsubstituted or mono- to pentasubstituted by halogen or -O-(C₁-C₄)-alkyl,

1.72 halogen,

1.73 -NH₂,

1.7.4 -OH,

1.7.5 -COOR¹⁶, wherein R¹⁶ is hydrogen atom or -(C₁-C₁₀)-alkyl,

1.7.6 -NO₂,

1.7.7 -S(O)_y-R¹⁴, wherein y is zero, 1 or 2, and R¹⁴ is -(C₁-C₁₀)-alkyl, phenyl, which is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, amino or -N(R¹³)₂,

wherein each R¹³ independently is hydrogen atom, phenyl, -(C₁-C₁₀)-alkyl, -C(O)-(C₁-C₇)-alkyl, -C(O)-phenyl, -C(O)-NH-(C₁-C₇)-alkyl, -C(O)-O-phenyl, -C(O)-NH-phenyl, -C(O)-O-(C₁-C₇)-alkyl, or -S(O)_y-R¹⁴, wherein R¹⁴ and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, or

the two R¹³ groups, together with the nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms,

1.7.8 -O-phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11,

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

1.7.10 -(C₃-C₇)-cycloalkyl or

1.7.11 =O,

1.8. -N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above,

1.9. -NH-C(O)-R¹⁵, wherein R¹⁵ is

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

wherein said radical is unsubstituted or mono- to penta-substitute with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -CF₃, benzyl, and -(C₁-C₁₀)-alkyl,

wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

1.9.2 -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above and -O-(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta-substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

1.9.3 -(C₃-C₇)-cycloalkyl,

1.9.4 -N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above, or

1.9.5 phenyl, wherein phenyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -O-(C₁-C₁₀)-alkyl, -CN, -CF₃, and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri-

substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, or two substituents of the phenyl radical together form a dioxolane ring,

- 5 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 with a substituent or substituents independently selected from the group of substituents 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,
- 10 1.13. $-(C_1-C_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group of substituents 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
- 15 1.17. $-CF_3$ or
- 1.18. $-CF_2-CF_3$;

R^4 is

- 20 1. $-(C_1-C_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,
2. $-CF_3$,
3. $-CF_2-CF_3$,
4. $-CN$,
- 25 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 unsubstituted or mono- to pentasubstituted independently of one another by
- 30 7.1 phenyl, which is unsubstituted or mono- to pentasubstituted 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 hydrogen atom or $-(C_1-C_{10})$ -alkyl,
- 35 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 pentasubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, amino, and $-N(R^{13})_2$,
- 40 wherein each R^{13} independently is 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, or $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, or
- 45 the two R^{13} groups, together with the nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms,
- 7.8 $-O$ -phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,
- 7.9 a radical selected from the group consisting of pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, thiophene, 2-isoxazoline, isothiazolidine, 2-isothiazoline, and thiomorpholine,
- 50 7.10 $-(C_3-C_7)$ -cycloalkyl or
- 7.11 $=O$,
- 55 8. $-N(R^{17})_2$, wherein each R^{17} independently is 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, or $-S(O)_y-R^{14}$, wherein R^{14} and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, or the two R^{17} groups, together with the nitrogen atom to which they are

bonded, form a heterocycle having 5 to 7 ring atoms,

9. -NH-C(O)-R¹⁵, wherein R¹⁵ is

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

wherein said radical is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -CF₃, benzyl and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

9.2 -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -O-(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

9.3 -(C₃-C₇)-cycloalkyl,

9.4 -N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above provided that -N(R¹³)₂ is not -NH₂, or

9.5 phenyl, wherein phenyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, -O-(C₁-C₁₀)-alkyl, -CN, -CF₃, and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, or two substituents of the phenyl radical form a dioxolane ring,

10. -C(O)-R¹², wherein R¹² is phenyl or -(C₁-C₇)-alkyl, wherein alkyl or phenyl are mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

11. -C(O)-O-R¹², wherein R¹² is as defined in 10. above,

12. -O-(C₁-C₆)-alkyl-O-(C₁-C₆)-alkyl,

13. -O-(C₀-C₄)-alkyl-(C₃-C₇)-cycloalkyl, or

14. -(C₁-C₄)-alkyl-N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above;

R⁵ is

1. a hydrogen atom,

2. -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.4 above,

3. -C(O)-R⁹, wherein R⁹ is

-NH₂, -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under 7.1 to 7.4, or -N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above, or

4. -S(O)₂-R⁹, wherein R⁹ is as defined in 3. above; or

R⁴ and R⁵, together with the atom to which they are bonded form a heterocycle; or

R³ and R⁵, together with the atom to which they are bonded form a heterocycle containing an additional oxygen atom in the ring; and

or R⁶, R⁷ and R⁸, independently of one another are hydrogen atom or methyl; or

in case b):

the substituents R¹, R² and R⁴ independently of one another are as defined under 1.1 to 1.18 in case a) above; R³ is

1. -CF₃,

2. -CF₂-CF₃,

3. -CN,

4. -COOH,

5. -NO₂,

6. $-\text{NH}_2$,
 7. $-\text{O}-(\text{C}_1-\text{C}_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to penta substituted independently of one another by

5 7.1 phenyl, which is unsubstituted or mono to pentasubstituted by halogen or $-\text{O}-(\text{C}_1-\text{C}_4)$ -alkyl,
 7.2 halogen,
 7.3 $-\text{NH}_2$,
 7.4 $-\text{OH}$,
 7.5 $-\text{COOR}^{16}$, wherein R^{16} is hydrogen atom or $-(\text{C}_1-\text{C}_{10})$ -alkyl,
 10 7.6 $-\text{NO}_2$,
 7.7 $-\text{S}(\text{O})_y-\text{R}^{14}$ wherein y is zero, 1 or 2, R^{14} is $-(\text{C}_1-\text{C}_{10})$ -alkyl, phenyl, which is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of
 15 substituents defined under 1.7.1 to 1.7.11, amino, and $-\text{N}(\text{R}^{13})_2$,
 wherein each R^{13} independently is hydrogen atom phenyl, $-(\text{C}_1-\text{C}_{10})$ -alkyl, $-\text{C}(\text{O})-(\text{C}_1-\text{C}_7)$ -alkyl, $-\text{C}(\text{O})$ -phenyl, $-\text{C}(\text{O})-\text{NH}-(\text{C}_1-\text{C}_7)$ -alkyl, $-\text{C}(\text{O})-\text{O}$ -phenyl, $-\text{C}(\text{O})-\text{NH}$ -phenyl, $-\text{C}(\text{O})-\text{O}-(\text{C}_1-\text{C}_7)$ -alkyl, or $-\text{S}(\text{O})_y-\text{R}^{14}$, wherein R^{14} and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under 1.7.1 to 1.7.11, or the two R^{13} groups, together with the nitrogen atom to which
 20 they are bonded, form a heterocycle having 5 to 7 ring atoms,
 7.8 $-\text{O}$ -phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,
 7.9 a radical selected from the group consisting of pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isox-
 25 azolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene, and thiomorpholine,
 7.10 $-(\text{C}_3-\text{C}_7)$ -cycloalkyl, or
 7.11 $=\text{O}$,

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

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

9.1 a radical selected from the group consisting of pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isox-
 35 azolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene, and thiomorpholine,

wherein said radical is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, $-\text{CF}_3$, benzyl, and $-(\text{C}_1-\text{C}_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

40 9.2 $-(\text{C}_1-\text{C}_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, and $-\text{O}-(\text{C}_1-\text{C}_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

45 9.3 $-(\text{C}_3-\text{C}_7)$ -cycloalkyl,

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

9.5 phenyl, wherein phenyl is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 above, $-\text{O}-(\text{C}_1-\text{C}_{10})$ -alkyl, $-\text{CN}$, $-\text{CF}_3$, and $-(\text{C}_1-\text{C}_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to tri-
 50 substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above, or two substituents of the phenyl radical form a dioxolane ring,

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

11. $-\text{C}(\text{O})-\text{R}^{12}$, wherein R^{12} is phenyl or $-(\text{C}_1-\text{C}_7)$ -alkyl, wherein alkyl or phenyl are unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

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

13. $-(\text{C}_1-\text{C}_{10})$ -alkyl, wherein alkyl is unsubstituted or mono- to pentasubstituted with a substituent or sub-

stituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 above,

14. -O-(C₁-C₆)-alkyl-O-(C₁-C₆)-alkyl,

15. -O-(C₀-C₄)-alkyl-(C₃-C₇)-cycloalkyl or

16. -(C₁-C₄)-alkyl-N(R¹³)₂, wherein R¹³ is as defined in 1.7.7 above;

R⁵ is as defined as R⁵ in case a) above; and

R⁶, R⁷ and R⁸ independently of one another are hydrogen atom or methyl, in the manufacture of a medicament for the treatment of multiple myeloma.

2. Use of N-(6-chloro-9H-β-carbolin-8-yl)-nicotinamide or a stereoisomer or physiologically tolerable salt thereof in the manufacture of a medicament for the treatment of multiple myeloma.

3. Use of claim 1 wherein:

the inhibitor of IκB kinase is a compound of case a);

B₆, B₇, B₈, and B₉ are each a carbon atom; and

R⁴ is -NH-C(O)-R¹⁵, wherein R¹⁵ is as defined under 9.1 to 9.5 in claim 1.

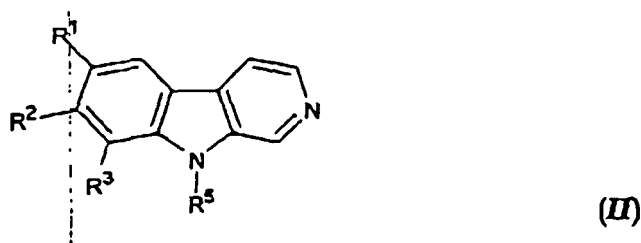
4. Use of claim 3, wherein R¹⁵ is:

a radical selected from the group consisting of pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene, and thiomorpholine,

wherein said radical is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 in claim 1, -CF₃, benzyl, and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 in claim 1; or

phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group consisting of substituents defined under 1.7.1 to 1.7.11 in claim 1, -O-(C₁-C₁₀)-alkyl, -CN, -CF₃, and -(C₁-C₁₀)-alkyl, wherein alkyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under 1.7.1 to 1.7.11 in claim 1, or two substituents of the phenyl radical form a dioxolane ring.

5. Use of an inhibitor of IκB kinase of formula (II)



or a stereoisomer or physiologically tolerable salt thereof; wherein:

R¹ and R² are independently of one another hydrogen atom, halogen, cyano, amino, -O-(C₁-C₄)-alkyl, nitro, -CF₃, -CF₂-CF₃, -S(O)_y-R¹⁴, or -N(R¹⁸)₂, wherein

y is 1 or 2;

R¹⁴ is amino, -(C₁-C₇)-alkyl, or phenyl, wherein the alkyl or phenyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group consisting of:

(a) phenyl, which is unsubstituted or mono- to pentasubstituted by halogen or -O-(C₁-C₄)-alkyl;

(b) halogen;

(c) -NH₂;

(d) -OH;

(e) -COOR¹⁶, wherein R¹⁶ is hydrogen atom or -(C₁-C₁₀)-alkyl;

(f) $-\text{NO}_2$;

(g) $-\text{S}(\text{O})_y-\text{R}^{14}$, wherein y is zero, 1 or 2, and R^{14} is $-(\text{C}_1-\text{C}_{10})$ -alkyl, phenyl, which is unsubstituted or mono- to pentasubstituted with a substituent or substituents independently selected from the group defined under (a) to (k), amino or $-\text{N}(\text{R}^{13})_2$,

wherein each R^{13} independently is hydrogen atom, phenyl, $-(\text{C}_1-\text{C}_{10})$ -alkyl, $-\text{C}(\text{O})-(\text{C}_1-\text{C}_7)$ -alkyl, $-\text{C}(\text{O})$ -phenyl, $-\text{C}(\text{O})-\text{NH}-(\text{C}_1-\text{C}_7)$ -alkyl, $-\text{C}(\text{O})-\text{O}$ -phenyl, $-\text{C}(\text{O})-\text{NH}$ -phenyl, $-\text{C}(\text{O})-\text{O}-(\text{C}_1-\text{C}_7)$ -alkyl, or $-\text{S}(\text{O})_y-\text{R}^{14}$, wherein R^{14} and y are as defined above, and wherein alkyl or phenyl in each case is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under (a) to (k), or the two R^{13} groups, together with the nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms;

(h) $-\text{O}$ -phenyl, wherein phenyl is unsubstituted or mono- to penta- substituted with a substituent or substituents independently selected from the group defined under (a) to (k);

(i) a radical selected from the group consisting of pyrrolidine, tetrahydropyridine, piperidine, piperazine, imidazoline, pyrazolidine, furan, morpholine, pyridine, pyridazine, pyrazine, oxolan, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophene, and thiomorpholine,

(j) $-(\text{C}_3-\text{C}_7)$ -cycloalkyl; and

(k) $=\text{O}$;

each R^{18} independently is hydrogen atom, $-(\text{C}_1-\text{C}_7)$ -alkyl- $\text{C}(\text{O})-(\text{C}_1-\text{C}_7)$ -alkyl, $-\text{C}(\text{O})$ -phenyl, $-\text{C}(\text{O})$ -pyridyl, $-\text{C}(\text{O})-\text{NH}-(\text{C}_1-\text{C}_4)$ -alkyl, $-\text{C}(\text{O})-\text{O}$ -phenyl, $-\text{C}(\text{O})-\text{O}-(\text{C}_1-\text{C}_4)$ -alkyl or $-(\text{C}_1-\text{C}_{10})$ -alkyl, wherein pyridyl or phenyl in each case is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under (a) to (k) above, $-\text{CF}_3$, benzyl, and $-(\text{C}_1-\text{C}_{10})$ alkyl, and wherein alkyl in each case is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under (a) to (k) above; or

the two R^{18} groups, together with nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms;

R^3 is cyano, amino, $-\text{O}-(\text{C}_1-\text{C}_4)$ -alkyl, nitro, $-\text{CF}_3$, $-\text{CF}_2-\text{CF}_3$, $-\text{S}(\text{O})_y-\text{R}^{14}$, or $-\text{N}(\text{R}^{18})_2$, wherein y is 1 or 2;

R^{14} is amino, $-(\text{C}_1-\text{C}_7)$ -alkyl, or phenyl, wherein the alkyl or phenyl is unsubstituted or mono- to tri substituted with a substituent or substituents independently selected from the group of substituents defined under (a) to (k) above;

each R^{18} independently is hydrogen atom, $-(\text{C}_1-\text{C}_7)$ -alkyl- $\text{C}(\text{O})-(\text{C}_1-\text{C}_7)$ -alkyl, $-\text{C}(\text{O})$ -phenyl, $-\text{C}(\text{O})$ -pyridyl, $-\text{C}(\text{O})-\text{NH}-(\text{C}_1-\text{C}_4)$ -alkyl, $-\text{C}(\text{O})-\text{O}$ -phenyl, $-\text{C}(\text{O})-\text{O}-(\text{C}_1-\text{C}_4)$ -alkyl or $-(\text{C}_1-\text{C}_{10})$ -alkyl, wherein pyridyl or phenyl in each case is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under (a) to (k) above, $-\text{CF}_3$, benzyl, and $-(\text{C}_1-\text{C}_{10})$ alkyl, and wherein alkyl in each case is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under (a) to (k) above, or

the two R^{18} groups, together with nitrogen atom to which they are bonded, form a heterocycle having 5 to 7 ring atoms; and

R^5 is hydrogen atom, $-(\text{C}_1-\text{C}_{10})$ -alkyl, $-\text{C}(\text{O})-\text{R}^9$, or $-\text{S}(\text{O})_2-\text{R}^9$, wherein

R^9 is $-(\text{C}_1-\text{C}_{10})$ -alkyl, $-\text{O}-(\text{C}_1-\text{C}_{10})$ -alkyl, or phenyl;

alkyl, in each instance, is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under (a) to (k) above; and

phenyl is unsubstituted or mono- to tri- substituted with a substituent or substituents independently selected from the group of substituents defined under (a) to (k) above and $-\text{N}(\text{R}^{18})_2$, wherein R^{18} is as defined above, in the manufacture of a medicament for the treatment of multiple myeloma.

6. Use of claim 5, wherein:

R^1 is bromo, $-\text{CF}_3$ or chloro;

R^2 is hydrogen atom or $-\text{O}-(\text{C}_1-\text{C}_2)$ -alkyl;

R^3 is $-\text{N}(\text{R}^{18})_2$, wherein each R^{18} independently is hydrogen atom, $-\text{N}-\text{C}(\text{O})$ -pyridyl, $-\text{C}(\text{O})$ -phenyl, $-(\text{C}_1-\text{C}_7)$ -alkyl, $-\text{C}(\text{O})-(\text{C}_1-\text{C}_4)$ -alkyl or $-\text{C}(\text{O})-\text{O}-(\text{C}_1-\text{C}_4)$ -alkyl, wherein alkyl or phenyl, in each instance, is unsubstituted or mono- to trisubstituted with a substituent or substituents independently selected from the group consisting of

halogen and $-\text{O}-(\text{C}_1-\text{C}_2)$ -alkyl; and

R^5 is hydrogen atom, methyl or $-\text{S}(\text{O})_2-\text{CH}_3$.

7. Use of claim 5, wherein:

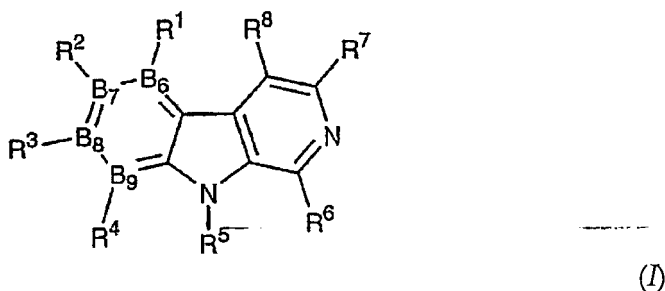
R¹ is chloro, R³ is -H-C(O)-CH₂-O-CH₃, and R² and R⁵ are each hydrogen atom; or

R¹ is chloro, R³ is -N-C(O)-pyridyl, wherein pyridyl is unsubstituted or substituted by chloro, R² is hydrogen atom or -O-CH₃, and R⁵ is hydrogen atom; or

R¹ is chloro, R³ is -N-C(O)-phenyl, wherein phenyl is mono- or di- substituted by fluoro, and R² and R⁵ are each hydrogen atom.

Patentansprüche

1. Verwendung eines Inhibitors der IκB Kinase mit der Formel (I)



oder eines Stereoisomers oder physiologisch verträglichen Salzes davon, wobei:

B₆, B₇, B₈ und B₉ unabhängig ausgewählt sind aus der Gruppe bestehend aus Kohlenstoffatom und Stickstoffatom, wobei eine Gesamtheit von mehr als zwei von B₆, B₇, B₈ und B₉ Stickstoffatome sind; und

im Fall a):

die Substituenten R¹, R² und R³ unabhängig von einander sind

1.1 Wasserstoffatom,

1.2 Halogen,

1.3 -CN,

1.4 -COOH,

1.5 -NO₂,

1.6 -NH₂,

1.7 -O-(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt sich aus der Gruppe bestehend aus

1.7.1 Phenyl, das unsubstituiert oder mono- bis penta-substituiert ist durch Halogen oder -O-(C₁-C₄)-Alkyl,

1.7.2 Halogen,

1.7.3 -NH₂,

1.7.4 -OH,

1.7.5 -COOR¹⁶, wobei R¹⁶ ein Wasserstoffatom oder -(C₁-C₁₀)-Alkyl ist,

1.7.6 -NO₂,

1.7.7 -S(O)_y-R¹⁴, wobei y Null, 1 oder 2 ist, und R¹⁴ - (C₁-C₁₀)-Alkyl, Phenyl ist, das unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten, der unabhängig ausgewählt ist aus der Gruppe, die unter 1.7.1 bis 1.7.11 definiert ist, Amino oder -N(R¹³)₂,

wobei jedes R¹³ unabhängig Wasserstoffatom, Phenyl, -O-(C₁-C₁₀)-Alkyl, -C(O)-(C₁-C₇)-Alkyl, -C(O)-Phenyl, -C(O)-NH-(C₁-C₇)-Alkyl, -C(O)-O-Phenyl, -C(O)-NH-Phenyl, -C(O)-O-(C₁-C₇)-Alkyl oder -S(O)_y-R¹⁴, wobei R¹⁴ und y definiert sind wie oben, und wobei Alkyl oder Phenyl jeweils unsubstituiert oder mono- bis penta-substituiert sind mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe, die unter 1.7.1 bis 1.7.11 definiert ist, oder

die zwei R¹³-Gruppen zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Heterozyklus mit 5 bis 7 Ringatomen bilden,

1.7.8 -O-Phenyl, wobei Phenyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe, die unter 1.7.1 bis 1.7.11 definiert ist,
 1.7.9 ein Radikal ausgewählt aus der Gruppe bestehend aus Pyrrolidin, Tetrahydropyridin, Piperidin, Piperazin, Imidazolin, Pyrazolidin, Furan, Morpholin, Pyridin, Pyridazin, Pyrazin, Oxolan, Imidazolin, Isoxazolidin, 2-Isoxazolin, Isothiazolidin, 2-Isythiazolin, Thiophen und Thiomorpholin,
 1.7.10 -(C₃-C₇)-Zykloalkyl oder
 1.7.11 =O,

1.8 -N(R¹³)₂, wobei R¹³ wie oben in 1.7.7 definiert ist,

1.9 -NH-C(O)-R¹⁵, wobei R¹⁵ ist

1.9.1 ein Radikal ausgewählt aus der Gruppe bestehend aus Pyrrolidin, Tetrahydropyridin, Piperidin, Piperazin, Imidazolin, Pyrazolidin, Furan, Morpholin, Pyridin, Pyridazin, Pyrazin, Oxolan, Imidazolin, Isoxazolidin, 2-Isoxazolin, Isothiazolidin, 2-Isythiazolin, Thiophen und Thiomorpholin,
 wobei besagter Radikal unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind, -CF₃, Benzyl, und -(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,

1.9.2 -(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind, und -O-(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,

1.9.3 -(C₃-C₇)-Zykloalkyl oder

1.9.4 -N(R¹³)₂, wobei R¹³ wie oben in 1.7.7. definiert ist, oder

1.9.5 Phenyl, wobei Phenyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind, -O-(C₁-C₁₀)-Alkyl, -CN, -CF₃, und -(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind, oder zwei Substituenten des Phenylradikals zusammen einen Dioxolan Ring bilden,

1.10 -S(O)_yR¹⁴, wobei R¹⁴ und y wie oben in 1.7.7. definiert sind,

1.11 -C(O)-R¹², wobei R¹² Phenyl oder -(C₁-C₇)-Alkyl ist, wobei Alkyl oder Phenyl unsubstituiert oder mono- bis penta-substituiert sind mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,

1.12 -C(O)-O-R¹², wobei R¹² wie oben in 11. definiert ist,

1.13 -(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,

1.14 -O-(C₁-C₆-Alkyl-O-(C₁-C₆)-Alkyl,

1.15 -O-(C₀-C₄)-Alkyl-O-(C₃-C₇)-Zykloalkyl,

1.16 -(C₁-C₄)-Alkyl-N(R¹³)₂, wobei R¹³ wie oben in 1.7.7. definiert ist,

1.17 -CF₃ oder

1.18 -CF₂-CF₃;

R⁴ ist

1. -(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,

2. -CF₃,

3. -CF₂-CF₃,

4. -CN,

5. -S(O)_y-R¹⁴, wobei R¹⁴ und y wie oben in 1.7.7. definiert sind,

6. -NH₂,

7. -O-(C₁-C₁₀)-Alkyl, wobei Alkyl unabhängig von einander unsubstituiert oder mono- bis penta-substituiert

ist durch

7.1 Phenyl, das unsubstituiert oder mono- bis penta-substituiert ist durch Halogen oder -O-(C₁-C₄)-Alkyl,
 7.2 Halogen,
 7.3 -NH₂,
 7.4 -OH,
 7.5 -COOR¹⁶, wobei R¹⁶ ein Wasserstoffatom oder -(C₁-C₁₀)-Alkyl ist,
 7.6 -NO₂,
 7.7 -S(O)_y-R¹⁴, wobei y Null, 1 oder 2 ist, und R¹⁴ -(C₁-C₁₀)-Alkyl, Phenyl ist, das unsubstituiert oder
 mono- bis penta-substituiert ist mit einem Substituent oder Substituenten oder Substituenten unab-
 hängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,
 Amino und -N(R¹³)₂,
 wobei jedes R¹³ unabhängig ist Wasserstoffatom, Phenyl, -(C₁-C₁₀)-Alkyl, -C(O)-(C₁-C₇)-Alkyl, -C
 (O)-Phenyl, -C(O)-NH-(C₁-C₇)-Alkyl, -C(O)-O-Phenyl, -C(O)-NH-Phenyl, -C(O)-O-(C₁-C₇)-Alkyl oder
 -S(O)_y-R¹⁴, wobei R¹⁴ und y definiert sind wie oben, und wobei Alkyl oder Phenyl jeweils unsubstituiert
 oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt
 aus der Gruppe, die unter 1.7.1 bis 1.7.11 definiert ist, oder
 die zwei R¹³-Gruppen zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Hetero-
 zyklus mit 5 bis 7 Ringatomen bilden,
 7.8 -O-Phenyl, wobei Phenyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent
 oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis
 1.7.11 oben definiert sind,
 7.9 ein Radikal ausgewählt aus der Gruppe bestehend aus Pyrrolidin, Tetrahydropyridin, Piperidin,
 Piperazin, Imidazolin, Pyrazolidin, Furan, Morpholin, Pyridin, Pyridazin, Pyrazin, Oxolan, Imidazolin,
 Isoxazolidin, 2-Isoxazolin, Isothiazolidin, 2-Isotiazolin, Thiophen und Thiomorpholin,
 7.10 -(C₃-C₇)-Zykloalkyl oder
 7.11 =O,

8. -N(R¹⁷)₂, wobei jedes R¹⁷ unabhängig ist Wasserstoffatom, Phenyl, -(C₁-C₁₀)-Alkyl, -C(O)-(C₁-C₇)-Alkyl,
 -C(O)-Phenyl, -C(O)-NH-(C₁-C₇)-Alkyl, -C(O)-O-Phenyl, -C(O)-NH-Phenyl, -C(O)-O-(C₁-C₇)-Alkyl oder -S
 (O)_y-R¹⁴, wobei R¹⁴ und y definiert sind wie oben, und wobei Alkyl oder Phenyl jeweils unsubstituiert oder
 mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der
 Gruppe, die unter 1.7.1 bis 1.7.11 definiert ist, oder die zwei R¹⁷-Gruppen zusammen mit dem Stickstoffatom,
 an das sie gebunden sind, einen Heterozyklus mit 5 bis 7 Ringatomen bilden,
 9. -NH-C(O)-R¹⁵, wobei R¹⁵ ist

9.1 ein Radikal ausgewählt aus der Gruppe bestehend aus Pyrrolidin, Tetrahydropyridin, Piperidin,
 Piperazin, Imidazolin, Pyrazolidin, Furan, Morpholin, Pyridin, Pyridazin, Pyrazin, Oxolan, Imidazolin,
 Isoxazolidin, 2-Isoxazolin, Isothiazolidin, 2-Isotiazolin, Thiophen und Thiomorpholin,
 wobei besagter Radikal unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder
 Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Substituenten, die unter 1.7.1
 bis 1.7.11 oben definiert sind, -CF₃, Benzyl und (C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono-
 bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe
 der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,
 9.2 -(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent
 oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Substituenten, die unter
 1.7.1 bis 1.7.11 oben definiert sind, und -O-(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert ist oder mono-
 bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der
 Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,
 9.3 -(C₃-C₇)-Zykloalkyl oder
 9.4 -N(R¹³)₂, wobei R¹³ wie oben in 1.7.7. definiert ist, vorausgesetzt, dass -N(R¹³)₂ nicht -NH₂ ist, oder
 9.5 Phenyl, wobei Phenyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent
 oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Substituenten, die unter
 1.7.1 bis 1.7.11 oben definiert sind, -O-(C₁-C₁₀)-Alkyl, -CN, -CF₃, und -(C₁-C₁₀)-Alkyl, wobei Alkyl
 unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig
 ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind, oder die
 zwei Substituenten des Phenylradikals zusammen einen Dioxolan Ring bilden,

10. -C(O)-R¹², wobei R¹² Phenyl oder -(C₁-C₇)-Alkyl ist, wobei Alkyl oder Phenyl unsubstituiert oder mono- bis penta-substituiert sind mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,
 11. -C(O)-O-R¹², wobei R¹² wie oben in 10. definiert ist,
 12. -O-(C₁-C₆)-Alkyl-O-(C₁-C₆)-Alkyl,
 13. -O-(C₀-C₄)-Alkyl-(C₃-C₇)-Zykloalkyl, oder
 14. -(C₁-C₄)-Alkyl-N(R¹³)₂, wobei R¹³ wie oben in 1.7.7. definiert ist;

R⁵ ist

1. ein Wasserstoffatom,
 2. -(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe, die unter 1.7.1 bis 1.7.4 oben definiert ist,
 3. -C(O)-R⁹, wobei R⁹ ist
 -NH₂, -(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe, die unter 7.1 bis 7.4 definiert ist, oder -N(R¹³)₂, wobei R¹³ wie in 1.7.7 oben definiert ist, oder
 4. -S(O)₂-R⁹, wobei R⁹ wie oben in 3. definiert ist; oder

R⁴ und R⁵ zusammen mit dem Atom, an das sie gebunden sind, einen Heterozyklus bilden; oder
 R³ und R⁵ zusammen mit dem Atom, an das sie gebunden sind, einen Heterozyklus bilden, der ein zusätzliches Sauerstoffatom in dem Ring enthält; und
 R⁶, R⁷ und R⁸ unabhängig von einander ein Wasserstoffatom oder Methyl sind;

oder
 im Fall b):

die Substituenten R¹, R² und R⁴ unabhängig von einander wie unter 1.1 bis 1.18 im Fall a) oben definiert sind;
 R³ ist

1. -CF₃,
 2. -CF₂-CF₃,
 3. -CN,
 4. -COOH,
 5. -NO₂,
 6. -NH₂,
 7. -O-(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist unabhängig von einander durch

7.1 Phenyl, das unsubstituiert ist oder mono- bis penta-substituiert ist durch Halogen oder -O-(C₁-C₄)-Alkyl,

7.2 Halogen,

7.3 -NH₂,

7.4 -OH,

7.5 -COOR¹⁶, wobei R¹⁶ ein Wasserstoffatom oder -(C₁-C₁₀)-Alkyl ist,

7.6 -NO₂,

7.7 -S(O)_y-R¹⁴, wobei y Null, 1 oder 2 ist, und R¹⁴ - (C₁-C₁₀)-Alkyl, Phenyl ist, das unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus den Substituenten, die unter 1.7.1 bis 1.7.11 definiert sind, Amino und -N(R¹³)₂,

wobei jedes R¹³ unabhängig ist Wasserstoffatom, Phenyl, -(C₁-C₁₀)-Alkyl, -C(O)-(C₁-C₇)-Alkyl, -C(O)-Phenyl, -C(O)-NH-(C₁-C₇)-Alkyl, -C(O)-O-Phenyl, -C(O)-NH-Phenyl, -C(O)-O-(C₁-C₇)-Alkyl oder -S(O)_y-R¹⁴, wobei R¹⁴ und y definiert sind wie oben, und wobei Alkyl oder Phenyl jeweils unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe, die unter 1.7.1 bis 1.7.11 definiert ist, oder

die zwei R¹³-Gruppen zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Heterozyklus mit 5 bis 7 Ringatomen bilden,

7.8 -O-Phenyl, wobei Phenyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent

oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,

7.9 ein Radikal ausgewählt aus der Gruppe bestehend aus Pyrrolidin, Tetrahydropyridin, Piperidin, Piperazin, Imidazolin, Pyrazolidin, Furan, Morpholin, Pyridin, Pyridazin, Pyrazin, Oxolan, Imidazolin, Isoxazolidin, 2-Isoxazolin, Isothiazolidin, 2-Isothiazolin, Thiophen und Thiomorpholin,

7.10 $-(C_3-C_7)$ -Zykloalkyl oder

7.11 $=O$,

8. $-N(R^{13})_2$, wobei R^{13} wie oben in 1.7.7 definiert ist,

9. $-NH-C(O)-R^{15}$, wobei R^{15} ist

9.1 ein Radikal ausgewählt aus der Gruppe bestehend aus Pyrrolidin, Tetrahydropyridin, Piperidin, Piperazin, Imidazolin, Pyrazolidin, Furan, Morpholin, Pyridin, Pyridazin, Pyrazin, Oxolan, Imidazolin, Isoxazolidin, 2-Isoxazolin, Isothiazolidin, 2-Isothiazolin, Thiophen und Thiomorpholin,

wobei besagter Radikal unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind, $-CF_3$, Benzyl, und $-(C_1-C_{10})$ -Alkyl, wobei Alkyl unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,

9.2 $-(C_1-C_{10})$ -Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind, und $-O-(C_1-C_{10})$ -Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,

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

9.4 $-N(R^{13})_2$, wobei R^{13} wie oben in 1.7.7. definiert ist, oder

9.5 Phenyl, wobei Phenyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind, $-O-(C_1-C_{10})$ -Alkyl, $-CN$, $-CF_3$, und $-(C_1-C_{10})$ -Alkyl, wobei Alkyl unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind, oder die zwei Substituenten des Phenylradikals zusammen einen Dioxolan Ring bilden,

10. $-S(O)_y-R^{14}$, wobei R^{14} und y wie oben in 1.7.7. definiert sind,

11. $-C(O)-R^{12}$, wobei R^{12} Phenyl oder $-(C_1-C_7)$ -Alkyl ist, wobei Alkyl oder Phenyl unsubstituiert oder mono- bis penta-substituiert sind mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,

12. $-C(O)-O-R^{12}$, wobei R^{12} wie oben in 11. definiert ist,

13. $-(C_1-C_{10})$ -Alkyl, wobei Alkyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 oben definiert sind,

14. $-O-(C_1-C_6)$ -Alkyl- $-O-(C_1-C_6)$ -Alkyl,

15. $-O-(C_0-C_4)$ -Alkyl- $-(C_3-C_7)$ -Zykloalkyl,

16. $-(C_1-C_4)$ -Alkyl- $-N(R^{13})_2$, wobei R^{13} wie oben in 1.7.7. definiert ist;

R^5 definiert ist wie im Fall a) oben; und

R^6 , R^7 und R^8 unabhängig von einander ein Wasserstoffatom oder Methyl sind, für die Herstellung eines Medikaments zur Behandlung des multiplen Myeloms.

2. Verwendung von N-(6-Chloro-9H- β -Carbolin-8-yl)-Nicotinamid oder eines Stereoisomers oder physiologisch verträglichen Salzes davon zur Herstellung eines Medikaments zur Behandlung des multiplen Myeloms.

3. Verwendung gemäß Anspruch 1, wobei:

der Inhibitor der I κ B Kinase eine Verbindung des Falles a) ist;

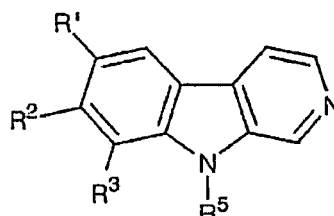
B_6 , B_7 , B_8 und B_9 jeweils ein Kohlenstoffatom sind; und

R^4 $-NH-C(O)-R^{15}$ ist, wobei R^{15} wie in Anspruch 1 unter 9.1 bis 9.5 definiert ist.

4. Verwendung gemäß Anspruch 3, wobei R¹⁵ ist:

ein Radikal ausgewählt aus der Gruppe bestehend aus Pyrrolidin, Tetrahydropyridin, Piperidin, Piperazin, Imidazolin, Pyrazolidin, Furan, Morpholin, Pyridin, Pyridazin, Pyrazin, Oxolan, Imidazolin, Isoxazolidin, 2-Isoxazolin, Isothiazolidin, 2-Isothiazolin, Thiophen und Thiomorpholin, wobei besagter Radikal unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Substituenten, die unter 1.7.1 bis 1.7.11 in Anspruch 1 definiert sind, -CF₃, Benzyl, und - (C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 in Anspruch 1 definiert sind, oder Phenyl, wobei Phenyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Substituenten, die unter 1.7.1 bis 1.7.11 in Anspruch 1 definiert sind, -O-(C₁-C₁₀)-Alkyl, -CN, -CF₃, und -(C₁-C₁₀)-Alkyl, wobei Alkyl unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter 1.7.1 bis 1.7.11 in Anspruch 1 definiert sind, oder zwei Substituenten des Phenylradikals zusammen einen Dioxolan Ring bilden.

5. Verwendung eines Inhibitors der IκB Kinase mit der Formel (II)



(II)

oder eines Stereoisomers oder physiologisch verträglichen Salzes davon, wobei:

R¹ und R² unabhängig von einander Wasserstoffatom, Halogen, Cyano, Amino, -O-(C₁-C₄)-Alkyl, Nitro, -CF₃, -CF₂-CF₃, -S(O)_y-R¹⁴ oder -N(R¹⁸)₂ sind, wobei y 1 oder 2 ist;

R¹⁴ Amino, -(C₁-C₇)-Alkyl oder Phenyl ist, wobei das Alkyl oder Phenyl unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus:

- (a) Phenyl, das unsubstituiert oder mono- bis penta-substituiert ist durch Halogen oder -O-(C₁-C₄)-Alkyl,
- (b) Halogen,
- (c) -NH₂,
- (d) -OH,
- (e) -COOR¹⁶, wobei R¹⁶ ein Wasserstoffatom oder -(C₁-C₁₀)-Alkyl ist,
- (f) -NO₂,
- (g) -S(O)_y-R¹⁴, wobei y Null, 1 oder 2 ist, und R¹⁴ -(C₁-C₁₀)-Alkyl, Phenyl ist, das unsubstituiert oder mono- bis penta-substituiert ist, mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe, die unter (a) bis (k) definiert ist, Amino und -N(R¹³)₂, wobei jedes R¹³ unabhängig ist Wasserstoffatom, Phenyl, -(C₁-C₁₀)-Alkyl, -C(O)-(C₁-C₇)-Alkyl, -C(O)-Phenyl, -C(O)-NH-(C₁-C₇)-Alkyl, -C(O)-O-Phenyl, -C(O)-NH-Phenyl, -C(O)-O-(C₁-C₇)-Alkyl oder -S(O)_y-R¹⁴, wobei R¹⁴ und y definiert sind wie oben, und wobei Alkyl oder Phenyl jeweils unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe, die unter (a) bis (k) definiert ist, oder die zwei R¹³-Gruppen zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Heterozyklus mit 5 bis 7 Ringatomen bilden,
- (h) -O-Phenyl, wobei Phenyl unsubstituiert oder mono- bis penta-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe, die unter (a) bis (k) definiert ist,
- (i) ein Radikal ausgewählt aus der Gruppe bestehend aus Pyrrolidin, Tetrahydropyridin, Piperidin, Piperazin, Imidazolin, Pyrazolidin, Furan, Morpholin, Pyridin, Pyridazin, Pyrazin, Oxolan, Imidazolin, Isoxazolidin, 2-

Isioxazolin, Isothiazolidin, 2-Isiothiazolin, Thiophen und Thiomorpholin,

(j) $-(C_3-C_7)$ -Zykloalkyl; und

(k) $=O$,

wobei R^{18} jeweils unabhängig ist Wasserstoffatom, $-(C_1-C_7)$ -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 oder $-(C_1-C_{10})$ -Alkyl, wobei Pyridyl oder Phenyl jeweils unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die oben unter (a) bis (k) definiert sind, $-CF_3$, Benzyl, und $-(C_1-C_{10})$ -Alkyl, und wobei Alkyl jeweils unsubstituiert oder mono- bis tri-substituiert mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter (a) bis (k) oben definiert sind; oder

die zwei R^{18} -Gruppen zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Heterozyklus mit 5 bis 7 Ringatomen bilden;

R^3 ist Zyano, Amino, $-O-(C_1-C_4)$ -Alkyl, Nitro, $-CF_3$, $-CF_2-CF_3$, $-S(O)_y-R^{14}$ oder $-N(R^{18})_2$, wobei

y 1 oder 2 ist;

R^{14} Amino, $-(C_1-C_7)$ -Alkyl oder Phenyl ist, wobei das Alkyl oder Phenyl unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter (a) bis (k) oben definiert sind;

wobei R^{18} jeweils unabhängig ist Wasserstoffatom, $-(C_1-C_7)$ -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 oder $-(C_1-C_{10})$ -Alkyl, wobei Pyridyl oder Phenyl jeweils unsubstituiert oder mono- bis tri-substituiert sind mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die oben unter (a) bis (k) oben definiert sind, $-CF_3$, Benzyl, und $-(C_1-C_{10})$ -Alkyl, und wobei Alkyl jeweils unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter (a) bis (k) oben definiert sind; oder

die zwei R^{18} -Gruppen zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Heterozyklus mit 5 bis 7 Ringatomen bilden; und

R^5 Wasserstoffatom, $-O-(C_1-C_{10})$ -Alkyl, $-C(O)-R^9$ oder $-S(O)_2-R^9$ ist, wobei R^9 $-(C_1-C_{10})$ -Alkyl, $-O-(C_1-C_{10})$ -Alkyl oder Phenyl ist;

Alkyl, bei jedem Vorkommen, unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter (a) bis (k) oben definiert ist; und Phenyl unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe der Substituenten, die unter (a) bis (k) oben definiert sind und $-N(R^{18})_2$, wobei R^{18} wie oben definiert ist, für die Herstellung eines Medikaments zur Behandlung des multiplen Myeloms.

6. Verwendung gemäß Anspruch 5, wobei:

R^1 Brom, $-CF_3$ oder Chlor ist;

R^2 ein Wasserstoffatom oder $-O-(C_1-C_2)$ -Alkyl ist;

R^9 $-N(R^{18})_2$ ist, wobei R^{18} jeweils unabhängig ist Wasserstoffatom, $-N-C(O)$ -Pyridyl, $-C(O)$ -Phenyl, $-(C_1-C_7)$ -Alkyl, $-C(O)-(C_1-C_4)$ -Alkyl oder $-C(O)-O-(C_1-C_4)$ -Alkyl, wobei Alkyl oder Phenyl bei jedem Vorkommen unsubstituiert oder mono- bis tri-substituiert ist mit einem Substituent oder Substituenten unabhängig ausgewählt aus der Gruppe bestehend aus Halogen und $-O-(C_1-C_2)$ -Alkyl; und

R^5 Wasserstoffatom, Methyl oder $-S(O)_2-CH_3$ ist.

7. Verwendung gemäß Anspruch 5, wobei:

R^1 Chlor ist, R^3 $-H-C(O)-CH_2-O-CH_3$ ist, und R^2 und R^5 jeweils Wasserstoffatome sind; oder

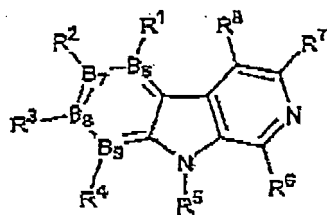
R^1 Chlor ist, R^3 $-N-C(O)$ -Pyridyl ist, wobei Pyridyl unsubstituiert oder substituiert ist durch Chlor, R^2 Wasserstoffatom oder $-O-CH_3$ ist, und R^5 Wasserstoffatom ist;

oder

R^1 Chlor ist, R^3 $-N-C(O)$ -Phenyl ist, wobei Phenyl mono- oder di-substituiert durch Fluor ist, und R^2 und R^5 jeweils Wasserstoffatome sind.

Revendications

1. - Utilisation d'un inhibiteur de la IκB kinase de formule (I)



(I)

ou d'un stéréoisomère ou d'un sel physiologiquement tolérable de celui-ci, dans laquelle :

- B₆, B₇, B₈ et B₉ sont indépendamment choisis dans le groupe constitué par un atome de carbone et un atome d'azote, où un total de pas plus de deux de B₆, B₇, B₈ et B₉ sont des atomes d'azote ; et

dans le cas a) :

- les substituants R¹, R² et R³ indépendamment les uns des autres sont :

1.1 un atome d'hydrogène,

1.2 un halogène,

1.3 -CN,

1.4 -COOH,

1.5 -NO₂,

1.6 -NH₂,

1.7 -O- alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par

1.7.1 phényle, qui est non substitué ou mono- à penta-substitué par halogène ou -O-alkyle en C₁-C₄,

1.7.2 halogène,

1.7.3 -NH₂,

1.7.4 -OH,

1.7.5 -COOR¹⁶, où R¹⁶ est un atome d'hydrogène ou alkyle en C₁-C₁₀,

1.7.6 -NO₂,

1.7.7 -S(O)_y-R¹⁴, où y est zéro, 1 ou 2, et R¹⁴ est alkyle en C₁-C₁₀, phényle, qui est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe défini sous 1.7.1 à 1.7.11, amino ou -N(R¹³)₂,

où chaque R¹³ est indépendamment un atome d'hydrogène, phényle, alkyle en C₁-C₁₀, -C(O)- alkyle en C₁-C₇, -C(O)-phényle, -C(O)-NH-alkyle en C₁-C₇, -C(O)-O-phényle, -C(O)-NH-phényle, -C(O)-O-alkyle en C₁-C₇ ou -S(O)_y-R¹⁴, où R¹⁴ et y sont tels que définis ci-dessus, et où alkyle ou phényle dans chaque cas est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe défini sous 1.7.1 à 1.7.11, ou les deux groupes R¹³, conjointement avec l'atome d'azote auquel ils sont liés, forment un hétérocycle ayant 5 à 7 atomes de noyau,

1.7.8. -O-phényle, où phényle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe défini sous 1.7.1 à 1.7.11,

1.7.9. un radical choisi dans le groupe constitué par pyrrolidine, tétrahydropyridine, pipéridine, pipérazine, imidazoline, pyrazolidine, furanne, morpholine, pyridine, pyridazine, pyrazine, oxolane, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophène et thiomorpholine,

1.7.10 cycloalkyle en C₃-C₇ ou

1.7.11 =O,

1.8 -N(R¹³)₂, où R¹³ est tel que défini sous 1.7.7 ci-dessus,

1.9 -NH-C(O)-R¹⁵, où R¹⁵ est

1.9.1 un radical choisi dans le groupe constitué par pyrrolidine, tétrahydropyridine, pipéridine, pipérazine, imidazoline, pyrazolidine, furanne, morpholine, pyridine, pyridazine, pyrazine, oxolane, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophène et thiomorpholine,

où ledit radical est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 ci-dessus, -CF₃, benzyle et alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous

1.7.1 à 1.7.11 ci-dessus,
1.9.2 alkyl en C₁-C₁₀, où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 ci-dessus et -O-alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

1.9.3 cycloalkyle en C₃-C₇,

1.9.4 -N(R¹³)₂, où R¹³ est tel que défini en 1.7.7 ci-dessus, ou

1.9.5 phényle, où phényle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 ci-dessus, -O- alkyle en C₁-C₁₀, -CN, -CF₃ et alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus, ou deux substituants du radical phényle forment ensemble un noyau de dioxolane,

1.10. -S(O)_y-R¹⁴, où R¹⁴ et y sont tels que définis en 1.7.7 ci-dessus,

1.11. -C(O)-R¹², où R¹² est phényle ou alkyle en C₁-C₇, où alkyle ou phényle sont non substitués ou mono- à penta-substitués par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

1.12. -C(O)-O-R¹², où R¹² est tel que défini en 1.1. ci-dessus,

1.13. alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

1.14. -O-alkyle en (C₁-C₆)-O-alkyle en (C₁-C₆),

1.15. -O-alkyle en (C₀-C₄)-cycloalkyle en (C₃-C₇),

1.16. -alkyle en (C₁-C₄)-N(R¹³)₂, où R¹³ est tel que défini en 1.7.7 ci-dessus,

1.17. -CF₃ ou

1.18. -CF₂-CF₃ ;

R₄ est :

1. alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

2. -CF₃,

3. -CF₂-CF₃,

4. -CN,

5. -S(O)_y-R¹⁴, où R¹⁴ et y sont tels que définis dans 1.7.7 ci-dessus,

6. -NH₂,

7. -O-alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à penta-substitué indépendamment les uns des autres par :

7.1 phényle, qui est non substitué ou mono- à penta-substitué par un halogène ou -O-alkyle en C₁-C₄,

7.2 halogène,

7.3 -NH₂,

7.4 -OH,

7.5 -COOR¹⁶, où R¹⁶ est un atome d'hydrogène ou alkyle en C₁-C₁₀,

7.6 -NO₂,

7.7 -S(O)_y-R¹⁴, où y est zéro, 1 ou 2, R¹⁴ est alkyle en C₁-C₁₀, un phényle, qui est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus, amino et -N(R¹³)₂,

où chaque R¹³ est indépendamment un atome d'hydrogène, phényle, alkyle en C₁-C₁₀, -C(O)-alkyle en C₁-C₇, -C(O)-phényle, -C(O)-NH-alkyle en C₁-C₇, -C(O)-O-phényle, -C(O)-NH-phényle, -C(O)-O-alkyle en C₁-C₇, ou -S(O)_y-R¹⁴, où R¹⁴ et y sont tels que définis ci-dessus, et où alkyle et phényle dans chaque cas est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe défini sous 1.7.1. à 1.7.11, ou

les deux groupes R^{13} , conjointement avec l'atome d'azote auquel ils sont liés, forment un hétérocycle ayant 5 à 7 atomes de noyau,

7.8 -O-phényle, où phényle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

7.9 un radical choisi dans le groupe constitué par pyrrolidine, tétrahydropyridine, pipéridine, pipérazine, imidazoline, pyrazolidine, furanne, morpholine, pyridine, pyridazine, pyrazine, oxolane, imidazoline, isoxazolidine, thiophène, 2-isoxazoline, isothiazolidine, 2-isothiazoline, et thiomorpholine,

7.10 cycloalkyle en C_3 - C_7 ou

7.11 =O,

8. $-N(R^{17})_2$, où chaque R^{17} est indépendamment un atome d'hydrogène, phényle, alkyle en C_1 - C_{10} , -C(O)-alkyle en C_1 - C_7 , -C(O)-phényle, -C(O)-NH-alkyle en C_1 - C_7 , -C(O)-O-phényle, -C(O)-NH-phényle, -C(O)-O-alkyle en C_1 - C_7 , ou -S(O)_y- R^{14} , où R^{14} et y sont tels que définis ci-dessus, et où alkyle ou phényle dans chaque cas est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe défini sous 1.7.1. à 1.7.11, ou les deux groupés R^{17} , conjointement avec l'atome d'azote auquel ils sont liés, forment un hétérocycle ayant 5 à 7 atomes de noyau,

9. -NH-C(O)- R^{15} , où R^{15} est:

9.1 un radical choisi dans le groupe constitué par pyrrolidine, tétrahydropyridine, pipéridine, pipérazine, imidazoline, pyrazolidine, furanne, morpholine, pyridine, pyridazine, pyrazine, oxolane, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophène et thiomorpholine,

où ledit radical est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 ci-dessus, -CF₃, benzyle et alkyle en C_1 - C_{10} , où alkyle est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

9.2 alkyle en C_1 - C_{10} , où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 ci-dessus, -O-alkyle en C_1 - C_{10} , où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

9.3 cycloalkyle en C_3 - C_7 ,

9.4 $-N(R^{13})_2$, où R^{13} est tel que défini en 1.7.7 ci-dessus à la condition que $-N(R^{13})_2$ ne soit pas -NH₂, ou

9.5 phényle, où phényle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 ci-dessus, -O-alkyle en C_1 - C_{10} , -CN, -CF₃, et alkyle en C_1 - C_{10} , où alkyle est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus, ou deux substituants du radical phényle forment un noyau dioxolane,

10. -C(O)- R^{12} , où R^{12} est phényle ou alkyle en C_1 - C_7 , où alkyle ou phényle sont mono- à penta-substitués par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

11. -C(O)-O- R^{12} , où R^{12} est tel que défini en 10. ci-dessus,

12. -O-alkyle en (C_1 - C_6) -O-alkyle en (C_1 - C_6),

13. -O-alkyle en (C_0 - C_4) -cycloalkyle en (C_3 - C_7), ou

14. alkyle en (C_1 - C_4)- $N(R^{13})_2$, où R^{13} est tel que défini dans 1.7.7 ci-dessus ;

R^5 est :

1. un atome d'hydrogène,

2. alkyle en C_1 - C_{10} , où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe défini sous 1.7.1. à 1.7.4 ci-dessus,

3. -C(O)- R^9 , où R^9 est

-NH₂, alkyle en C_1 - C_{10} , où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe défini sous 7.1. à 7.4, ou -N(R^{13})₂, où R^{13} est tel que défini en 1.7.7 ci-dessus, ou

4. $-S(O)_2-R^9$, où R^9 est tel que défini en 3. ci-dessus ; ou R^4 et R^5 , conjointement avec l'atome auquel ils sont liés, forment un hétérocycle ; ou

R^3 et R^5 , conjointement avec l'atome auquel ils sont liés, forment un hétérocycle contenant un atome d'oxygène supplémentaire dans le noyau ; et

R^6 , R^7 et R^8 , indépendamment les uns des autres sont un atome d'hydrogène ou méthyle ; ou

dans le cas b) :

les substituants R^1 , R^2 et R^4 indépendamment les uns des autres sont tels que définis sous 1.1 à 1.18 dans le cas a) ci-dessus ;

R^3 est :

1. $-CF_3$,

2. $-CF_2CF_3$,

3. $-CN$,

4. $-COOH$,

5. $-NO_2$,

6. $-NH_2$

7. $-O$ -alkyle en C_1-C_{10} , où alkyle est non substitué ou mono- à penta-substitué indépendamment les uns des autres par :

7.1 phényle, qui est non substitué ou mono- à penta-substitué par un halogène ou $-O$ -alkyle en C_1-C_4 ,

7.2 halogène,

7.3 $-NH_2$,

7.4 $-OH$,

7.5 $-COOR^{16}$, où R^{16} est un atome d'hydrogène ou alkyle en C_1-C_{10} ,

7.6 $-NO_2$,

7.7 $-S(O)_y-R^{14}$, où y est zéro, 1 ou 2, R^{14} est alkyle en C_1-C_{10} , phényle, qui est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11, amino et $-N(R^{13})_2$,

où chaque R^{13} est indépendamment un atome d'hydrogène, phényle, alkyle en C_1-C_{10} , $-C(O)$ -alkyle en C_1-C_7 , $-C(O)$ -phényle, $-C(O)$ -NH-alkyle en C_1-C_7 , $-C(O)$ -O-phényle, $-C(O)$ -NH-phényle, $-C(O)$ -O-alkyle en C_1-C_7 , ou $S(O)_y-R^{14}$, où R^{14} et y sont tels que définis ci-dessus, et où alkyle ou phényle dans chaque cas est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe défini sous 1.7.1 à 1.7.11, ou

les deux groupes R^{13} , conjointement avec l'atome d'azote auquel ils sont liés, forment un hétérocycle ayant 5 à 7 atomes de noyau,

7.8 $-O$ -phényle, où phényle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

7.9 un radical choisi dans le groupe constitué par pyrrolidine, tétrahydropyridine, pipéridine, pipérazine, imidazoline, pyrazolidine, furanne, morpholine, pyridine, pyridazine, pyrazine, oxolane, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophène et thiomorpholine,

7.10 cycloalkyle en C_3-C_7 , ou

7.11 $=O$,

8. $-N(R^{13})_2$, où R^{13} est tel que défini en 1. 7. 7 ci-dessus,

9. $-NH-C(O)-R^{15}$, où R^{15} est :

9.1 un radical choisi dans le groupe constitué par pyrrolidine, tétrahydropyridine, pipéridine, pipérazine, imidazoline, pyrazolidine, furanne, morpholine, pyridine, pyridazine, pyrazine, oxolane, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophène et thiomorpholine,

où ledit radical est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 ci-dessus, $-CF_3$, benzyle et alkyle en C_1-C_{10} , où alkyle est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

9.2 alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 ci-dessus, et -O-alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

9.3 cycloalkyle en C₃-C₇,

9.4 -N(R¹³)₂, où R¹³ est tel que défini en 1. 7. 7 ci-dessus, ou

9.5 phényle, où phényle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 ci-dessus, -O-alkyle en C₁-C₁₀, -CN, -CF₃ et alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus, ou deux substituants du radical phényle forment un noyau dioxolane,

10. -S(O)_y-R¹⁴, où R¹⁴ et y sont tels que définis en 1.7.7 ci-dessus,

11. -C(O)-R¹², où R¹² est phényle ou alkyle en C₁-C₇, où alkyle ou phényle sont non substitués ou mono- à penta-substitués par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

12. -C(O)-O-R¹², où R¹² est tel que défini en 11. ci-dessus,

13. alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 ci-dessus,

14. -O-alkyle en (C₁-C₆)-O-alkyle en (C₁-C₆),

15. -O-alkyle en (C₀-C₄)-cycloalkyle en (C₃-C₇), ou

16. alkyle en (C₁-C₄)-N(R¹³)₂, où R¹³ est tel que défini en 1.7.7 ci-dessus ;

R⁵ est défini comme R⁵ dans le cas a) ci-dessus ; et

R⁶, R⁷ et R⁸ indépendamment les uns des autres, sont atome d'hydrogène ou méthyle, pour la fabrication d'un médicament pour le traitement du myélome multiple.

2. - Utilisation d'un N-(6-chloro-9H-β-carbolin-8-yl)-nicotinamide ou d'un stéréoisomère ou d'un sel physiologiquement tolérable de celui-ci pour la fabrication d'un médicament pour le traitement du myélome multiple.

3. - Utilisation selon la revendication 1, dans laquelle :

- l'inhibiteur de la *κ*B kinase est un composé du cas a) ;

- B₆, B₇, B₈ et B₉ sont chacun un atome de carbone ; et

- R⁴ est -NH-C(O)-R¹⁵, où R¹⁵ est tel que défini sous 9.1 à 9.5 dans la revendication 1.

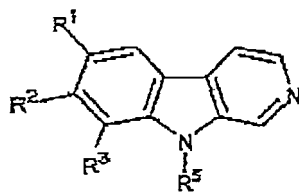
4. - Utilisation selon la revendication 3, dans laquelle R¹⁵ est :

un radical choisi dans le groupe constitué par pyrrolidine, tétrahydropyridine, pipéridine, pipérazine, imidazoline, pyrazolidine, furanne, morpholine, pyridine, pyridazine, pyrazine, oxolane, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophène et thiomorpholine,

où ledit radical est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 dans la revendication 1, -CF₃, un benzyle et un alkyle en C₁-C₁₀, où l'alkyle est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 dans la revendication 1 ; ou

phényle, où phényle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par les substituants définis sous 1.7.1 à 1.7.11 dans la revendication 1, -O-alkyle en C₁-C₁₀, -CN, -CF₃ et alkyle en C₁-C₁₀, où alkyle est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous 1.7.1 à 1.7.11 dans la revendication 1, ou deux substituants du radical phényle forment un noyau dioxolane.

5. - Utilisation d'un inhibiteur de la *κ*B kinase de formule (I)



(II)

ou d'un stéréoisomère ou d'un sel physiologiquement tolérable de celui-ci ;
où :

- R¹ et R² indépendamment l'un de l'autre sont un atome d'hydrogène, un halogène, cyano, amino, -O-alkyle en C₁-C₄, nitro, -CF₃, -CF₂-CF₃, -S(O)_y-R¹⁴ ou -N(R¹⁸)₂, où y est 1 ou 2 ;

R¹⁴ est amino, alkyle en C₁-C₇ ou phényle, où alkyle ou phényle est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par :

- (a) phényle, qui est non substitué ou mono- à penta-substitué par halogène ou -O-alkyle en C₁-C₄ ;
- (b) halogène ;
- (c) -NH₂ ;
- (d) -OH ;
- (e) -COOR¹⁶, où R¹⁶ est un atome d'hydrogène ou un alkyle en C₁-C₁₀ ;
- (f) -NO₂ ;
- (g) -S(O)_y-R¹⁴, où y est zéro, 1 ou 2, et R¹⁴ est alkyle en C₁-C₁₀, phényle, qui est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe défini sous (a) à (k), amino ou -N(R¹³)₂, où chaque R¹³ indépendamment est un atome d'hydrogène, phényle, alkyle en C₁-C₁₀, -C(O)-alkyle en C₁-C₇, -C(O)-phényle, -C(O)-NH-alkyle en C₁-C₇, -C(O)-O-phényle, -C(O)-NH-phényle, -C(O)-O-alkyle en C₁-C₇, ou -S(O)_y-R¹⁴, où R¹⁴ et y sont tels que définis ci-dessus, et où alkyle ou phényle dans chaque cas est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe défini sous (a) à (k), ou les deux groupes R¹³, conjointement avec l'atome d'azote auquel ils sont liés, forment un hétérocycle ayant 5 à 7 atomes de noyau ;
- (h) -O-phényle, où phényle est non substitué ou mono- à penta-substitué par un substituant ou des substituants indépendamment choisis dans le groupe défini sous (a) à (k) ;
- (i) un radical choisi dans le groupe constitué par pyrrolidine, tétrahydropyridine, pipéridine, pipérazine, imidazoline, pyrazolidine, furanne, morpholine, pyridine, pyridazine, pyrazine, oxolane, imidazoline, isoxazolidine, 2-isoxazoline, isothiazolidine, 2-isothiazoline, thiophène et thiomorpholine,
- (j) cycloalkyle en C₃-C₇ ; et
- (k) =O ;

chaque R¹⁸ est indépendamment un atome d'hydrogène, alkyle en (C₁-C₇), -C(O)-alkyle en (C₁-C₇), -C(O)-phényle, -C(O)-pyridyle, -C(O)-NH-alkyle en C₁-C₄, -C(O)-O-phényle, -C(O)-O-alkyle en C₁-C₄ ou alkyle en C₁-C₁₀, où pyridyle ou phényle dans chaque cas est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous (a) à (k) ci-dessus, -CF₃, benzyle et alkyle en C₁-C₁₀, et où alkyle dans chaque cas est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous (a) à (k) ci-dessus ; ou

les deux groupes R¹⁸, conjointement avec l'atome d'azote auquel ils sont liés, forment un hétérocycle ayant 5 à 7 atomes de noyau ;

R³ est cyano, amino, -O-alkyle en C₁-C₄, nitro, -CF₃, -CF₂-CF₃, -S(O)_y-R¹⁴, ou -N(R¹⁸)₂, où y est 1 ou 2 ;

R¹⁴ est amino, alkyle en C₁-C₇ ou phényle, où l'alkyle ou le phényle est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants défini sous (a) à (k) ci-dessus ; chaque R¹⁸ indépendamment est un atome d'hydrogène, alkyle en (C₁-C₇), -C(O)-alkyle en (C₁-C₇), -C(O)-phényle, -C(O)-pyridyle, -C(O)-NH-alkyle en C₁-C₄, -C(O)-O-phényle, -C(O)-O-alkyle en C₁-C₄ ou alkyle en C₁-C₁₀, où pyridyle ou phényle dans chaque cas est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous

(a) à (k) ci-dessus, -CF₃, benzyle et alkyle en C₁-C₁₀, et où alkyle dans chaque cas est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous (a) à (k) ci-dessus, ou les deux groupes R¹⁸, conjointement avec l'atome d'azote auquel ils sont liés, forment un hétérocycle ayant 5 à 7 atomes de noyau ; et

R⁵ est un atome d'hydrogène, alkyle en C₁-C₁₀, -C(O)-R⁹ ou -S(O)₂-R⁹, où

R⁹ est alkyle en C₁-C₁₀, -O-alkyle en C₁-C₁₀ ou phényle ;

alkyle, dans chaque cas, est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants définis sous (a) à (k) ci-dessus ; et

phényle est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe des substituants défini sous (a) à (k) ci-dessus et - N(R¹⁸)₂, où R¹⁸ est tel que défini ci-dessus,

pour la fabrication d'un médicament pour le traitement du myélome multiple.

6. - Utilisation selon la revendication 5, dans laquelle :

- R¹ est bromo, -CF₃ ou chloro ;

- R² est un atome d'hydrogène ou O-alkyle en C₁-C₂ ;

- R³ est -N(R¹⁸)₂, où chaque R¹⁸ est indépendamment un atome d'hydrogène, -N-C(O)-pyridyle, -C(O)-phényle, alkyle en C₁-C₇, -C(O)-alkyle en C₁-C₄, ou -C(O)-O-alkyle en C₁-C₄, où alkyle ou phényle, dans chaque cas, est non substitué ou mono- à tri-substitué par un substituant ou des substituants indépendamment choisis dans le groupe constitué par halogène et -O-alkyle en C₁-C₂ ; et

- R⁵ est un atome d'hydrogène, un méthyle ou -S(O)₂-CH₃.

7. - Utilisation selon la revendication 5, dans laquelle :

- R¹ est chloro, R³ est -H-C(O)-CH₂-O-CH₃, et R² et R⁵ sont chacun un atome d'hydrogène ; ou

- R¹ est chloro, R³ est -N-C(O)-pyridyle, où pyridyle est non substitué ou substitué par chloro, R² est un atome d'hydrogène ou -O-CH₃, et R⁵ est un atome d'hydrogène ;

ou

- R¹ est chloro, R³ est -N-C(O)-phényle, où phényle est mono- ou di-substitué par un fluore, et R² et R⁵ sont chacun un atome d'hydrogène.

FIG. 1A

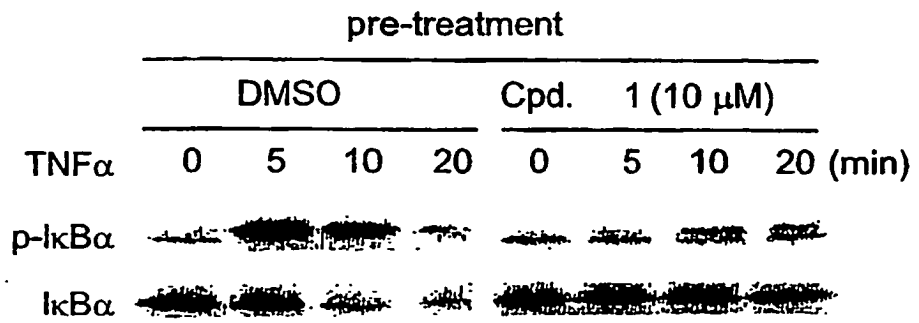


FIG. 1B

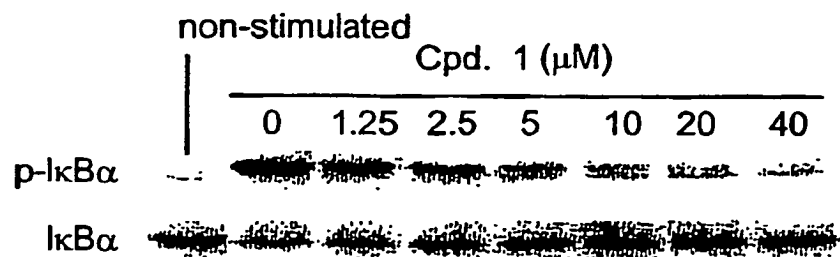
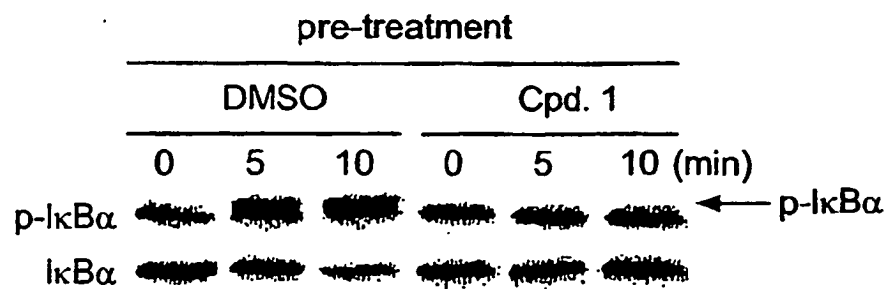


FIG. 1C



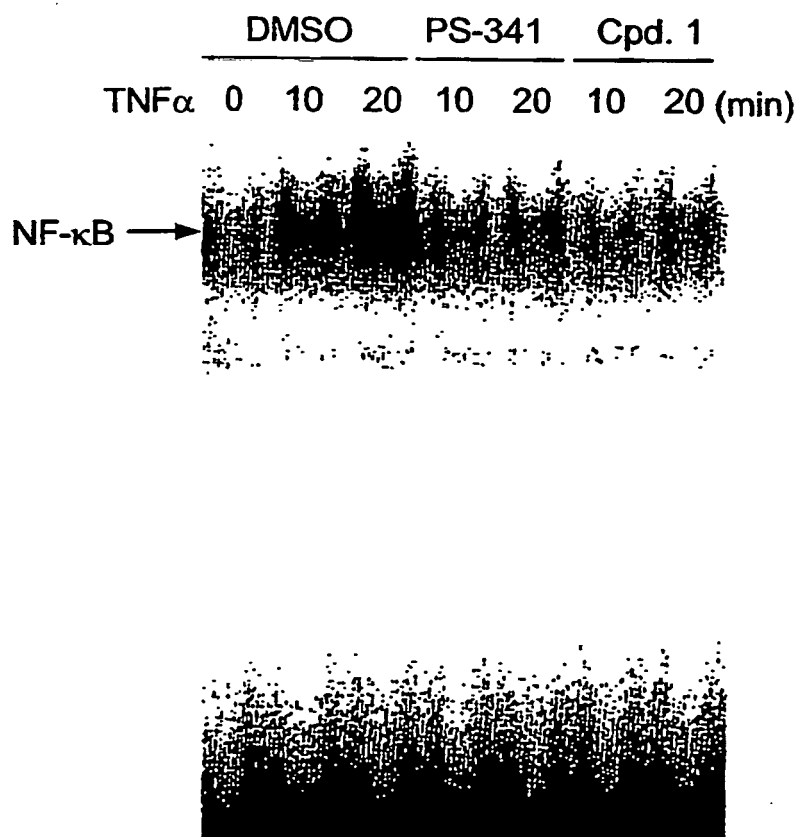


FIG. 2

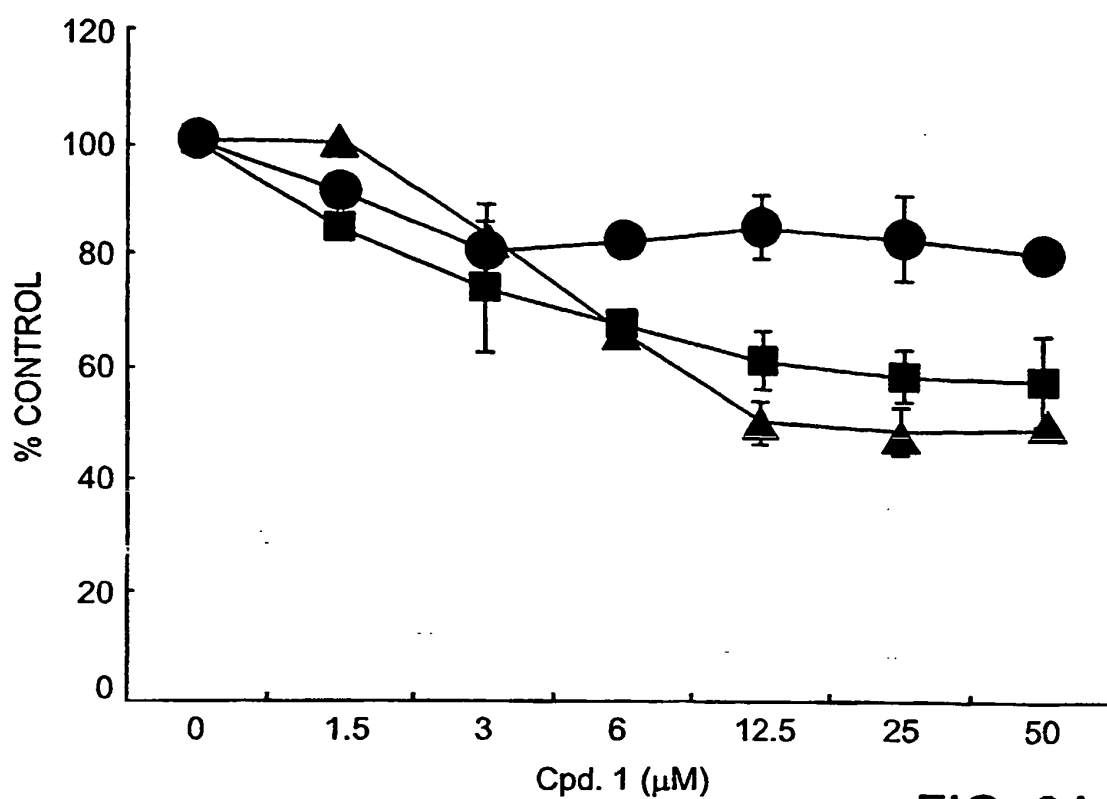
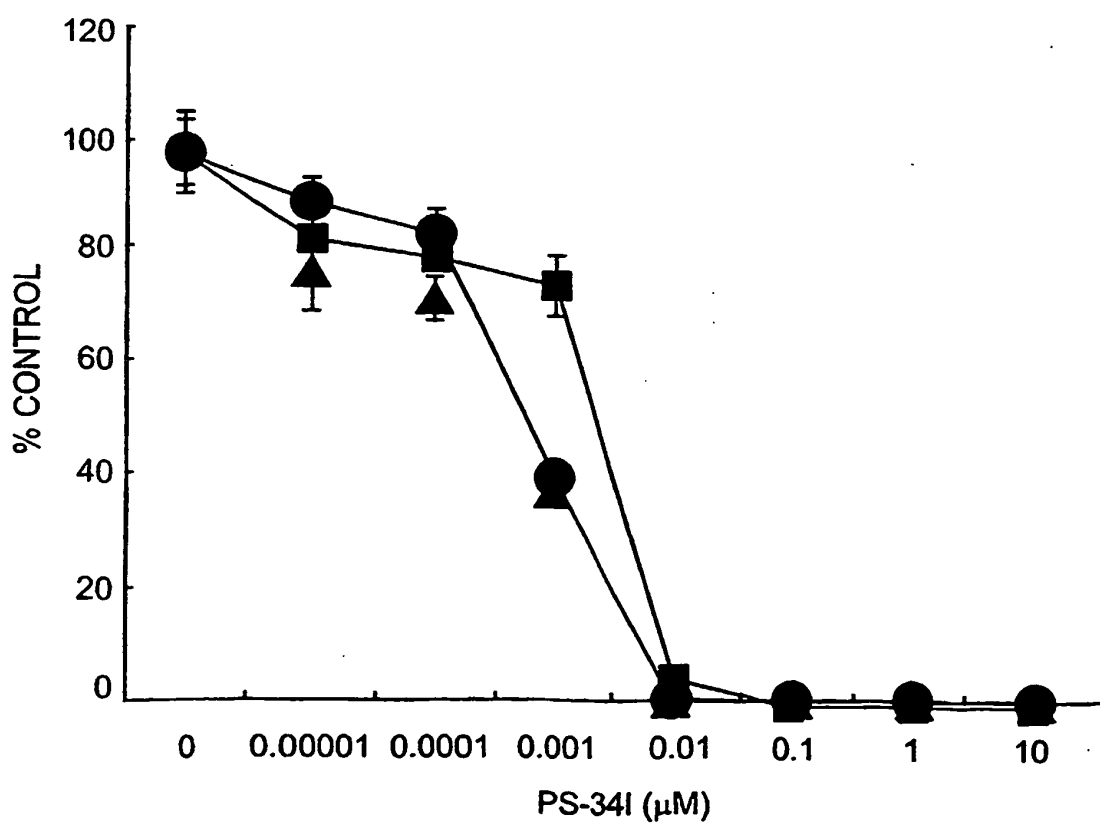


FIG. 3A



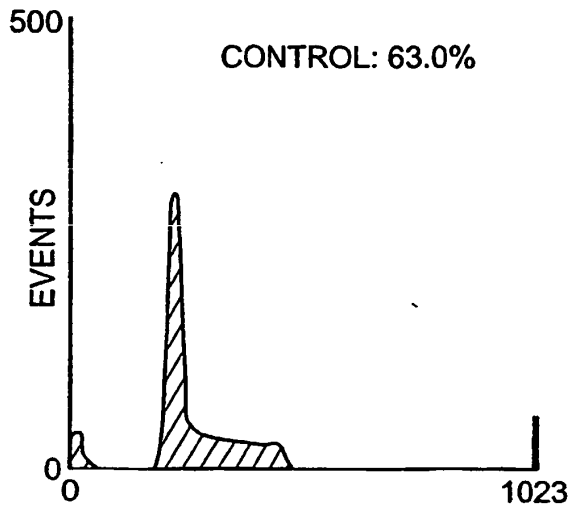


FIG. 4A

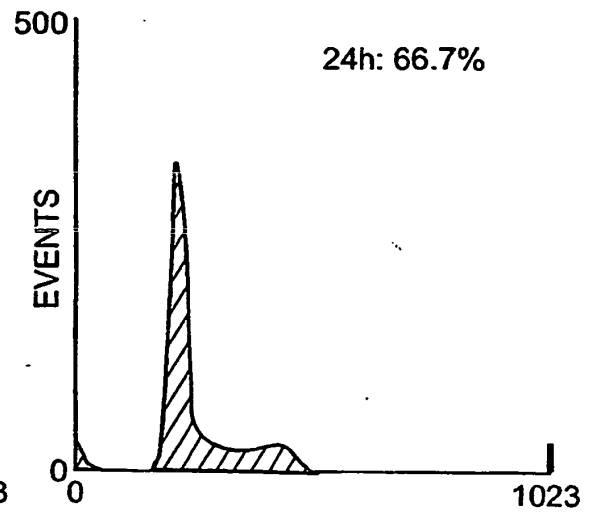


FIG. 4B

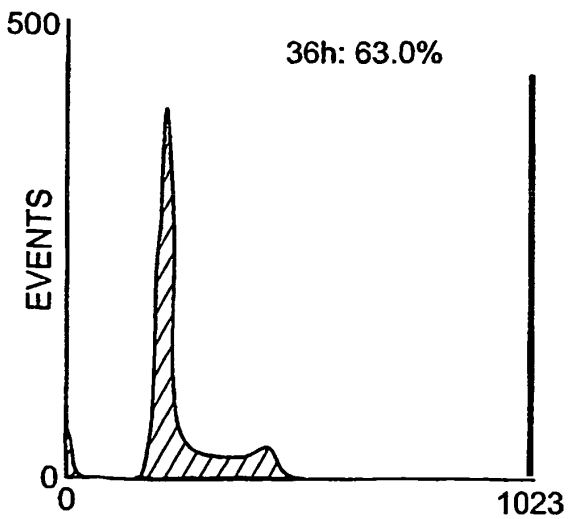


FIG. 4C

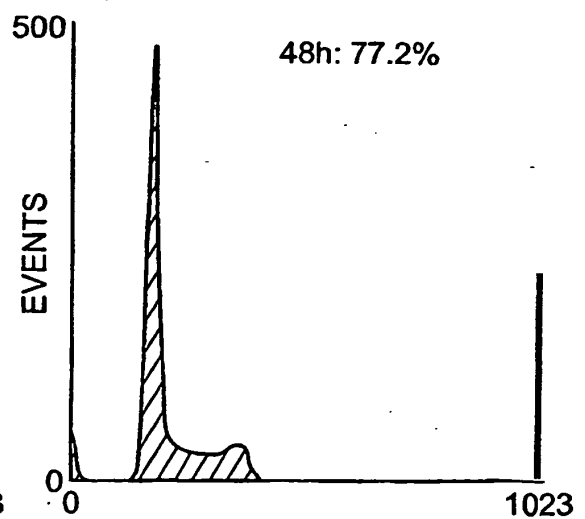


FIG. 4D

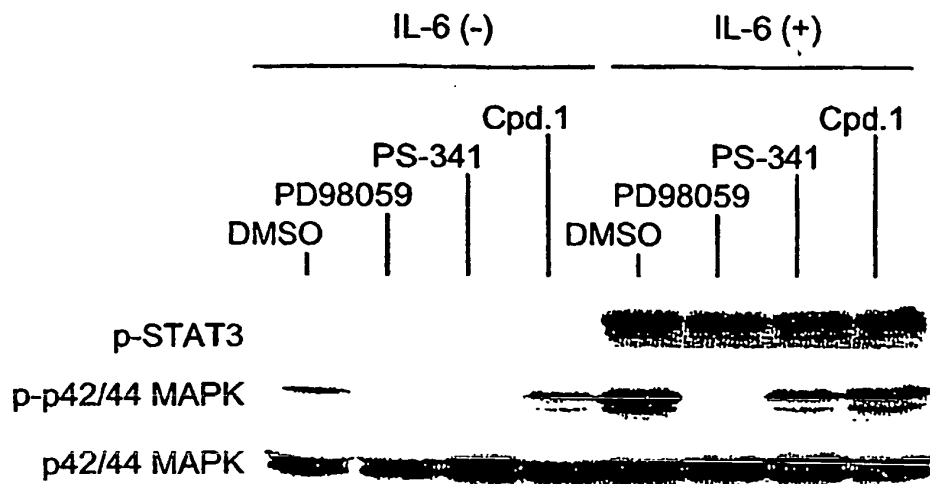


FIG. 5

FIG. 6A

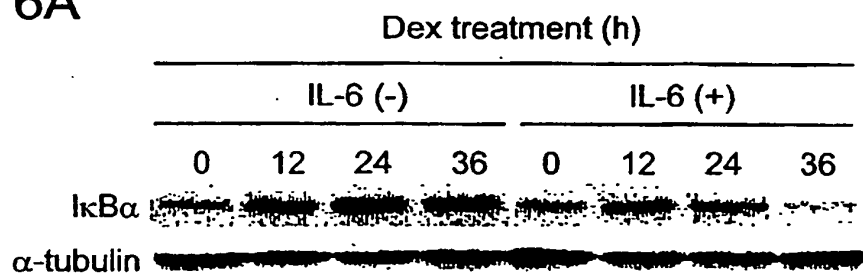


FIG. 6B

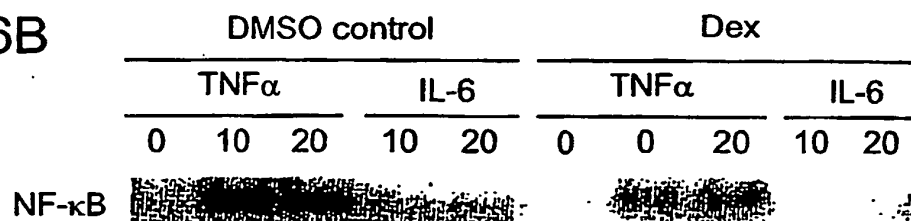
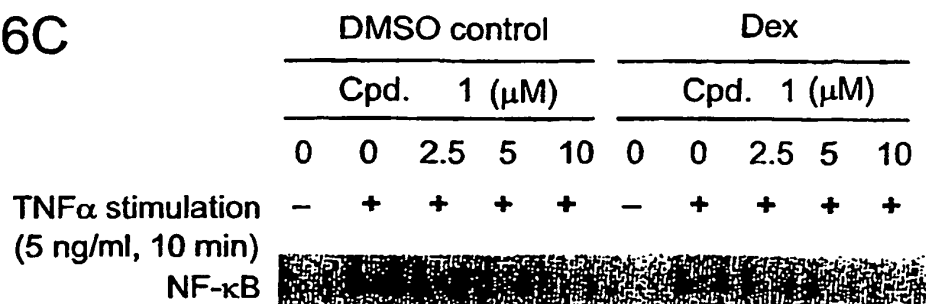


FIG. 6C



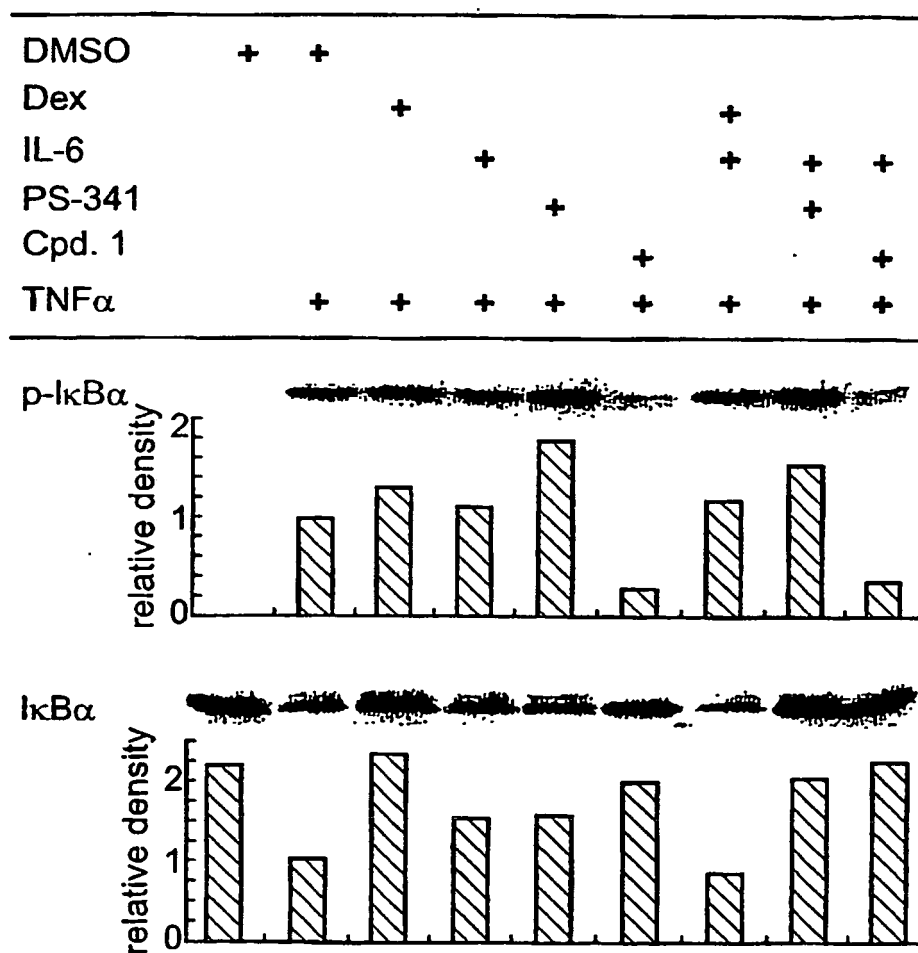
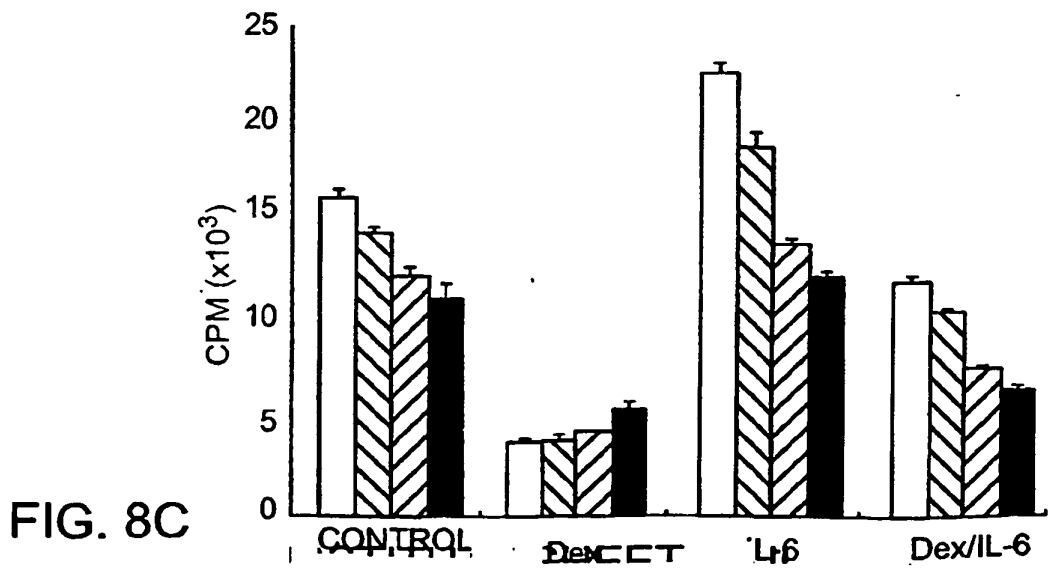
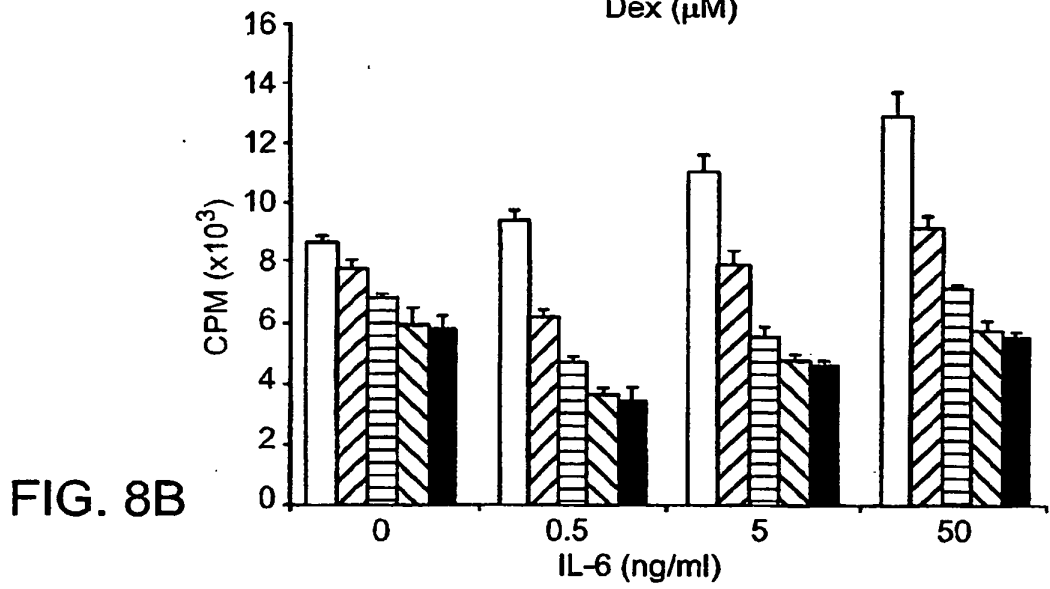
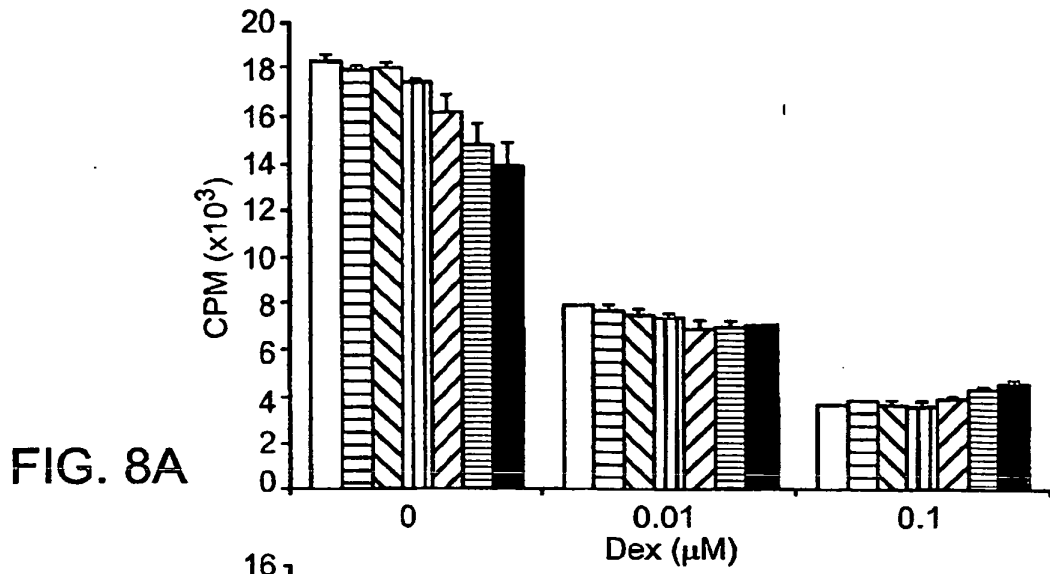


FIG. 7



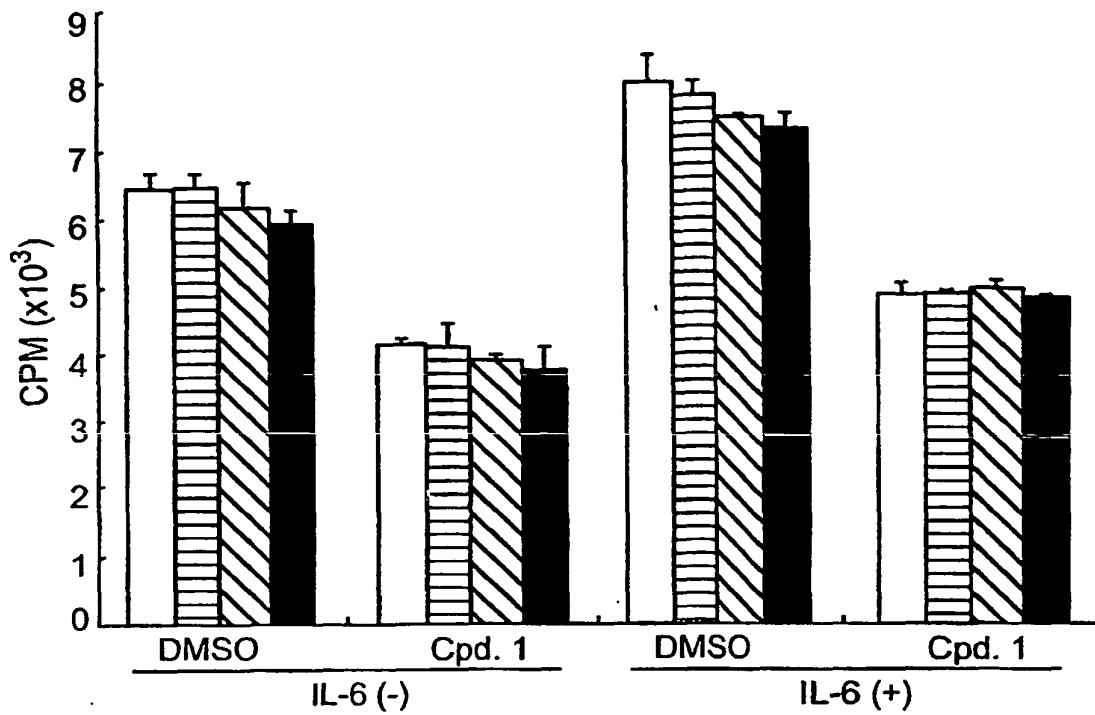
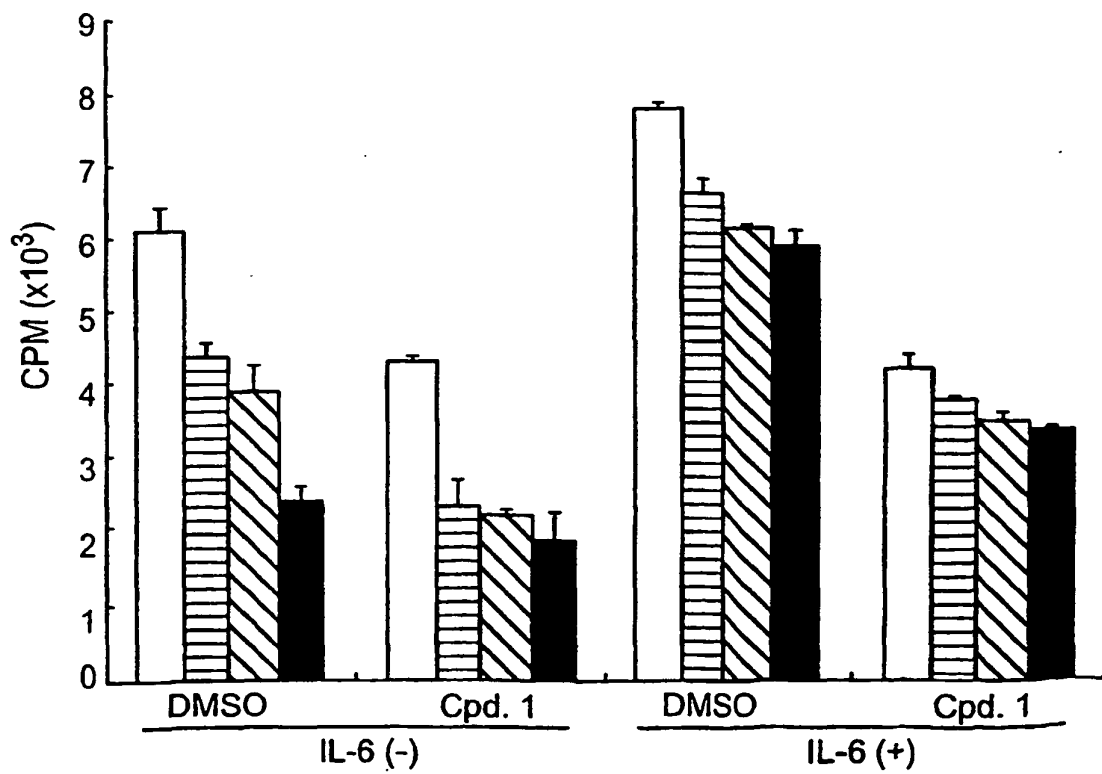


FIG. 9A



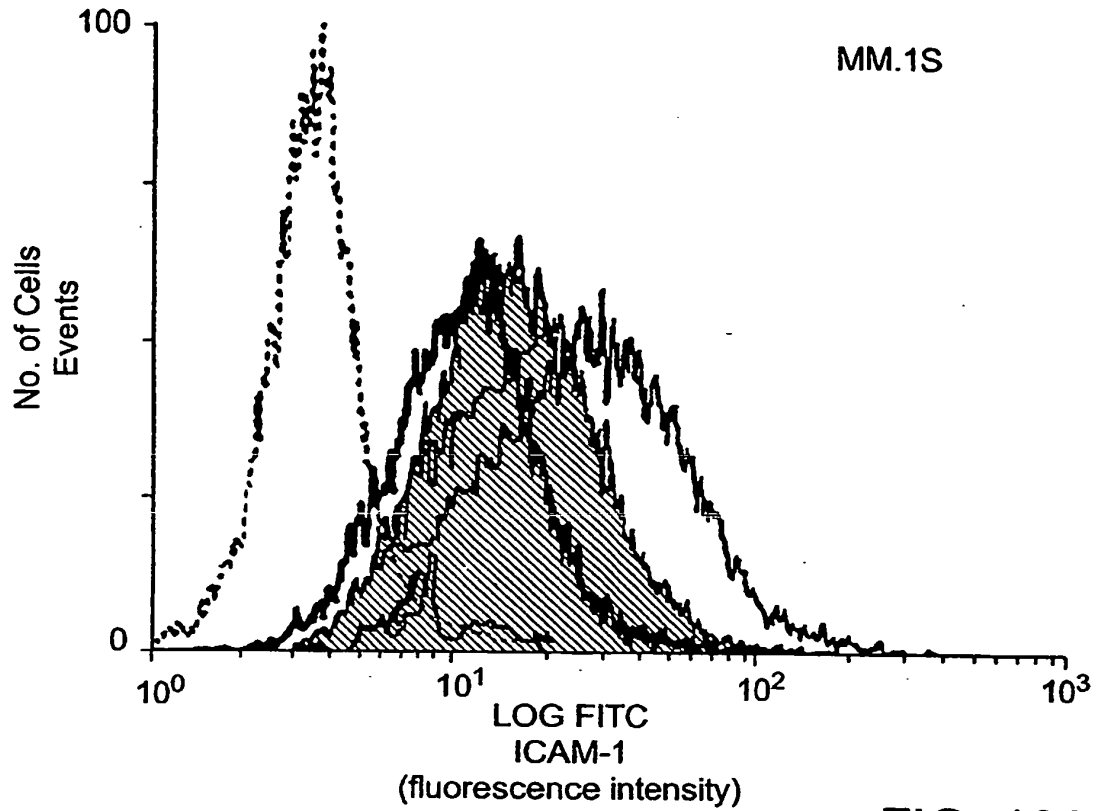


FIG. 10A

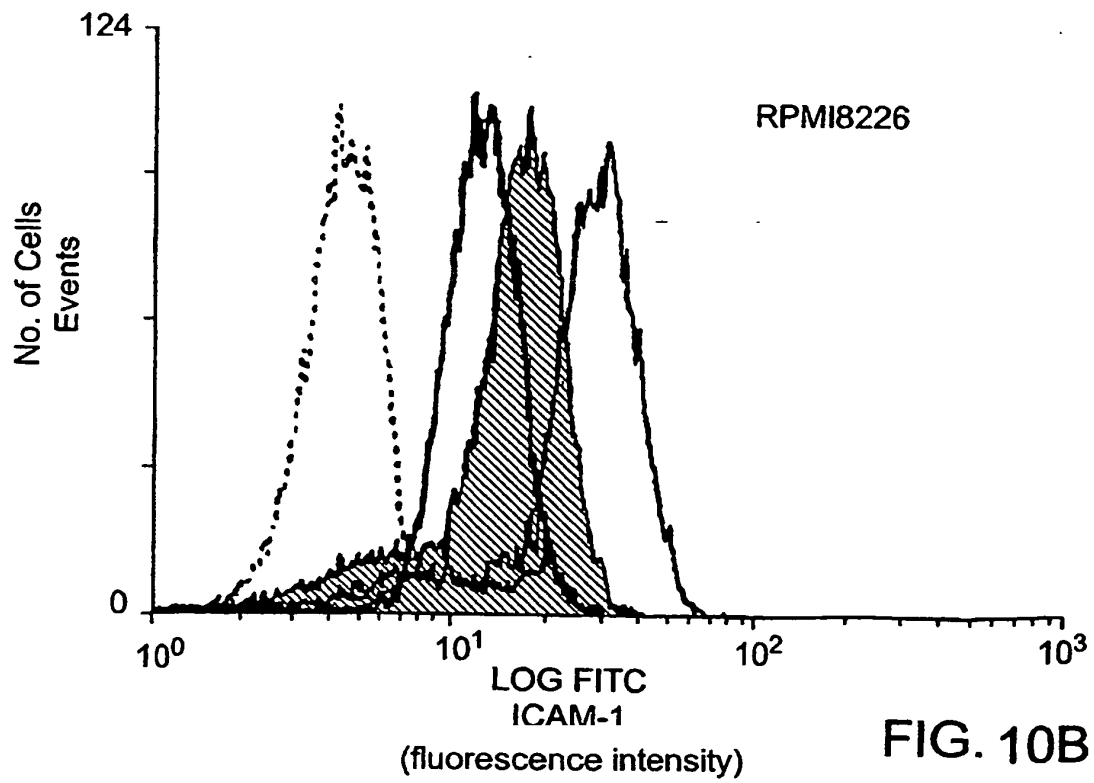


FIG. 10B

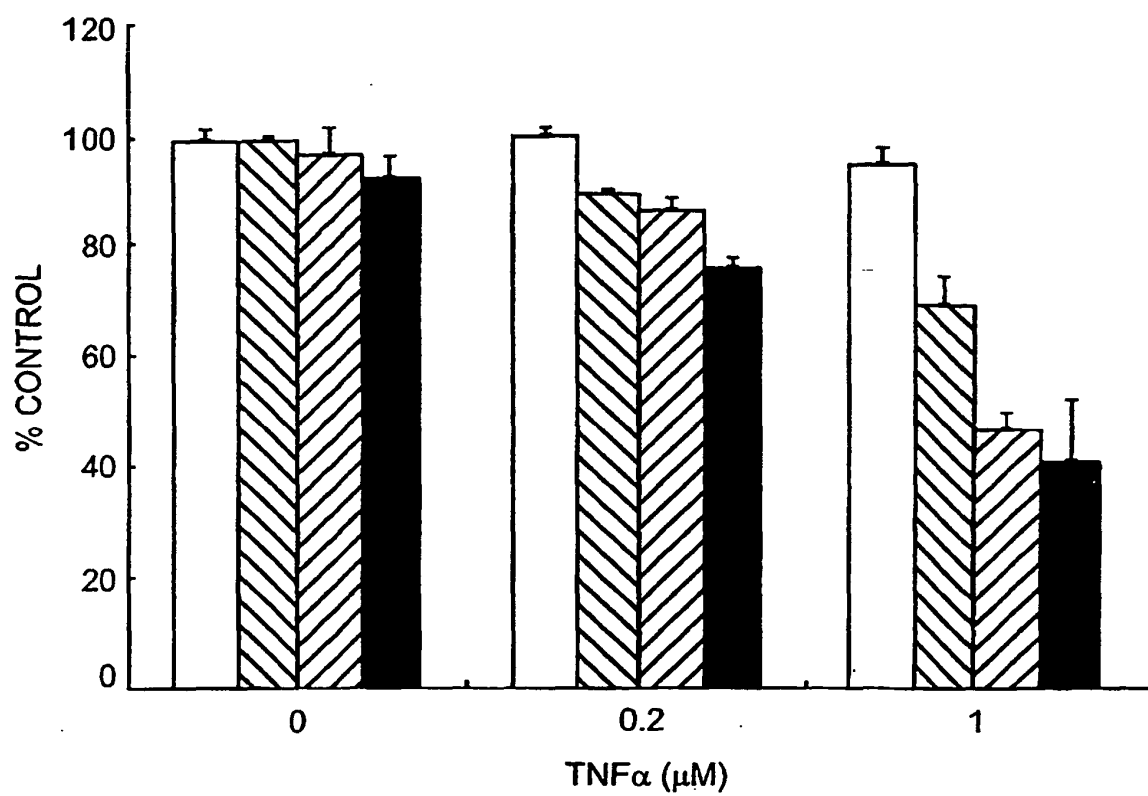


FIG. 11

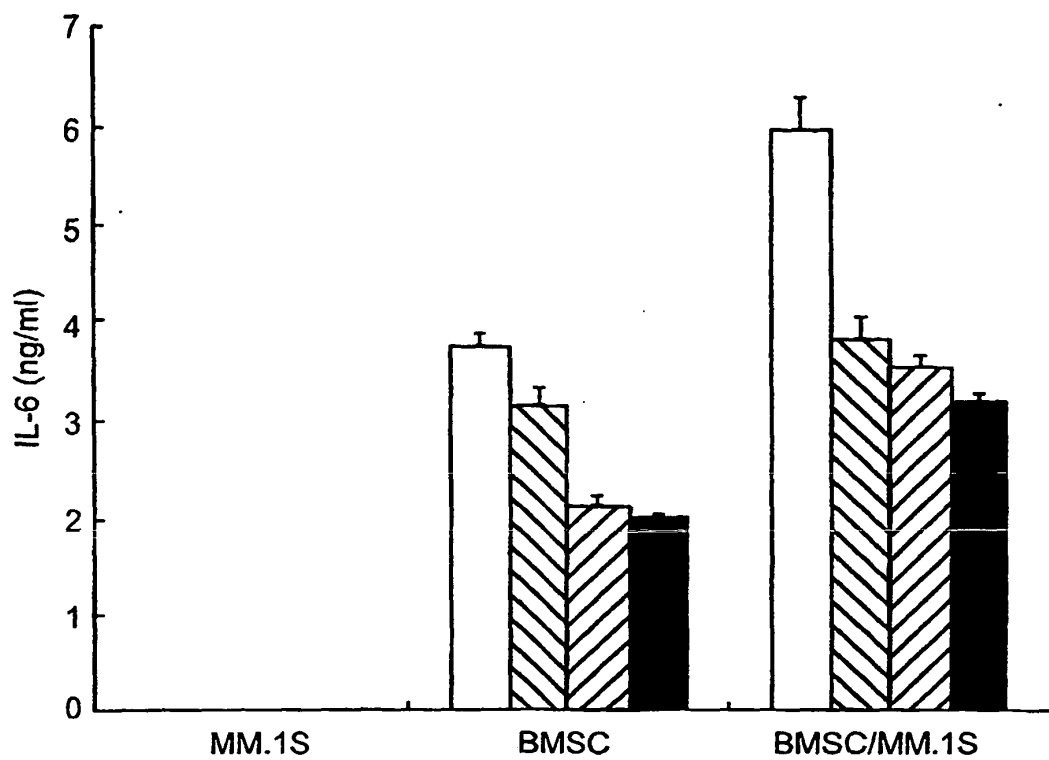


FIG. 12A

