(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 November 2005 (10.11.2005)

PCT

(10) International Publication Number
WO 2005/105097 A2

(51) International Patent Classification[7]: A61K 31/513, A61P 29/00, 37/00

(21) International Application Number: PCT/EP2005/051892

(22) International Filing Date: 27 April 2005 (27.04.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

04010122.2	28 April 2004 (28.04.2004)	EP
60/581,110	21 June 2004 (21.06.2004)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

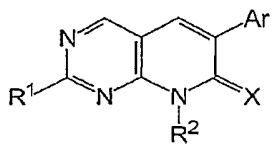
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRIDOPYRIMIDINE DERIVATIVES



(I)

(57) Abstract: The present invention relates to the use of pyridopyrimidine derivatives having the general formula (I) wherein X represents =NH, =N-Acyl, =O, or =S; R^1 represents $-NR^3R^4$, $-SR^3$, $-SO-R^3$, $-SO_2-R^3$, $-OR^3$; R^2, R^3, and R^4 are independently of each other hydrogen, $-(CH_2)_nPh^*$, heteroaryl, C_3-C_7-cycloalkyl, C_1-C_6-alkyl, C_1-C_6-alkanoyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl; wherein the cycloalkyl, alkyl, alkanoyl, alkenyl, alkynyl residues can optionally substituted by one or more of the following groups: $-NR^5R^6$, phenyl, substituted phenyl, thioalkyl, alkyloxy, hydroxy, carboxy, halogen, cycloalkyl; R^5 and R^6 are independently of each other hydrogen, $(CH_2)_nPh^*$, heteroaryl, C_3-C_7-cycloalkyl, C_1-C_6-alkyl, C_1-C_6-alkanoyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl; R^5 and R^6 can be taken together with the nitrogen to which they are attached to complete a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, oxygen, and sulfur; Ph* represents phenyl or substituted phenyl; n is 0, 1, 2, or 3; R^4 can optionally be $-CO-R^3$, $-CO-OR^3$, $-SO_2-R^3$, $-SO_2-NR^5R^6$, $-CO-NR^5R^6$, $-CS-NR^5R^6$, $-C(=NH)-R^3$, $-C(=NH)-NR^5R^6$; R^3 and R^4 can be taken together with the nitrogen to which they are attached to complete a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, oxygen, and sulfur; Ar represents phenyl, substituted phenyl, or heteroaryl; and pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of inflammatory diseases, neurodegenerative disorders, immunological diseases, neuroimmunological diseases, autoimmune diseases, diabetes, transplant rejection, infective diseases, prion diseases, cardiovascular diseases and disorders.

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Pyridopyrimidine derivatives

The present invention relates to novel uses of known pyridopyrimidine derivatives, especially for prophylaxis and/or treatment of inflammations and inflammatory diseases, neurodegenerative disorders, immunological diseases, neuroimmunological diseases, autoimmune diseases, diabetes, transplant rejection, infective diseases, prion diseases, cardiovascular diseases and disorders.

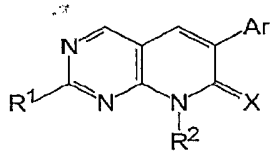
The international patent application WO 96/34867 relates to the compounds of the present invention and their use as inhibitors of protein tyrosin kinases. WO 96/34867 discloses the use of the compounds of the present invention as pharmaceutically active agents in treating cancer, atherosclerosis, restenosis, and psoriasis.

Object of the present invention is to provide compounds useful for prophylaxis and/or treatment of inflammatory diseases.

This object is solved by the use of the compounds of claim 1. Further advantageous features, aspects and details of the invention are evident from the dependent claims, the description, and the examples.

Description

The present invention relates to the use of the compounds having the general formula (I)



(I)

wherein

X represents =NH, =N-Acyl, =O, or =S;

R^1 represents $-NR^3R^4$, $-SR^3$, $-SO-R^3$, $-SO_2-R^3$, $-OR^3$;

R^2, R^3, and R^4 represent independently of each other hydrogen, $-(CH_2)_nPh^*$, heteroaryl, C_3-C_7-cycloalkyl, C_1-C_6-alkyl, C_1-C_6-alkanoyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl;

wherein

the cycloalkyl, alkyl, alkanoyl, alkenyl, alkynyl residues can optionally be substituted by one or more of the following groups:

$-NR^5R^6$, phenyl, substituted phenyl, thioalkyl, alkyloxy, hydroxy, carboxy, halogen, C_3-C_7-cycloalkyl;

R^5 and R^6 represent independently of each other hydrogen, $-(CH_2)_nPh^*$, heteroaryl, C_3-C_7-cycloalkyl, C_1-C_6-alkyl, C_1-C_6-alkanoyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl;

R^5 and R^6 can be taken together with the nitrogen to which they are attached to complete a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

Ph* represents phenyl or substituted phenyl;

n is 0, 1, 2, or 3;

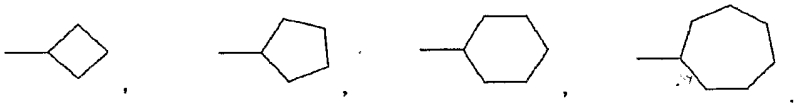
R^4 can optionally be $-CO-R^3$, $-CO-OR^3$, $-SO_2-R^3$, $-SO_2-NR^5R^6$, $-CO-NR^5R^6$, $-CS-NR^5R^6$, $-C(=NH)-R^3$, $-C(=NH)-NR^5R^6$;

R^3 and R^4 can be taken together with the nitrogen to which they are attached to complete a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

Ar represents phenyl, substituted phenyl, or heteroaryl;

and pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of inflammatory diseases.

As used herein, the term "C_3-C_7-cycloalkyl" refers to 



As used herein, the term "C_1-C_6-alkyl" refers to $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$,

$-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, and $-CH(CH_3)-C(CH_3)_3$.

Preferred are $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, and $-C_5H_{11}$. Especially preferred are $-CH_3$, $-C_2H_5$, $-C_3H_7$, and $-CH(CH_3)_2$.

As used herein, the term "C_2-C_6-alkenyl" refers to $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH=CH-C_2H_5$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH-CH_3$, $-CH=CH-CH=CH_2$, $-C_3H_6-CH=CH_2$, $-C_2H_4-CH=CH-CH_3$, $-CH_2-CH=CH-C_2H_5$, $-CH=CH-C_3H_7$, $-CH_2-CH=CH-CH=CH_2$, $-CH=CH-CH=CH-CH_3$, $-CH=CH-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, $-C_2H_4-C(CH_3)=CH_2$, $-CH_2-CH(CH_3)-CH=CH_2$, $-CH(CH_3)-CH_2-CH=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-CH_2-C(CH_3)=CH-CH_3$, $-CH(CH_3)-CH=CH-CH_3$, $-CH=CH-CH(CH_3)_2$, $-CH=C(CH_3)-C_2H_5$, $-C(CH_3)=CH-C_2H_5$, $-C(CH_3)=C(CH_3)_2$, $-C(CH_3)_2-CH=CH_2$, $-CH(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, $-C_4H_8-CH=CH_2$, $-C_3H_6-CH=CH-CH_3$, $-C_2H_4-CH=CH-C_2H_5$, $-CH_2-CH=CH-C_3H_7$, $-CH=CH-C_4H_9$, $-C_3H_6-C(CH_3)=CH_2$, $-C_2H_4-CH(CH_3)-CH=CH_2$, $-CH_2-CH(CH_3)-CH_2-CH=CH_2$, $-CH(CH_3)-C_2H_4-CH=CH_2$, $-C_2H_4-CH=C(CH_3)_2$, $-C_2H_4-C(CH_3)=CH-CH_3$, $-CH_2-CH(CH_3)-CH=CH-CH_3$, $-CH(CH_3)-CH_2-CH=CH-CH_3$, $-CH_2-CH=CH-CH(CH_3)_2$, $-CH_2-CH=C(CH_3)-C_2H_5$, $-CH_2-C(CH_3)=CH-C_2H_5$, $-CH(CH_3)-CH=CH-C_2H_5$, $-CH=CH-CH_2-CH(CH_3)_2$, $-CH=CH-CH(CH_3)-C_2H_5$, $-CH=C(CH_3)-C_3H_7$, $-C(CH_3)=CH-C_3H_7$, $-CH_2-CH(CH_3)-C(CH_3)=CH_2$, $-CH(CH_3)-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)_2-CH=CH_2$, $-C(CH_3)_2-CH_2-CH=CH_2$, $-CH_2-C(CH_3)=C(CH_3)_2$, $-CH(CH_3)-CH=C(CH_3)_2$, $-C(CH_3)_2-CH=CH-CH_3$, $-CH(CH_3)-C(CH_3)=CH-CH_3$, $-CH=C(CH_3)-CH(CH_3)_2$, $-C(CH_3)=CH-CH(CH_3)_2$, $-C(CH_3)=C(CH_3)-C_2H_5$, $-CH=CH-C(CH_3)_3$, $-C(CH_3)_2-C(CH_3)=CH_2$, $-CH(C_2H_5)-C(CH_3)=CH_2$, $-C(CH_3)(C_2H_5)-CH=CH_2$, $-CH(CH_3)-C(C_2H_5)=CH_2$, $-CH_2-C(C_3H_7)=CH_2$, $-CH_2-C(C_2H_5)=CH-CH_3$, $-CH(C_2H_5)-CH=CH-CH_3$, $-C(C_4H_9)=CH_2$, $-C(C_3H_7)=CH-CH_3$, $-C(C_2H_5)=CH-C_2H_5$, $-C(C_2H_5)=C(CH_3)_2$, $-C[C(CH_3)_3]=CH_2$, $-C[CH(CH_3)(C_2H_5)]=CH_2$, $-C[CH_2-CH(CH_3)_2]=CH_2$, $-C_2H_4-CH=CH-CH=CH_2$, $-CH_2-CH=CH-CH_2-CH=CH_2$,

$-CH=CH-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH=CH-CH_3$,
$-CH=CH-CH_2-CH=CH-CH_3$, $-CH=CH-CH=CH-C_2H_5$,
$-CH_2-CH=CH-C(CH_3)=CH_2$, $-CH_2-CH=C(CH_3)-CH=CH_2$,
$-CH_2-C(CH_3)=CH-CH=CH_2$, $-CH(CH_3)-CH=CH-CH=CH_2$,
$-CH=CH-CH_2-C(CH_3)=CH_2$, $-CH=CH-CH(CH_3)-CH=CH_2$,
$-CH=C(CH_3)-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH_2-CH=CH_2$,
$-CH=CH-CH=C(CH_3)_2$, $-CH=CH-C(CH_3)=CH-CH_3$,
$-CH=C(CH_3)-CH=CH-CH_3$, $-C(CH_3)=CH-CH=CH-CH_3$,
$-CH=C(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-C(CH_3)=CH_2$,
$-C(CH_3)=C(CH_3)-CH=CH_2$, and $-CH=CH-CH=CH-CH=CH_2$, .

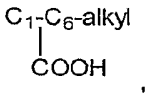
Preferred are $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$. Especially preferred are $-CH=CH_2$, $-CH_2-CH=CH_2$, and $-CH=CH-CH_3$.

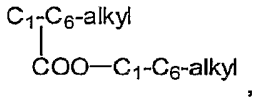
As used herein, the term "C_2-C_6-alkynyl" refers to $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2-C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-C\equiv C-C_2H_5$, $-C_3H_6-C\equiv CH$, $-C_2H_4-C\equiv C-CH_3$, $-CH_2-C\equiv C-C_2H_5$, $-C\equiv C-C_3H_7$, $-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C\equiv C-CH_3$, $-C_4H_8-C\equiv CH$, $-C_3H_6-C\equiv C-CH_3$, $-C_2H_4-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-C_3H_7$, $-C\equiv C-C_4H_9$, $-C_2H_4-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C_2H_4-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv C-CH_3$, $-CH(CH_3)-CH_2-C\equiv C-CH_3$, $-CH(CH_3)-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-CH(CH_3)_2$, $-C\equiv C-CH(CH_3)-C_2H_5$, $-C\equiv C-CH_2-CH(CH_3)_2$, $-C\equiv C-C(CH_3)_3$, $-CH(C_2H_5)-C\equiv C-CH_3$, $-C(CH_3)_2-C\equiv C-CH_3$, $-CH(C_2H_5)-CH_2-C\equiv CH$, $-CH_2-CH(C_2H_5)-C\equiv CH$, $-C(CH_3)_2-CH_2-C\equiv CH$, $-CH_2-C(CH_3)_2-C\equiv CH$, $-CH(CH_3)-CH(CH_3)-C\equiv CH$, $-CH(C_3H_7)-C\equiv CH$, $-C(CH_3)(C_2H_5)-C\equiv CH$, $-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-C\equiv CH$, $-C\equiv C-C\equiv C-CH_3$, $-CH(C\equiv CH)_2$, $-C_2H_4-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-CH_2-C\equiv CH$, $-C\equiv C-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-C\equiv C-CH_3$, $-C\equiv C-CH_2-C\equiv C-CH_3$, $-C\equiv C-C\equiv C-C_2H_5$, $-C\equiv C-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-C\equiv C-C\equiv CH$, $-CH(C\equiv CH)-CH_2-C\equiv CH$, $-C(C\equiv CH)_2-CH_3$, $-CH_2-CH(C\equiv CH)_2$, $-CH(C\equiv CH)-C\equiv C-CH_3$,
$-C\equiv C-CH=CH_2$, $-CH=CH-C\equiv CH$, $-CH_2-C\equiv C-CH=CH_2$,
$-CH_2-CH=CH-C\equiv CH$, $-C\equiv C-CH=CH-CH_3$, $-CH=CH-C\equiv C-CH_3$,
$-C\equiv C-CH_2-CH=CH_2$, $-CH=CH-CH_2-C\equiv CH$, $-C\equiv C-CH_2-C\equiv CH$,
$-C(CH_3)=CH-C\equiv CH$, $-CH=C(CH_3)-C\equiv CH$, $-C\equiv C-C(CH_3)=CH_2$, and
$-C\equiv C-C\equiv C-C\equiv CH$.

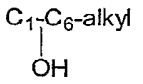
Preferred are $-C\equiv CH$, $-C\equiv C-CH_3$.

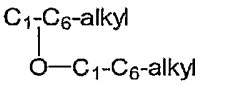
As used herein, the term "halogen" refers to –F, –Cl, –Br, and –I.

As used herein, the term "substituted phenyl" refers to phenyl substituted by 1, 2, or 3 groups independently selected from halogen, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_1-C_6-thioalkyl, C_1-C_6-alkenyl, C_1-C_6-alkynyl, C_1-C_6-alkoxy, –SH, –OH, –CN, $-NO_2$, $-NH_2$, $-CF_3$, $-OCF_3$, –COOH, $-COOR^8$, $-O-CO-R^8$, $-NR^5R^6$. The alkyl and alkoxy groups can be substituted as defined above. Typical groups are, for instance,

carboxyalkyl: 

alkoxycarbonylalkyl: 

hydroxyalkyl: 

alkoxyalkyl: 

Disubstituted phenyl is most preferred, and 2,6-disubstituted phenyl is especially preferred.

As used herein, the term "$-(CH_2)_nPh^*$" refers to phenyl or substituted phenyl.

As used herein, the term "heteroaryl" refers to heteroaromatic groups which have from 4 to 9 ring atoms, from 1 to 4 of which are selected from O, N and/or S. Preferred groups have 1 or 2 heteroatoms in a 5- or 6-membered aromatic ring. Mono and bicyclic ring systems are included. Typical heteroaryl groups include phenyl, 3-chlorophenyl, 2,6-dibromophenyl, 3-methylpyridyl, benzothienyl, 2,4,6-tribromophenyl, 4-ethylbenzothienyl, 3,4-diethylfuranyl, naphthyl, 4,7-dichloronaphthyl, pyrrolyl, thiophenyl, furanyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrimidyl, pyrazyl, pyradizyl, tetrahydroquinolyl, quinolyl, isoquinolyl, benzoimidazolyl, benzothiazolyl, benzooxazolyl, benzo[1,3]dioxolyl, indolyl, benzofuranyl, benzothiophenyl, indazolyl, chrom-2-onyl, and the like.

Preferred heteroaryl groups are phenyl and substituted phenyl.

As used herein, the term "Ar" refers to phenyl, substituted phenyl, or heteroaryl.

As used herein, the term "thioalkyl" refers to the residue –S–C_1-C_6-alkyl, wherein C_1-C_6-alkyl has the meanings as defined above. Preferably the following groups are concerned –S–CH_3, –S–C_2H_5, –S–C_3H_7, –S–$CH(CH_3)_2$, –S–C_4H_9, –S–CH_2–$CH(CH_3)_2$, –S–$CH(CH_3)$–C_2H_5, –S–$C(CH_3)_3$, and –S–C_5H_{11}. Most preferred are –S–CH_3, –S–C_2H_5, –S–C_3H_7, –S–$CH(CH_3)_2$, and –S–$C(CH_3)_3$.

As used herein, the term "alkyloxy" or "alkoxy" refers to the residue –O–C_1-C_6-alkyl, wherein C_1-C_6-alkyl has the meanings as defined above. Preferably the following groups are concerned –O–CH_3, –O–C_2H_5, –O–C_3H_7, –O–$CH(CH_3)_2$, –O–C_4H_9, –O–CH_2–$CH(CH_3)_2$, –O–$CH(CH_3)$–C_2H_5, –O–$C(CH_3)_3$, and –O–C_5H_{11}. Most preferred are –O–CH_3, –O–C_2H_5, –O–C_3H_7, –O–$CH(CH_3)_2$, and –O–$C(CH_3)_3$.

As used herein, the term "C_1-C_6-alkanoyl" refers to groups which are linked through a carbonyl (–C(=O)–) moiety and are represented by the general formula –CO–C_1-C_6-alkyl, wherein C_1-C_6-alkyl has the meanings as defined above. Preferred are –CO–CH_3, –CO–C_2H_5, –CO–C_3H_7, –CO–$CH(CH_3)_2$, –CO–C_4H_9, –CO–CH_2–$CH(CH_3)_2$, –CO–$CH(CH_3)$–C_2H_5, –CO–$C(CH_3)_3$, and –CO–C_5H_{11}. Most preferred are –CO–CH_3, –CO–C_2H_5, –CO–C_3H_7, –CO–$CH(CH_3)_2$, and –CO–$C(CH_3)_3$.

As used herein, the term "acyl" means an aryl or C_1-C_6-alkyl group bonded through a carbonyl group (–CO–). Thus "acyl" refers to –CO–Ar and –CO–C_1-C_6-alkyl, wherein C_1-C_6-alkyl has the meaning as defined above and Ar refers to phenyl, substituted phenyl and heteroaryl, wherein substituted phenyl and heteroaryl have the meanings as defined above.

The C_1-C_6-alkyl, C_1-C_6-alkenyl, C_1-C_6-alkynyl, and C_1-C_6-alkoxy groups as described above can optionally be substituted with one, two or more substituents. Said substituents may be part of the C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_1-C_6-thioalkyl, C_1-C_6-alkenyl, C_1-C_6-alkynyl, and C_1-C_6-alkoxy groups listed above and/or may be selected from the group comprising phenyl, hydroxy, amino, substituted amino, halogen, carboxy, and 5- or 6-membered heterocyclic rings having 1 or 2 heteroatoms selected from nitrogen, oxygen, and/or sulfur.

"Substituted amino" means an amino group bearing one or two or three groups selected from C_1-C_6-alkyl and/or –$(CH_2)_n$Ph*. "Substituted amino" can be represented by the preferred general formulas –NH–C_1-C_6-alkyl, –N(C_1-C_6-

alkyl)$_2$, $-N^+(C_1\text{-}C_6\text{-alkyl})_3$, $-NH-(CH_2)_nPh^*$, $-N[(CH_2)_nPh^*]_2$, wherein Ph* has the meanings as defined above.

In preferred embodiments, R^1 in formula (I) is a $-NR^3R^4$ group, wherein R^3 and R^4 independently of each other are hydrogen, C_1-C_6-alkyl, C_1-C_6-alkyl substituted with the group $-NR^5R^6$. If R^3 is hydrogen, it is preferred that R^4 represents C_1-C_5-alkanoyl or C_1-C_6-alkanoyl substituted with –COOH.

Examples of such $-NR^3R^4$ groups include amino, methylamino, diisopropylamino, acetyl-amino, propionyl-amino, 3-aminopropyl-amino, 3-ethylaminobutyl-amino, 3-di-n-propylamino-propylamino, 4-diethylamino-butylamino, 3-carboxypropionyl-amino. R^3 and R^4 can be taken together with the nitrogen to which they are attached to complete a ring, which may contain 2 or more heteroatoms, preferably nitrogen. Examples of such cyclic $-NR^3R^4$ groups include pyrrolidinyl, piperazinyl, 4-methylpiperazinyl, 4-benzylpiperazinyl, pyridinyl, piperidinyl, pyrazinyl, morpholinyl, and the like.

R^3 and R^4 can additionally complete a cyclic ring which is substituted with 1 or 2 oxo groups. For example, when R^3 is hydrogen and R^4 is alkanoyl in which the alkyl residue bears a substituent such as carboxy or halogen, such group can be cyclized to form cyclic ketones. Typical groups include 2-ketopyrrolidinyl and 1-pyrrolidinyl-2,5-dione. A preferred group of compounds are those wherein R^3 is hydrogen and R^4 is aryl, especially phenyl and phenyl substituted with groups such as aminoalkyl and aminoalkoxy, e.g. dimethylaminoethyl or dimethylaminoethoxy.

Preferred compounds for the inventive uses are those wherein Ar is phenyl or phenyl substituted with 1 or 2 groups selected from C_1-C_6-alkyl and/or halogen, especially –Cl and –Br.

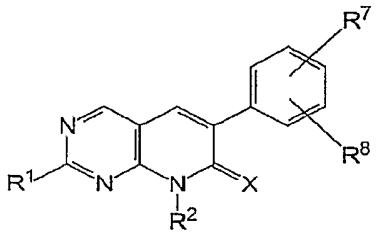
Further preferred compounds are those wherein R^2 is C_1-C_6-alkyl, C_2-C_6-alkenyl, $-(CH_2)_nPh^*$ such as phenyl or benzyl, or C_3-C_7-cycloalkyl such as cyclopropyl.

An especially preferred group of compounds are those wherein X is O.

Another preferred group of compounds are those wherein X is NH. These are imines and are especially useful as intermediates leading to compounds wherein X is O.

Further preferred compounds for the inventive uses are compounds wherein R^1 is NH_2 or NHR^3, wherein R^3 is C_1-C_6-alkyl optionally substituted with NR^5R^6.

An especially preferred group of compounds is represented by the general formula (II)



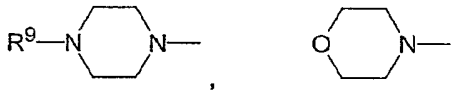
(II)

wherein

R^1, R^2, and X have the meanings as defined above; and

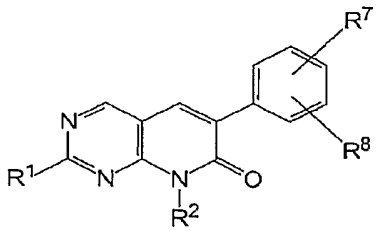
R^7 and R^8 independently of each other represent C_1-C_6-alkyl and/or halogen.

Preferred alkyl groups are substituted with $-NR^5R^6$, wherein R^5 and R^6 are independently of each other hydrogen or alkyl, or together with the nitrogen to which they are attached complete a cyclic ring having 2 heteroatoms, for example

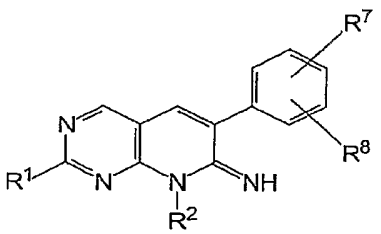


wherein R^9 is hydrogen, C_1-C_6-alkyl, or $-(CH_2)_nPh^*$.

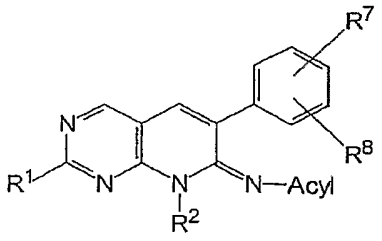
Other preferred groups of compounds have the following general formulas (IIa) – (IId)



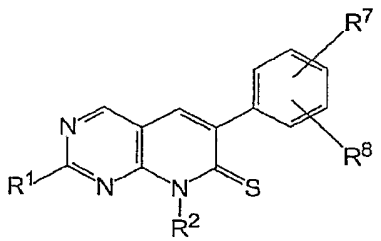
(IIa)



(IIb)



(IIc) ,



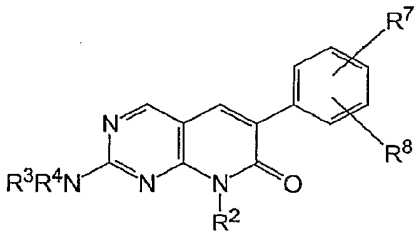
(IId) ,

wherein R^1, R^2, R^7, and R^8 have the meanings as defined above.

It should be realized that when R^2 is hydrogen, the compounds can exist in two tautomeric forms as shown:



Most preferred are the uses of the compounds having the general formula (III)

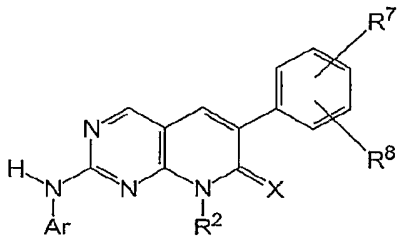


(III)

wherein R^2, R^3, R^4, R^7, and R^8 have the meanings as defined above.

Concerning general formula (III) still further preferred is, when
R^2 represents C_1-C_6-alkyl;
R^3 represents hydrogen or C_1-C_6-alkyl;
R^4 represents C_1-C_6-alkyl or substituted C_1-C_6-alkyl; and
R^7 and R^8 independently of each other represent C_1-C_6-alkyl and/or halogen.

Also Most preferred are the uses of the compounds having the general formula (IV)



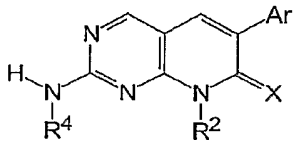
(IV)

wherein R^2, R^3, R^4, R^7, and R^8 have the meanings as defined above.

Concerning general formula (IV) still further preferred is, when
R^2 represents C_1-C_6-alkyl or substituted C_1-C_6-alkyl;
X represents =O or =NH; and
Ar represents phenyl, substituted phenyl, pyridyl, or substituted pyridyl.

Concerning general formulas (III) and (IV) ideally, R^2 is alkyl such as methyl or ethyl, and R^7 and R^8 are halogen such as –Cl or –Br. The most preferred Ar group is phenyl, ideally phenyl substituted with one, two, or three groups selected from halogen, C_1-C_6-alkyl, hydroxy, C_1-C_6-alkoxy, carboxy, C_1-C_6-alkoxycarbonyl, and C_1-C_6-alkyl substituted with hydroxy, carboxy, alkoxycarbonyl, amino, C_1-C_6-alkylamino, and di-C_1-C_6-alkylamino.

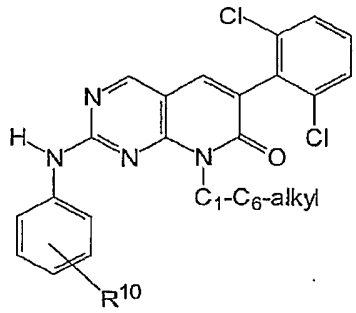
Another group of preferred compounds is represented by the general formula (V)



(V)

wherein
R^2 represents C_1-C_6-alkyl or substituted C_1-C_6-alkyl;
X represents =O or =NH; and
Ar represents phenyl or substituted phenyl.

An especially preferred use is said of the compounds of general formula (Va)



(Va)

wherein R^{10} is phenyl, chloro, bromo, methyl, methoxy, hydroxy, hydroxymethyl, 2-diethylaminoethoxy, methoxycarbonylmethyl, carboxy, carboxymethyl, ethoxycarbonyl, 2-carboxyethyl, or 2-ethoxycarbonylethyl.

The compounds of the general formulas (I) – (V) are able to form pharmaceutically acceptable salts with organic and inorganic acids.

Examples of suitable acids for such acid addition salt formation are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, citric acid, oxalic acid, malonic acid, salicylic acid, p-aminosalicylic acid, malic acid, fumaric acid, succinic acid, ascorbic acid, maleic acid, sulfonic acid, phosphonic acid, perchloric acid, nitric acid, formic acid, propionic acid, gluconic acid, lactic acid, tartaric acid, hydroxymaleic acid, pyruvic acid, phenylacetic acid, benzoic acid, p-aminobenzoic acid, p-hydroxybenzoic acid, methanesulfonic acid, ethanesulfonic acid, nitrous acid, hydroxyethanesulfonic acid, ethylenesulfonic acid, p-toluenesulfonic acid, naphthylsulfonic acid, sulfanilic acid, camphersulfonic acid, china acid, mandelic acid, o-methylmandelic acid, hydrogen-benzenesulfonic acid, picric acid, adipic acid, D-o-tolyltartaric acid, tartronic acid, α-toluic acid, (o, m, p)-toluic acid, naphthylamine sulfonic acid, and other mineral or carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner.

The compounds of the general formulas (I) – (V) are also able to form pharmaceutically acceptable salts with organic and inorganic bases.

Examples for suitable organic and inorganic bases are bases derived from metal ions, e.g., aluminum, alkali metal ions, such as sodium or potassium, alkaline earth metal ions such as calcium or magnesium, or an amine salt ion or alkali- or alkaline-earth hydroxides, -carbonates or -bicarbonates. Examples include aqueous sodium hydroxide, lithium hydroxyde, potassium carbonate, ammonia and sodium bicarbonate, ammonium salts, primary, secondary and tertiary amines, such as, e.g., lower alkylamines such as methylamine, t-butylamine, procaine, ethanolamine, arylalkylamines such as dibenzylamine and N,N-dibenzylethylenediamine, lower alkylpiperidines such as N-ethylpiperidine, cycloalkylamines such as cyclohexylamine or dicyclohexylamine, morpholine, glucamine, N-methyl- and N,N-dimethylglucamine, 1-adamantylamine, benzathine, or salts derived from amino acids like arginine, lysine, ornithine or amides of originally neutral or acidic amino acids or the like.

Especially preferred for the inventive uses are the following compounds of formula (I):

6-(2,6-Dimethyl-phenyl)-7-imino-8-methyl-7,8-dihydro-pyrido-[2,3-d]pyrimidin-2-ylamine;

6-(2-Methyl-phenyl)-7-imino-8-methyl-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamine;

6-Phenyl-7-imino-8-methyl-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamine;

6-(2,6-Dichlorophenyl)-8-methyl-2-[3-(4-methylpiperazin-1-yl)-propylamino]-8H-pyrido[2,3-d]pyrimidin-7-one;

6-(2,6-Dichlorophenyl)-8-methyl-2-methylamino-8H-pyrido[2,3-d]pyrimidin-7-one;

6-(2,6-Dichlorphenyl)-2-dimethylamino-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;

6-(2,6-Dichlorphenyl)-2-ethylamino-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;

6-(2,6-Dichlorphenyl)-2-(2-hydroxyethyl-amino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;

6-(2,6-Dichlorphenyl)-2-isopropylamino-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;

2-Butylamino-6-(2,6-dichlorphenyl)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;

2-Benzylamino-6-(2,6-dichlorphenyl)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;

6-(2,6-Dichlorphenyl)-8-methyl-2-(3-morpholin-4-yl-propylamino)-8H-pyrido[2,3-d]-pyrimidin-7-one;

6-(2,6-Dichlorophenyl)-2-[2-(3,4-dimethoxy-phenyl)-ethylamino]-8-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one;

6-(2,6-Dichlorophenyl)-8-methyl-2-[(pyridin-2-ylmethyl)-amino)-8H-pyrido[2,3-d]pyrimidin-7-one;

6-(2,6-Dichlorophenyl)-8-methyl-2-[(pyridin-3-ylmethyl)-amino]-8H-pyrido[2,3-d]pyrimidin7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-(2-pyridin-2-yl-ethylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-{3-[4-(2-methoxy-phenyl)-piperazin-1-yl]-propylamino}-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-[4-(4-methylpiperazin-1-yl)-butylamino]-8H-pyrido[2,3-d]pyrimidin-7-one;
6-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-hexanoic acid tert-butyl ester;
6-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-hexanoic acid;
6-(2,6-Dichlorophenyl)-8-ethyl-2-[3-(4-methyl-piperazin-1-yl)-propylamino]-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-[5-(4methylpiperazin-1-yl)-pentylamino]-8H-pyrido[2,3-d]pyrimidin-7-one;
4-{4-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-phenyl}-butyric acid ethyl ester;
4-{4-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-phenyl}-butyric acid;
2-Amino-6-(2,6-dichlorophenyl)-8-methyl-pyrido[2,3-d]pyrimidin-7(8H)-one;
2-Amino-6-phenyl-8-methyl-pyrido[2,3-d]-pyrimidin-7(8H)-one;
2-Amino-6-(2,6-dichlorophenyl)-8-ethyl-pyrido[2,3-d]pyrimidine-7(8H)-one;
2-Amino-6-(2,6-dichlorophenyl)-8-propyl-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-8-butyl-6-(2,6-dichlorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dichlorophenyl)-8-isobutyl-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dichlorophenyl)-8-(3-dimethyl-aminopropyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
[2-Amino-6-(2,6-dichlorophenyl)-7-oxo-7H-pyrido[2,3-d]pyrimidin-8-yl]-acetic acid methyl ester;
[2-Amino-6-(2,6-dichlorophenyl)-7-oxo-7H-pyrido[2,3-d]pyrimidin-8-yl]-acetic acid tert-butyl ester;
[2-Amino-6-(2,6-dichlorophenyl)-7-oxo-7H-pyrido[2,3-d]pyrimidin-8-yl]-acetic acid;
2-Amino-8-benzyl-6-(2,6-dichlorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-8-(3-bromobenzyl)-6-(2,6-dichlorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
4-[2-Amino-6-(2,6-dichlorophenyl)-7-oxo-7H-pyrido[2,3-d]pyrimidin-8-ylmethyl]-benzoic acid methyl ester;

2-Amino-8-(2,6-dichlorobenzyl)-6-(2,6-dichlorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dichlorophenyl)-8-(4-methoxybenzyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dichlorophenyl)-8-pyridin-4-ylmethyl-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dichlorophenyl)-8-(3-phenylpropyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dimethylphenyl)-8-methyl-pyrido[2,3-d]-pyrimidin-7(8H)-one;
2-Amino-6-(2-methylphenyl)-8-methyl-pyrido[2,3-d]pyrimidin-7(8H)-one;
[6-(2,6-Dichlorophenyl)-7-imino-8-methyl-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]-(3-diethylamino-propyl)-amine;
[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]-(3-diethylamino-propyl)-amine;
N-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]acetamide;
2-Amino-6-(2,6-dichlorophenyl)-8-methyl-pyrido[2,3]-pyrimidin-7(8H)-thione;
N-[6-(2,6-Dichlorophenyl)-7-oxo-8-methyl-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yl]-succinamic acid;
1-[6-(2,6-Dichlorophenyl)-7-oxo-8-methyl-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]-pyrrolidine-2,5-dione;
6-(2,6-Dichlorophenyl)-2-hydroxy-8-methyl-8H-pyrido-[2,3-d]pyrimidin-7-ylideneamine;
6-(2,6-Dichlorophenyl)-2-(2-ethoxy-ethoxy)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-ylideneamine;
6-(2,6-Dichlorophenyl)-2-hydroxy-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-[2-(diethylamino)ethoxy]-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-ylideneamine;
6-(2,6-Dichlorophenyl)-8-ethyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-ylideneamine;
6-(2,6-Dichlorophenyl)-2-methanesulfinyl-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-methanesulfonyl-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one;

6-(2,6-Dichlorophenyl)-8-ethyl-2-methane-sulfonyl-8H-pyrido[2,3-d]pyrimidin-7-one;
N-[6-(2,6-Dichlorophenyl)-8-methyl-2-methyl-sulfanyl-8H-pyrido[2,3-d]pyrimidin-7-ylidene]-acetamide;
N-[6-(2,6-Dichlorophenyl)-8-ethyl-2-methyl-sulfanyl-8H-pyrido[2,3-d]pyrimidin-7-ylidene]-acetamide;
N-[6-(2,6-Dichlorophenyl)-2-(4-diethylaminobutylamino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-ylidene]-acetamide;
6-(2,6-Dichlorophenyl)-8-methyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
2-(3-Bromophenylamino)-6-(2,6-dichlorophenyl)-8-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one;
2-(4-Chlorophenylamino)-6-(2,6-dichlorophenyl)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
2-(Benzo[1,3]dioxol-5-ylamino)-6-(2,6-dichlorophenyl)-8-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-(pyridin-4-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-p-tolylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(4-methoxyphenyl-amino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-ethyl-2-phenyl-amino-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(2-methoxyphenyl-amino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(3-methoxyphenyl-amino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(4-methoxy-3-methyl-phenylamino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-ethyl-2-(4-methoxy-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-ethyl-2-(4-hydroxy-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(4-ethoxyphenyl-amino)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(3,4-dimethoxy-phenylamino)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-ethyl-2-(3,4,5-trimethoxyphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;

6-(2,6-Dichlorophenyl)-8-methyl-2-(pyridin-3-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-[4-(2-diethyl-aminoethoxy)-phenylamino]-8-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(3-hydroxymethyl-phenylamino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(3,5-dimethoxy-phenylamino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
{4-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-phenyl}-acetic acid methyl ester;
6-(2,6-Dichlorophenyl)-2-(6-methoxypyridin-3-ylamino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
{4-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-phenyl}-acetic acid;
6-(2,6-Dichlorophenyl)-2-(3-hydroxyphenyl-amino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
4-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-benzoic acid ethyl ester;
3-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-benzoic acid ethyl ester;
3-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)-benzoic acid;
6-(2,6-Dichlorophenyl)-8-ethyl-2-(pyridin-4-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
[6-(2-Bromo-6-chlorophenyl)-8-ethyl-7-imino-7,8-dihydropyrido[2,3-d]pyrimidin-8-yl]-phenylamine;
6-(2-Bromo-6-chlorophenyl)-8-ethyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
(8-Ethyl-7-imino-6-phenyl-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2-phenylamine;
8-Ethyl-6-phenyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
(6-(3,5-Dimethylphenyl)-8-ethyl-7-imino-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-phenylamine;
6-(3,5-Dimethylphenyl)-8-ethyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
8-Ethyl-2-phenylamino-6-thiophen-3-yl-8H-pyrido[2,3-d]pyrimidin-7-one;
8-Ethyl-7-imino-6-thiophen-2-yl-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-phenylamine;
8-Ethyl-2-phenylamino-6-thiophen-2-yl-8H-pyrido[2,3-d]pyrimidin-7-one;

(8-Ethyl-7-imino-6-pyridin-4-yl-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-phenylamine;
8-Ethyl-2-phenylamino-6-pyridin-4-yl-8H-pyrido[2,3-d]pyrimidin-7-one;
(8-Ethyl-7-imino-6-naphthalen-2-yl-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)-phenylamine;
8-Ethyl-6-naphthalen-2-yl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
(6-Biphenyl-4-yl-8-ethyl-7-imino-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)-phenylamine;
6-Biphenyl-4-yl-8-ethyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Cyclohexylamino-6-(2,6-dichlorophenyl)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one.

The compounds of the present invention can be synthesized according to the procedures as outlined in PCT/US96/05819 (WO 96/34867), especially as described on pages 15 – 27 and schemes I – VII (cf. pages 28 – 35).

As described above, the compounds according to formula (I) or any other formula (II) – (V) are pharmaceutically active agents for prophylaxis and/or treatment of inflammatory diseases. Thus, these compounds are used for the manufacture of a pharmaceutical formulation for prophylaxis and/or treatment of inflammations and inflammatory diseases in mammals, including humans.

Inflammatory diseases can emanate from infectious and non-infectious inflammatory conditions which may result from infection by an invading organism or from irritative, traumatic, metabolic, allergic, autoimmune, or idiopathic causes as shown in the following list.

I. Acute infections
   A. Viral B. Bacterial

II. Noninfectious causes

III. Chronic (granulomatous) diseases
   A. Bacterial B. Spirochetal
   C. Mycotic (Fungal) D. Idiopathic

IV. Allergic, immune, and idiopathic disorders
- A. Hypersensitivity reactions
- B. Immune and idiopathic disorders

V. Miscellaneous inflammatory conditions
- A. Parasitic infections
- B. Inhalation causes: - Acute (thermal) injury
  - Pollution and inhalant allergy
  - Carcinogens
- C. Radiation injury: - Radionecrosis

Thus, the compounds disclosed herein can be used for prophylaxis and/or treatment of inflammations caused by invading organisms such as viruses, bacteria, prions, and parasites as well as for prophylaxis and/or treatment of inflammations caused by irritative, traumatic, metabolic, allergic, autoimmune, or idiopathic reasons.

Consequently, the disclosed compounds are useful for prophylaxis and/or treatment of inflammatory diseases which are initiated or caused by viruses, parasites, and bacteria which are connected to or involved in inflammations.

The following bacteria are know to cause inflammatory diseases: mycoplasma pulmonis (causes e.g. chronic lung diseases (CLD), murine chronic respiratory disease), ureaplasma urealyticum (causes pneumonia in newborns), mycoplasma pneumoniae and chlamydia pneumoniae (cause chronic asthma), C. pneumoniae (causes atherosclerosis, pharyngitis to pneumonia with empyema, human coronary heart disease), Helicobacter pylori (human coronary heart disease, stomach ulcers).

The following viruses are known to cause inflammatory diseases: herpesviruses especially cytomegalovirus (causes human coronary heart disease).

The compounds disclosed herein are useful for prophylaxis and/or treatment of inflammatory diseases caused and/or induced and/or initiated and/or enhanced by the afore-mentioned bacteria or viruses.

Furthermore, the compounds of formula (I) are useful for prophylaxis and/or treatment of inflammatory diseases of the central nervous system (CNS),

inflammatory rheumatic diseases, inflammatory diseases of blood vessels, inflammatory diseases of the middle ear, inflammatory bowel diseases, inflammatory diseases of the skin, inflammatory disease uveitis, inflammatory diseases of the larynx.

Examples for inflammatory diseases of the central nervous system (CNS) are algal disorders, protothecosis, bacterial disorders, abscessation, bacterial meningitis, idiopathic inflammatory disorders, eosinophilic meningoencephalitis, feline polioencephalomyelitis, granulomatous meningoencephalomyelitis, meningitis, steroid responsive meningitis-arteritis, miscellaneous meningitis / meningoencephalitis, meningoencephalitis in greyhounds, necrotizing encephalitis, pug dog encephalitis, pyogranulomatous meningoencephalomyelitis, shaker dog disease, mycotic diseases of the CNS, parasitic encephalomyelitis, prion protein induced diseases, feline spongiform encephalopathy, protozoal encephalitis-encephalomyelitis, toxoplasmosis, neosporosis, sarcocystosis, encephalitozoonosis, trypanosomiasis, acanthamebiasis, babesiosis, leishmaniasis, rickettsial disorders, rocky mountain spotted fever, canine ehrlichiosis, salmon poisoning, viral disorders, aujeszky's disease, borna disease, canine herpes virus encephalomyelitis, canine distemper encephalomyelitis, canine distemper encephalomyelitis in immature animals, multifocal distemper encephalomyelitis in mature animals, old dog encephalitis, chronic relapsing encephalomyelitis, post-vaccinal canine distemper encephalitis, feline immunodeficiency virus, feline infectious peritonitis, feline leukemia virus, infectious canine hepatitis, La Crosse virus encephalitis, parvovirus encephalitis, rabies, post-vaccinal rabies, tick-borne encephalitis in dogs.

Examples for inflammatory rheumatic diseases are rheumatoid arthritis, scleroderma, lupus, polymyositis, dermatomyositis, psoriatic arthritis, ankylosing spondylitis, Reiters's syndrome, juvenile rheumatoid arthritis, bursitis, tendinitis (tendonitis), and fibromyositis.

Examples for inflammatory diseases of blood vessels are vasculitis, autoantibodies in vasculitis, microscopic polyangiitis, giant cell arteritis, Takayasu's arteritis, vasculitis of the central nervous system, thromboangiitis obliterans (Buerger's Disease), vasculitis secondary to bacterial, fungal, and parasitic infection, vasculitis and rheumatoid arthritis, vasculitis in systemic lupus erythematosus, vasculitis in the idiopathic inflammatory myopathies, relapsing

polychondritis, systemic vasculitis in sarcoidosis, vasculitis and malignancy, and drug-induced vasculitis.

Examples for inflammatory diseases of the middle ear are acute suppurative otitis media, bullous myringitis, granular myringitis, and chronic suppurative otitis media, which can manifest as mucosal disease, cholesteatoma, or both.

Examples for inflammatory bowel diseases are ulcerative colitis, Crohn's disease.

Examples for inflammatory diseases of the skin are acute inflammatory dermatoses, urticaria (hives), spongiotic dermatitis, allergic contact dermatitis, irritant contact dermatitis, atopic dermatitis, erythemal multiforme (EM minor), Stevens-Johnson syndrome (SJS, EM major), toxic epidermal necrolysis (TEN), chronic inflammatory dermatoses, psoriasis, lichen planus, discoid lupus erythematosus, and acne vulgaris

Uveitis are inflammations located in and/or on the eye and may be associated with inflammation elsewhere in the body. In most circumstances, patients who have uveitis as part of a disease elsewhere in the body are aware of that illness. The majority of patients with uveitis do not have an apparent associated systemic illness. Causes of uveitis can be infectious causes, masquerade syndromes, suspected immune-mediated diseases, and/or syndromes confined primarily to the eye.

The following viruses are associated with inflammations: human immunodeficiency virus-I, herpes simplex virus, herpes zoster virus, and cytomegalovirus.

Bacterial or spirochetal caused, induced, initiated and/or enhanced inflammations are tuberculosis, leprosy, proprionobacterium, syphilis, Whipple's disease, leptospirosis, brucellosis, and lyme disease.

Parasitic (protozoan or helminthic) caused, induced, initiated and/or enhanced inflammations are toxoplasmosis, acanthameba, toxocariasis, cysticercosis, onchocerciasis.

Examples of inflammatory diseases caused, induced, initiated and/or enhanced by fungi are histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, sporotrichosis, blastomycosis, and cryptococcosis.

Masquerade syndromes are, for instance, leukemia, lymphoma, retinitis pigmentosa, and retinoblastoma.

Suspected immune-mediated diseases can be selected from the group comprising ankylosing spondylitis, Behcet's disease, Crohn's disease, drug or hypersensitivity reaction, interstitial nephritis, juvenile rheumatoid arthritis, Kawasaki's disease, multiple sclerosis, psoriatic arthritis, Reiter's syndrome, relapsing polychondritis, sarcoidosis, Sjogren's syndrome, systemic lupus erythematosus, ulcerative colitis, vasculitis, vitiligo, Vogt Koyanagi Harada syndrome.

Syndromes confined primarily to the eye are, for instance, acute multifocal placoid pigmentary epitheliopathy, acute retinal necrosis, birdshot choroidopathy, Fuch's heterochromic cyclitis, glaucomatocyclitic crisis, lens-induced uveitis, multifocal choroiditis, pars planitis, serpiginous choroiditis, sympathetic ophthalmia, and trauma.

Examples for inflammatory diseases of the larynx are gastroesophageal (laryngopharyngeal) reflux disease, pediatric laryngitis, acute laryngeal infections of adults, chronic (granulomatous) diseases, allergic, immune, and idiopathic disorders and miscellaneous inflammatory conditions.

Pediatric laryngitis is known as acute (viral or bacterial) infection such as laryngotracheitis (croup), supraglottitis (epiglottitis), diphtheria, and noninfectious causes are for example spasmodic croup and traumatic laryngitis.

Acute laryngeal infections of adults are, for instance, viral laryngitis, common upper respiratory infection, laryngotracheitis, herpes simplex, bacterial laryngitis, supraglottitis, laryngeal abscess, and gonorrhea.

Chronic (granulomatous) diseases can be selected from the group comprising bacterial diseases, tuberculosis, leprosy, scleroma, actinomycosis, tularemia, glanders, spirochetal (syphilis) diseases, mycotic (fungal) diseases, candidiasis, blastomycosis, histoplasmosis, coccidiomycosis, aspergillosis, idiopathic diseases, sarcoidosis, and Wegener's granulomatosis.

Allergic, immune, and idiopathic disorders are, for example, hypersensitivity reactions, angioedema, Stevens-Johnson syndrome, immune and idiopathic disorders, infections of the immunocompromised host, rheumatoid arthritis, systeic lupus erythematosus, cicatricial pemphigoid, relapsing polychondritis, Sjogren's syndrome, and amyloidosis.

Miscellaneous inflammatory conditions are, for instance, parasitic infections, trichinosis, leishmaniasis, schistosomiasis, syngamus laryngeus, inhalation laryngitis, acute (thermal) injury, pollution and inhalant allergy, carcinogens, radiation injury, radiation laryngitis, radionecrosis, vocal abuse, vocal-cord hemorrhage, muscle tension dysphonias, and contact ulcer and granuloma.

The compounds of the general formula (I) or any other general formula (II) – (V) are also useful for prophylaxis and/or treatment of several other diseases such as neurodegenerative disorders, immunological diseases, neuroimmunological diseases, autoimmune diseases, diabetes, transplant rejection, infective diseases, prion diseases, cardiovascular diseases and disorders especially thombosis, cardiac hypertrophy, and myocardial ischemia.

Cardiovascular diseases and disorders

Another aspect of the present invention is directed to the use of at least one compound of any one of the general formulas (I), (Ia) – (It) and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of cardiovascular diseases and cardiovascular disorders.

Examples of cardiovascular diseases and disorders are: aneurysm, stable angina, unstable angina, angina pectoris, angioneurotic edema, aortic valve stenosis, aortic aneurysm, arrhythmia, arrhythmogenic right ventricular dysplasia, arteriosclerosis, arteriovenous malformations, atrial fibrillation, Behcet syndrome, bradycardia, cardiac tamponade, cardiomegaly, congestive cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, carotid stenosis, cerebral hemorrhage, Churg-Strauss syndrome, diabetes, Ebstein's Anomaly, Eisenmenger complex, cholesterol embolism, bacterial endocarditis, fibromuscular dysplasia, congenital heart defects, heart diseases, congestive heart failure, heart valve diseases, heart attack, epidural hematoma, hematoma, subdural, Hippel-Lindau disease, hyperemia, hypertension, pulmonary hypertension, cardiac hypertrophy, left ventricular hypertrophy, right ventricular hypertrophy, hypoplastic left heart syndrome, hypotension, intermittent claudication, ischemic heart disease,

Klippel-Trenaunay-Weber syndrome, lateral medullary syndrome, long QT syndrome mitral valve prolapse, moyamoya disease, mucocutaneous lymph node syndrome, myocardial infarction, myocardial ischemia, myocarditis, pericarditis, peripheral vascular diseases, phlebitis, polyarteritis nodosa, pulmonary atresia, Raynaud disease, Sneddon syndrome, superior vena cava syndrome, syndrome X, tachycardia, Takayasu's arteritis, hereditary hemorrhagic telangiectasia, telangiectasis, temporal arteritis, tetralogy of fallot, thromboangiitis obliterans, thrombosis, thromboembolism, tricuspid atresia, varicose veins, vascular diseases, vasculitis, vasospasm, ventricular fibrillation, Williams syndrome, peripheral vascular disease, varicose veins and leg ulcers, deep vein thrombosis, Wolff-Parkinson-White syndrome.

Neurodegenerative disorders and neurodegeneration

Another aspect of the present invention is directed to the use of at least one compound of any one of the general formulas (I), (Ia) – (It) and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of neuro-degeneration and neurodegenerative disorders.

Among the hundreds of different neurodegenerative disorders, the attention has been given only to a handful, including Alzheimer disease, Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis.

It is worth to mention that the same neurodegenerative process can affect different areas of the brain, making a given disease appear very different from a symptomatic stand-point.

Neurodegenerative disorders of the central nervous system (CNS) can be grouped into diseases of the cerebral cortex (Alzheimer disease), the basal ganglia (Parkinson disease), the brain-stem and cerebellum, or the spinal cord (amyotrophic lateral sclerosis).

Examples for neurodegeneration and neurodegenerative disorders are Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, AIDS-related dementia, retinitis pigmentosa, spinal muscular atrophy and cerebrellar degeneration, fragile X-associated tremor/ataxia syndrome (FXTAS), progressive supranuclear palsy (PSP), and striatonigral degeneration (SND), which is included with olivopontocerebellear degeneration (OPCD), and Shy Drager syndrome (SDS) in a syndrome known as multiple system atrophy (MSA).

Immunological diseases

Another aspect of the present invention is directed to the use of at least one compound of any one of the general formulas (I), (Ia) – (It) and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of immunological diseases, neuroimmunological diseases, autoimmune diseases.

Immunological diseases are, for instance, asthma and diabetes, rheumatic and autoimmune diseases, AIDS, rejection of transplanted organs and tissues (cf. below), rhinitis, chronic obstructive pulmonary diseases, osteoporisis, ulcerative colitis, sinusitis, lupus erythematosus, recurrent infections, atopic dermatitis / eczema and occupational allergies, food allergies, drug allergies, severe anaphylactic reactions, anaphylaxis, and other manifestations of allergic disease, as well as uncommon problems such as primary immunodeficiencies, including antibody deficiency states, cell mediated immunodeficiencies (e.g., severe combined immunodeficiency, DiGeorge syndrome, Hyper-IgE syndrome, Wiskott-Aldrich syndrome, ataxia- telangiectasia), immune mediated cancers, and white cell defects.

In autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis (RA), multiple sclerosis (MS), immune-mediated or type 1 diabetes mellitus, immune mediated glomerulonephritis, scleroderma, pernicious anemia, alopecia, pemphigus, pemphigus vulgaris, myasthenia gravis, inflammatory bowel diseases, Crohn's disease, psoriasis, autoimmune thyroid diseases, and Hashimoto's disease, dermatomyositis, goodpastture syndrome, myasthenia gravis pseudoparalytica, ophtalmia sympatica, phakogene uveitis, chronical agressivce hepatitis, primary billiary cirrhosis, autoimunehemolytic anemy, Werlof disease, specific cells uncontrollably attack the body's own tissues and organs (autoimmunity), producing inflammatory reactions and other serious symptoms and diseases.

Hashimoto's thyroiditis is one of the most common autoimmune diseases. "Autoimmune disease" refers to a category of more than 80 chronic illnesses, each very different in nature, that can affect everything from the endocrine glands (like the thyroid) to organs like the kidneys, as well as to the digestive system.

There are many different autoimmune diseases, and they can each affect the body in different ways. For example, the autoimmune reaction is directed against the

brain in multiple sclerosis and the gut in Crohn's disease. In other autoimmune diseases such as systemic lupus erythematosus (lupus), affected tissues and organs may vary among individuals with the same disease. One person with lupus may have affected skin and joints whereas another may have affected skin, kidney, and lungs. Ultimately, damage to certain tissues by the immune system may be permanent, as with destruction of insulin-producing cells of the pancreas in Type 1 diabetes mellitus.

Transplant rejection

Another aspect of the present invention is directed to the use of at least one compound of any one of the general formulas (I), (Ia) – (It) and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of transplant rejection.

Transplant rejection is when a transplant recipient's immune system attacks a transplanted organ or tissue. No two people (except identical twins) have identical tissue antigens. Therefore, in the absence of immunosuppressive drugs, organ and tissue transplantation would almost always cause an immune response against the foreign tissue (rejection), which would result in destruction of the transplant. Though tissue typing ensures that the organ or tissue is as similar as possible to the tissues of the recipient, unless the donor is an identical twin, no match is perfect and the possibility of organ/tissue rejection remains.

The inventive compounds of any one of the general formulas (I), (Ia) – (It) are used as immunosuppressive drugs and/or anti-rejection drugs in order to prevent transplant rejection.

One example of transplant rejection is the graft-versus-host-disease (GVHD) that can occur following bone marrow transplant. The donor's immune cells in the transplanted marrow make antibodies against the host's (transplant patient's) tissues and attack the patient's vital organs. Transplant rejections (also known as graft rejection or tissue/organ rejection) may commonly occur when tissue or organs which need blood supply are transplanted. Said organs comprise especially inner organs such as heart, heart-lungs, lungs, liver, kidney, pancreas, spleen, skin, tissue, bone marrow, spinal marrow, hormone producing glands, gonads and gonadal glands.

Infective diseases

Another aspect of the present invention is directed to the use of at least one compound of any one of the general formulas (I), (Ia) – (It) and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of infective diseases including opportunistic infections.

Examples of infective diseases are AIDS, Alveolar Hydatid Disease (AHD, Echinococcosis), Amebiasis (Entamoeba histolytica Infection), Angiostrongylus Infection, Anisakiasis, Anthrax, Babesiosis (Babesia Infection), Balantidium Infection (Balantidiasis), Baylisascaris Infection (Raccoon Roundworm), Bilharzia (Schistosomiasis), Blastocystis hominis Infection (Blastomycosis), Boreliosis, Botulism, Brainerd Diarrhea, Brucellosis, BSE (Bovine Spongiform Encephalopathy), Candidiasis, Capillariasis (Capillaria Infection), CFS (Chronic Fatigue Syndrome), Chagas Disease (American Trypanosomiasis), Chickenpox (Varicella-Zoster virus), Chlamydia pneumoniae Infection, Cholera, Chronic Fatigue Syndrome, CJD (Creutzfeldt-Jakob Disease), Clonorchiasis (Clonorchis Infection), CLM (Cutaneous Larva Migrans, Hookworm Infection), Coccidioidomycosis, Conjunctivitis, Coxsackievirus A16 (Hand, Foot and Mouth Disease), Cryptococcosis, Cryptosporidium Infection (Cryptosporidiosis), Culex mosquito (Vector of West Nile Virus), Cutaneous Larva Migrans (CLM), Cyclosporiasis (Cyclospora Infection), Cysticercosis (Neurocysticercosis), Cytomegalovirus Infection, Dengue / Dengue Fever, Dipylidium Infection (Dog and Cat Flea Tapeworm), Ebola Virus Hemorrhagic Fever, Echinococcosis (Alveolar Hydatid Disease), Encephalitis, Entomoeba coli Infection, Entomoeba dispar Infection, Entomoeba hartmanni Infection, Entomoeba histolytica Infection (Amebiasis), Entomoeba polecki Infection, Enterobiasis (Pinworm Infection), Enterovirus Infection (Non-Polio), Epstein-Barr Virus Infection, Escherichia coli Infection, Foodborne Infection, Foot and mouth Disease, Fungal Dermatitis, Gastroenteritis, Group A streptococcal Disease, Group B streptococcal Disease, Hansen's Disease (Leprosy), Hantavirus Pulmonary Syndrome, Head Lice Infestation (Pediculosis), Helicobacter pylori Infection, Hematologic Disease, Hendra Virus Infection, Hepatitis (HCV, HBV), Herpes Zoster (Shingles), HIV Infection, Human Ehrlichiosis, Human Parainfluenza Virus Infection, Influenza, Isosporiasis (Isospora Infection), Lassa Fever, Leishmaniasis, Kala-azar (Kala-azar, Leishmania Infection), Leprosy, Lice (Body lice, Head lice, Pubic lice), Lyme Disease, Malaria, Marburg Hemorrhagic Fever, Measles, Meningitis, Mosquito-borne Diseases, Mycobacterium avium Complex (MAC) Infection, Naegleria Infection, Nosocomial Infections, Nonpathogenic Intestinal Amebae

Infection, Onchocerciasis (River Blindness), Opisthorciasis (Opisthorcis Infection), Parvovirus Infection, Plague, PCP (Pneumocystis carinii Pneumonia), Polio, Q Fever, Rabies, Respiratory Syncytial Virus (RSV) Infection, Rheumatic Fever, Rift Valley Fever, River Blindness (Onchocerciasis), Rotavirus Infection, Roundworms Infection, Salmonellosis, Salmonella Enteritidis, Scabies, Shigellosis, Shingles, Sleeping Sickness, Smallpox, Streptococcal Infection, Tapeworm Infection (Taenia Infection), Tetanus, Toxic Shock Syndrome, Tuberculosis, Ulcers (Peptic Ulcer Disease), Valley Fever, Vibrio parahaemolyticus Infection, Vibrio vulnificus Infection, Viral Hemorrhagic Fever, Warts, Waterborne infectious Diseases, West Nile Virus Infection (West Nile Encephalitis), Whooping Cough, Yellow Fever.

Prion diseases

Another aspect of the present invention is directed to the use of at least one compound of any one of the general formulas (I), (Ia) – (It) and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of prion diseases.

Prions are infectious agents which do not have a nucleic acid genome. It seems that a protein alone is the infectious agent. A prion has been defined as "small proteinaceous infectious particle which resists inactivation by procedures that modify nucleic acids". The discovery that proteins alone can transmit an infectious disease has come as a considerable surprise to the scientific community. Prion diseases are often called "transmissible spongiform encephalopathies", because of the post mortem appearance of the brain with large vacuoles in the cortex and cerebellum. Probably most mammalian species develop these diseases. Prion diseases are a group of neurodegenerative disorders of humans and animals and the prion diseases can manifest as sporadic, genetic or infectious disorders. Examples for prion diseases acquired by exogenous infection are the Bovine spongiform encephalitis (BSE) of cattle and the new variant of Creutzfeld-Jakob disease (vCJD) caused by BSE as well as scrapie of animals. Examples of human prion diseases include kuru, sporadic Creutzfeldt-Jakob disease (sCJD), familial CJD (fCJD), iatrogenic CJD (iCJD), Gerstmann-Sträussler-Scheinker (GSS) disease, fatal familial insomnia (FFI), and especially the new variant CJD (nvCJD or vCJD).

The name "prion" is used to describe the causative agents which underlie the transmissible spongiform encephalopathies. A prion is proposed to be a novel

infectious particle that differs from viruses and viroids. It is composed solely of one unique protein that resists most inactivation procedures such as heat, radiation, and proteases. The latter characteristic has led to the term protease-resistant isoform of the prion protein. The protease-resistant isoform has been proposed to slowly catalyze the conversion of the normal prion protein into the abnormal form.

The term "isoform" in the context of prions means two proteins with exactly the same amino acid sequence that are folded into molecules with dramatically different tertiary structures. The normal cellular isoform of the prion protein (PrP^C) has a high α-helix content, a low β-sheet content, and is sensitive to protease digestion. The abnormal, disease-causing isoform (PrP^{Sc})has a lower α-helix content, a much higher β-sheet content, and is much more resistant to protease digestion.

As used herein the term "prion diseases" refers to transmissible spongiform encephalopathies. Examples for prion diseases comprise Scrapie (sheep, goat), TME (transmissible mink encephalopathy; mink), CWD (chronic wasting disease; muledeer, deer, elk), BSE (bovine spongiform encephalopathy; cows, cattles), CJD (Creutzfeld-Jacob Disease), vCJD, GSS (Gerstmann-Sträussler-Scheinker syndrome), FFI (Fatal familial Insomnia), Kuru, and Alpers Syndrome. Preferred are BSE, vCJD, and CJD.

Description of figures:

Figure 1 shows the chemical structure of compound A,

Figure 2 shows the effect of Compound A on cellular p38 kinase activity. Serum-starved HeLa cells were treated with the indicated Compound A concentrations for 15 min and then either stimulated for 30 min with 10 µg/ml anisomycin or for 5 min with 50 ng/ml EGF prior to cell lysis. Total cell extracts were resolved by gel electrophoresis and then immunoblotted with specific antisera specifically recognizing phosphorylated Thr-344 in MAPKAP-K2 (upper left panel), Rsk1 dually phosphorylated on Thr-359 and Ser-363 (upper right panel), MAPKAP-K2 (lower left panel) or Rsk1 (lower right panel).

Figure 3 shows the cellular inhibition of RICK kinase by Compound A. COS-7 cells were transiently transfected with pPM7-RICK-KRdCst expression plasmid (1.35 µg/well) plus either control vector or pPM7-RICK plasmid encoding the full length kinase (0.15 µg/well). After [^{32}P]orthophosphate labelling and affinity purification using StrepTactin beads, cellular RICK-KRdC phosphorylation was visualized by autoradiography prior to protein detection with StrepTactin-HRP.

Figure 4 shows the inhibition of LPS-stimulated cytokine production in human PBMCs by Compound A. Following 15 min pretreatment with different Compound A concentrations, human PBMCs were stimulated with 1 µg/ml LPS. After 16 h, culture supernatants were harvested and the levels of the released cytokines TNFα, MIP-1α and IL-8 were quantified by ELISA. Cytokine levels in the absence of inhibitor were set to 100 % and their concentrations in the culture medium the presence of increasing Compound A doses are expressed relative to this value. Compared to control-treated monocytes, LPS stimulated the release of TNFα, MIP1 α and IL-8 by about 75-, 25- and 5-fold, respectively. Cytokine levels in the

supernatant from LPS-treated cells were 12 ng/ml (TNFα), 70 ng/ml (MIP-1α) and 247 ng/ml (IL-8).

Figure 5 HFF cells were pretreated with DMSO or the indicated Compound A concentrations for 15 min and then stimulated with either 50 µg/ml poly(I-C) or 1 µg/ml LPS. After 16 h, IL-8 levels in the cell culture supernatants were measured by ELISA.

Figure 6 Following preincubation with the indicated Compound A concentrations for 15 min, U373 astrocytoma cells were stimulated for 2 h with 50 µg/ml poly(I-C) prior to lysis and RNA isolation. After reverse transcription, quantitative PCR was performed to measure interferon-β (IFNβ) gene induction in control incubated and poly(I-C)-treated cells. Transcript levels from IFNβ-treated cells were set to 100% and the levels upon inhibitor treatment are shown relative to this value.

Experimental part:

The compounds according to general formula (I) are inhibitors of several protein-tyrosine kinases such as FGFR1 (fibroblast growth factor receptor), Src, Abl and c-kit as well as inhibitors of Wee1 kinase. It is known that Compound A was developed as tyrosine kinase inhibitor for cancer treatment.

Compound A was tested in in vitro assays of Src kinase activity using myelin basic protein as a substrate (Wang, Q., Smith, J. B., Harrison, M. L., and Geahlen, R. L., Biochem. Biophys. Res. Commun. 1991, 178, 1393-1399). Notably, Compound A inhibited Src with a subnanomolar IC50 value in said assays.

Cellular inhibition of p38 and RICK kinase (RICK: Rip-like interacting caspase-like apoptosis-regulatory protein (CLARP) kinase) activities by the compounds of general formula (I):

Our findings that the compounds of general formula (I) effectively targeted the Ser/Thr kinases p38 and RICK, which are both established signal transducers of

inflammatory responses, prompted us to study the effect of Compound A on their activities in intact cells (Lee, J. C., Laydon, J. T., McDonell, P. C., Gallagher, T. F., Kumar, S., Green, D., McNulty, D., Blumenthal, M. J., Heys, J. R., Landvatter, S. W., Strickler, J. E., McLaughlin, M. M., Siemens, I. R., Fisher, S. M., Livi, G. P., White, J. R., Adams, J. L., and Young, P. R. (1994) Nature 372, 739-746; Chin, A. I., Dempsey, P. W., Bruhn, K., Miller, J. F., and Cheng, G., Nature 2002, 416, 190-194; Kobayashi, K., Inohara, N., Hernandez, L. D., Galan, J. E., Nunez, G., Janeway, C. A., Medzhitov, R., and Flavell, R. A. (2002) Nature 416, 194-199).

To monitor cellular p38 activity, we analyzed the phosphorylation of its direct cellular substrate MAPKAP-K2 (MAPK-activated protein kinase 2) by immunoblotting with phospho-specific antiserum (Eyers, P A., van den Ijssel, P., Quinlan, R. A., Goedert, M., and Cohen, P., *FEBS Lett.* 1999, 451,191-196). Activation of p38 by anisomycin treatment triggered MAPKAP-K2 phosphorylation at Thr-344, and this stimulation was inhibited by Compound A in a dose-dependent manner with a cellular IC50 value somewhat below 10 nM (**Fig. 2**). Immunoblot analysis with MAPKAP-K2 protein-specific antibody showed the anisomycin-induced band shift of MAPKAP-K2 due to phosphorylation of the protein at multiple sites. This apparent change in molecular weight was also reverted by Compound A, albeit at slightly higher concentrations than phosphorylation at Thr-344.

To investigate the effect of Compound A on RICK activity in intact cells, we performed a recently described assay (Godl, K., Wissing, J., Kurtenbach, A., Habenberger, P., Blencke, S., Gutbrod, H., Salassidis, K., Stein-Gerlach, M., Missio, A., Cotten, M., and Daub, H., Proc. Natl. Acad. Sci. U. S. A. 2003, 100, 15434-15439) in which a kinase-inactive RICK fragment serves as a cellular phosphorylation substrate for co-expressed, wild-type enzyme. As shown in **Fig. 3**, dose-dependent inhibition of cellular RICK activity was detected in the presence of increasing Compound A concentrations, and 30 nM of the inhibitor already reduced the cellular substrate phosphorylation by more than 50%.

Cellular inhibition of cytokine production by the compounds of the general formula (I):

Our identification of p38 and RICK as cellular targets of the compounds of the general formula (I) raised the issue whether compounds such as Compound A might suppress inflammatory responses in addition to their cell growth-inhibitory properties. To test this, we first analyzed the effect of Compound A on LPS-

induced TNFα (tumor necrosis factor-α) release in primary human PBMCs (peripheral blood mononuclear cell) (Rutault, K. Hazzalin, C. A., and Mahadevan, L. C., J. Biol. Chem. 2001, 276, 6666-6674). As seen in **Fig. 4**, LPS-stimulated TNFα production was potently inhibited by Compound A with a cellular IC50 value of around 3 nM. This effect is might be functionally linked to the Compound A-mediated suppression of cellular MAPKAP-K2 phosphorylation shown in **Fig. 2**, since genetic evidence has established this cellular target of p38 kinase as essential transducer of LPS-stimulated TNF-α biosynthesis (Kotlyarov, A., Neininger, A., Schubert, C., Eckert, R., Birchmeier, C., Volk, H.-D., and Gaestel, M., Nat. Cell Biol. 1999, 1, 94-97). In addition to TNFα , we measured the levels of the chemokines macrophage inflammatory protein (MIP)-1α and interleukin (IL)-8. Lipopolysaccharide (LPS)-regulated biosynthesis of MIP-1α was also efficiently suppressed by Compound A with an IC50 of about 15 nM in human PBMCs.

As further shown in **Fig. 5**, Compound A also interfered with IL-8 biosynthesis upon exposure of human foreskin fibroblast (HFF) cells to the synthetic double-stranded RNA analogue poly(I:C), which acts on toll-like receptor 3 and triggers cellular signaling in a way similar to viral infection (Akira, S., Curr. Opin. Immunol. 2003, 15, 5-11). One of the hallmarks of antiviral responses is the induction of interferons (IFN) such as IFNβ. Using U373 astrocytoma cells, we investigated the effect of Compound A on poly(I:C)-triggered IFNβ gene induction by quantitative RT-PCR (Servant, M. J., Grandvaux, N., tenOever, B. R., Duguay, D., Lin, R., Hiscott, J., J. Biol. Chem. 2003, 278, 9441-7). Interestingly, concentrations of Compound A as low as 10 nM strongly impaired the synthesis of IFNβ mRNA (IFNβ: interferon-β) **(Fig. 6)**.

Taken together, our results establish the compounds of general formula (I) as small molecule antagonists of innate immune responses with potent anti-inflammatory properties.

Methods:

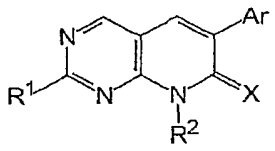
Frozen PBMCs were purchased from Cambrex Bio Science. Thawed and washed cells were re-suspended in RPMI medium containing 1% FBS and then seeded into 24 well dishes (1 x 10^6 cells per well). After 1 h, the medium was aspirated, the cell culture plates were washed with medium to remove non-adherent cells and fresh medium was added. The medium was exchanged again after a further 3.5 h prior to addition of either DMSO or different amounts of

Compound A and subsequent LPS (Sigma, serotype 055:B5) stimulation of the human PBMCs. 16 h later, supernatants were harvested and analyzed using ELISA kits from R&D Systems to quantitate the levels of TNFα, MIP-1α and IL-8 released into the medium. Prior to inhibitor and subsequent LPS or poly(I-C) treatment, confluent HFF cells were incubated with fresh DMEM containing 1 % FCS for 30 min. After 16 h of ligand stimulation, IL-8 levels in the supernatants were quantified. All cytokine assays were performed according to the manufacturer's instructions.

U373 cell stimulations were also performed in DMEM / 1% FCS, and total RNA was isolated 2h after poly(I-C) treatment using by the Trizol method (Invitrogen, Karlsruhe, Germany) followed by a DNase I digest on RNeasy columns (Qiagen, Hilden, Germany). Interferon-β (IFNβ) mRNA levels were determined by quantitative RT-PCR based on the 5' exonuclease activity of Taq polymerase on an ABI PRISM 7000 Sequence Detection System (Applied Biosystems, Darmstadt, Germany). RNA was reverse transcribed with Superscript II (Invitrogen, Karlsruhe, Germany) and oligo-dT primers according to the manufacturer's protocol. Gene-specific TaqMan probes were labelled with FAM™ at the 5' end and TAMRA™ at the 3' end of the oligonucleotides. GAPDH (determined with pre-developed TaqMan assay reagents from Applied Biosystems) served as a housekeeping gene. Primer sequences for IFNβ were: 5'-GACATCCCTGAGGA-GATTAAGCA-3' (forward), reverse: 5'-GGAGCATCTCATAGATGGTCAATG-3' (reverse), 5'-FAM-CGTCCTCCTTCTGGAACTGCTGCAG-TAMRA-3' (TaqMan probe).

CLAIMS

1. Use of compounds having the general formula (I)



(I)

wherein

X represents =NH, =N–Acyl, =O, or =S;

R^1 represents $-NR^3R^4$, $-SR^3$, $-SO-R^3$, $-SO_2-R^3$, $-OR^3$;

R^2, R^3, and R^4 represent independently of each other hydrogen, $-(CH_2)_nPh^*$, heteroaryl, C_3-C_7-cycloalkyl, C_1-C_6-alkyl, C_1-C_6-alkanoyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl;

wherein

the cycloalkyl, alkyl, alkanoyl, alkenyl, alkynyl residues can optionally substituted by one or more of the following groups: $-NR^5R^6$, phenyl, substituted phenyl, thioalkyl, alkyloxy, hydroxy, carboxy, halogen, C_3-C_7-cycloalkyl;

R^5 and R^6 represent independently of each other hydrogen, $-(CH_2)_nPh^*$, heteroaryl, C_3-C_7-cycloalkyl, C_1-C_6-alkyl, C_1-C_6-alkanoyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl;

R^5 and R^6 can be taken together with the nitrogen to which they are attached to complete a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

Ph* represents phenyl or substituted phenyl;

n is 0, 1, 2, or 3;

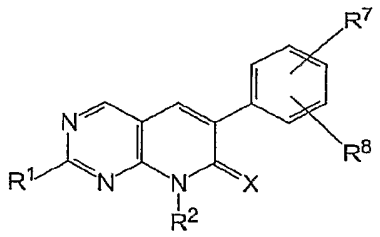
R^4 can optionally be $-CO-R^3$, $-CO-OR^3$, $-SO_2-R^3$, $-SO_2-NR^5R^6$, $-CO-NR^5R^6$, $-CS-NR^5R^6$, $-C(=NH)-R^3$, $-C(=NH)-NR^5R^6$;

R^3 and R^4 can be taken together with the nitrogen to which they are attached to complete a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

Ar represents phenyl, substituted phenyl, or heteroaryl;

and/or pharmaceutically acceptable salts thereof for the manufacture of a pharmaceutical formulation for prophylaxis and/or treatment of inflammatory diseases.

2. Use of a compound according to claim 1 having the general formula (II)



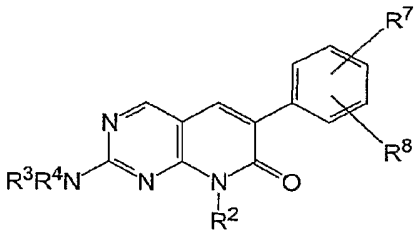
(II)

wherein

R^1, R^2, and X have the meanings as defined in claim 1; and

R^7 and R^8 independently of each other represent C_1-C_6-alkyl, halogen.

3. Use of a compound according to claim 2 having the general formula (III)



(III)

wherein

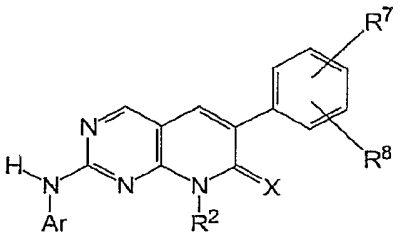
R^2 represents C_1-C_6-alkyl;

R^3 represents hydrogen or C_1-C_6-alkyl;

R^4 represents C_1-C_6-alkyl or substituted C_1-C_6-alkyl; and

R^7 and R^8 independently of each other represent C_1-C_6-alkyl, halogen.

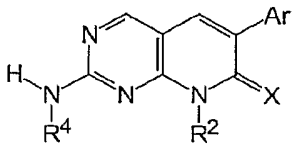
4. Use of a compound according to claim 1 having the general formula (III)



(IV)

wherein
R^2 represents C_1-C_6-alkyl or substituted C_1-C_6-alkyl;
X represents =O or =NH; and
Ar represents phenyl, substituted phenyl, pyridyl, or substituted pyridyl.

5. Use of a compound according to claim 1 having the general formula (III)



(V)

wherein
R^2 represents C_1-C_6-alkyl or substituted C_1-C_6-alkyl;
X represents =O or =NH; and
Ar represents phenyl or substituted phenyl.

6. Use of a compound according to claim 1 selected from the group comprising:
6-(2,6-Dimethyl-phenyl)-7-imino-8-methyl-7,8-dihydro-pyrido-[2,3-d]pyrimidin-2-ylamine;
6-(2-Methyl-phenyl)-7-imino-8-methyl-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamine;
6-Phenyl-7-imino-8-methyl-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamine;
6-(2,6-Dichlorophenyl)-8-methyl-2-[3-(4-methylpiperazin-1-yl)-propylamino]-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-methylamino-8H-pyrido[2,3-d]pyrimidin-7-one;

6-(2,6-Dichlorphenyl)-2-dimethylamino-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorphenyl)-2-ethylamino-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorphenyl)-2-(2-hydroxyethyl-amino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorphenyl)-2-isopropylamino-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Butylamino-6-(2,6-dichlorphenyl)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Benzylamino-6-(2,6-dichlorphenyl)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorphenyl)-8-methyl-2-(3-morpholin-4-yl-propylamino)-8H-pyrido[2,3-d]-pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-[2-(3,4-dimethoxy-phenyl)-ethylamino]-8-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-[(pyridin-2-ylmethyl)-amino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-[(pyridin-3-ylmethyl)-amino]-8H-pyrido[2,3-d]pyrimidin7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-(2-pyridin-2-yl-ethylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-{3-[4-(2-methoxy-phenyl)-piperazin-1-yl]-propylamino}-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-[4-(4-methylpiperazin-1-yl)-butylamino]-8H-pyrido[2,3-d]pyrimidin-7-one;
6-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-hexanoic acid tert-butyl ester;
6-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-hexanoic acid;
6-(2,6-Dichlorophenyl)-8-ethyl-2-[3-(4-methyl-piperazin-1-yl)-propylamino]-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-[5-(4methylpiperazin-1-yl)-pentylamino]-8H-pyrido[2,3-d]pyrimidin-7-one;
4-{4-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-phenyl}-butyric acid ethyl ester;
4-{4-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-phenyl}-butyric acid;

2-Amino-6-(2,6-dichlorophenyl)-8-methyl-pyrido[2,3-d]pyrimidin-7(8H)-one;
2-Amino-6-phenyl-8-methyl-pyrido[2,3-d]-pyrimidin-7(8H)-one;
2-Amino-6-(2,6-dichlorophenyl)-8-ethyl-pyrido[2,3-d]pyrimidine-7(8H)-one;
2-Amino-6-(2,6-dichlorophenyl)-8-propyl-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-8-butyl-6-(2,6-dichlorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dichlorophenyl)-8-isobutyl-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dichlorophenyl)-8-(3-dimethyl-aminopropyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
[2-Amino-6-(2,6-dichlorophenyl)-7-oxo-7H-pyrido[2,3-d]pyrimidin-8-yl]-acetic acid methyl ester;
[2-Amino-6-(2,6-dichlorophenyl)-7-oxo-7H-pyrido[2,3-d]pyrimidin-8-yl]-acetic acid tert-butyl ester;
[2-Amino-6-(2,6-dichlorophenyl)-7-oxo-7H-pyrido[2,3-d]pyrimidin-8-yl]-acetic acid;
2-Amino-8-benzyl-6-(2,6-dichlorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-8-(3-bromobenzyl)-6-(2,6-dichlorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
4-[2-Amino-6-(2,6-dichlorophenyl)-7-oxo-7H-pyrido[2,3-d]pyrimidin-8-ylmethyl]-benzoic acid methyl ester;
2-Amino-8-(2,6-dichlorobenzyl)-6-(2,6-dichlorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dichlorophenyl)-8-(4-methoxybenzyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dichlorophenyl)-8-pyridin-4-ylmethyl-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dichlorophenyl)-8-(3-phenylpropyl)-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Amino-6-(2,6-dimethylphenyl)-8-methyl-pyrido[2,3-d]-pyrimidin-7(8H)-one;
2-Amino-6-(2-methylphenyl)-8-methyl-pyrido[2,3-d]pyrimidin-7(8H)-one;
[6-(2,6-Dichlorophenyl)-7-imino-8-methyl-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]-(3-diethylamino-propyl)-amine;
[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]-(3-diethylamino-propyl)-amine;
N-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]acetamide;
2-Amino-6-(2,6-dichlorophenyl)-8-methyl-pyrido[2,3]-pyrimidin-7(8H)-thione;
N-[6-(2,6-Dichlorophenyl)-7-oxo-8-methyl-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yl]-succinamic acid;

1-[6-(2,6-Dichlorophenyl)-7-oxo-8-methyl-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]-pyrrolidine-2,5-dione;
6-(2,6-Dichlorophenyl)-2-hydroxy-8-methyl-8H-pyrido-[2,3-d]pyrimidin-7-ylideneamine;
6-(2,6-Dichlorophenyl)-2-(2-ethoxy-ethoxy)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-ylideneamine;
6-(2,6-Dichlorophenyl)-2-hydroxy-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-[2-(diethylamino)ethoxy]-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-ylideneamine;
6-(2,6-Dichlorophenyl)-8-ethyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-ylideneamine;
6-(2,6-Dichlorophenyl)-2-methanesulfinyl-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-methanesulfonyl-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-ethyl-2-methane-sulfonyl-8H-pyrido[2,3-d]pyrimidin-7-one;
N-[6-(2,6-Dichlorophenyl)-8-methyl-2-methyl-sulfanyl-8H-pyrido[2,3-d]pyrimidin-7-ylidene]-acetamide;
N-[6-(2,6-Dichlorophenyl)-8-ethyl-2-methyl-sulfanyl-8H-pyrido[2,3-d]pyrimidin-7-ylidene]-acetamide;
N-[6-(2,6-Dichlorophenyl)-2-(4-diethylaminobutylamino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-ylidene]-acetamide;
6-(2,6-Dichlorophenyl)-8-methyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
2-(3-Bromophenylamino)-6-(2,6-dichlorophenyl)-8-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one;
2-(4-Chlorophenylamino)-6-(2,6-dichlorophenyl)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
2-(Benzo[1,3]dioxol-5-ylamino)-6-(2,6-dichlorophenyl)-8-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one;

6-(2,6-Dichlorophenyl)-8-methyl-2-(pyridin-4-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-p-tolylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(4-methoxyphenyl-amino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-ethyl-2-phenyl-amino-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(2-methoxyphenyl-amino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(3-methoxyphenyl-amino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(4-methoxy-3-methyl-phenylamino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-ethyl-2-(4-methoxy-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-ethyl-2-(4-hydroxy-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(4-ethoxyphenyl-amino)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(3,4-dimethoxy-phenylamino)-8-ethyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-ethyl-2-(3,4,5-trimethoxyphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-8-methyl-2-(pyridin-3-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-[4-(2-diethyl-aminoethoxy)-phenylamino]-8-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(3-hydroxymethyl-phenylamino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
6-(2,6-Dichlorophenyl)-2-(3,5-dimethoxy-phenylamino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
{4-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-phenyl}-acetic acid methyl ester;
6-(2,6-Dichlorophenyl)-2-(6-methoxypyridin-3-ylamino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
{4-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-phenyl}-acetic acid;

6-(2,6-Dichlorophenyl)-2-(3-hydroxyphenyl-amino)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
4-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-benzoic acid ethyl ester;
3-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-benzoic acid ethyl ester;
3-[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)-benzoic acid;
6-(2,6-Dichlorophenyl)-8-ethyl-2-(pyridin-4-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one;
[6-(2-Bromo-6-chlorophenyl)-8-ethyl-7-imino-7,8-dihydropyrido[2,3-d]pyrimidin-8-yl]-phenylamine;
6-(2-Bromo-6-chlorophenyl)-8-ethyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
(8-Ethyl-7-imino-6-phenyl-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2-phenylamine;
8-Ethyl-6-phenyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
(6-(3,5-Dimethylphenyl)-8-ethyl-7-imino-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-phenylamine;
6-(3,5-Dimethylphenyl)-8-ethyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
8-Ethyl-2-phenylamino-6-thiophen-3-yl-8H-pyrido[2,3-d]pyrimidin-7-one;
8-Ethyl-7-imino-6-thiophen-2-yl-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-phenylamine;
8-Ethyl-2-phenylamino-6-thiophen-2-yl-8H-pyrido[2,3-d]pyrimidin-7-one;
(8-Ethyl-7-imino-6-pyridin-4-yl-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-phenylamine;
8-Ethyl-2-phenylamino-6-pyridin-4-yl-8H-pyrido[2,3-d]pyrimidin-7-one;
(8-Ethyl-7-imino-6-naphthalen-2-yl-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)-phenylamine;
8-Ethyl-6-naphthalen-2-yl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
(6-Biphenyl-4-yl-8-ethyl-7-imino-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)-phenylamine;
6-Biphenyl-4-yl-8-ethyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one;
2-Cyclohexylamino-6-(2,6-dichlorophenyl)-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one.

7. Use according to any one of the previous claims wherein the inflammatory disease is caused, induced, initiated and/or enhanced by bacteria, viruses, prions, parasites, fungi, and/or caused by irritative, traumatic, metabolic, allergic, autoimmune, or idiopathic reasons.

8. Use according to claim 7 wherein the viruses and bacteria are selected from the group comprising human immunodeficiency virus-I, herpes viruses, herpes simplex virus, herpes zoster virus, cytomegalovirus, mycoplasma pulmonis, ureaplasma urealyticum, mycoplasma pneumoniae, chlamydia pneumoniae, C. pneumoniae, Helicobacter pylori, and proprionobacterium.

9. Use according to any one of the previous claims wherein the inflammatory disease is selected from the group comprising inflammatory diseases of the central nervous system (CNS), inflammatory rheumatic diseases, inflammatory diseases of blood vessels, inflammatory diseases of the middle ear, inflammatory bowel diseases, inflammatory diseases of the skin, inflammatory disease uveitis, inflammatory diseases of the larynx.

10. Use according to claim 9 wherein the inflammatory diseases of the central nervous system (CNS), inflammatory rheumatic diseases, inflammatory diseases of blood vessels, inflammatory diseases of the middle ear, inflammatory bowel diseases, inflammatory diseases of the skin, inflammatory disease uveitis, inflammatory diseases of the larynx are selected from the group comprising:
abscessation, acanthameba, acanthamebiasis, acne vulgaris, actinomycosis, acute inflammatory dermatoses, acute laryngeal infections of adults, acute multifocal placoid pigmentary epitheliopathy, acute (thermal) injury, acute retinal necrosis, acute suppurative otitis media, algal disorders, allergic contact dermatitis, amyloidosis angioedema, ankylosing spondylitis, aspergillosis, atopic dermatitis, Aujeszky's disease, autoantibodies in vasculitis, babesiosis, bacterial disorders, bacterial laryngitis, bacterial meningitis, Behcet's disease, birdshot choroidopathy, blastomycosis, borna disease, brucellosis, bullous myringitis, bursitis, candidiasis, canine distemper encephalomyelitis, canine distemper encephalomyelitis in immature animals, canine ehrlichiosis, canine herpes virus encephalomyelitis, cholesteatoma, chronic (granulomatous) diseases, chronic inflammatory dermatoses,

chronic relapsing encephalomyelitis, chronic suppurative otitis media, cicatricial pemphigoid, coccidiomycosis, coccidioidomycosis, common upper respiratory infection, contact ulcer and granuloma, Crohn's disease, cryptococcosis, cysticercosis, dermatomyositis, diphtheria, discoid lupus erythematosus, drug-induced vasculitis, drug or hypersensitivity reaction, encephalitozoonosis, eosinophilic meningoencephalitis, erythemal multiforme (EM minor), feline leukemia virus, feline immunodeficiency virus, feline infectious peritonitis, feline polioencephalomyelitis, feline spongiform encephalopathy, fibromyositis, Fuch's heterochromic cyclitis, gastroesophageal (laryngopharyngeal) reflux disease, giant cell arteritis, glanders, glaucomatocyclitic crisis, gonorrhea granular myringitis, granulomatous meningoencephalomyelitis, herpes simplex, histoplasmosis, idiopathic diseases, idiopathic inflammatory disorders, immune and idiopathic disorders, infections of the immunocompromised host, infectious canine hepatitis, inhalation laryngitis, interstitial nephritis, irritant contact dermatitis, juvenile rheumatoid arthritis, Kawasaki's disease, La Crosse virus encephalitis, laryngeal abscess, laryngotracheitis (croup), leishmaniasis, lens-induced uveitis, leprosy, leptospirosis, leukemia, lichen planus, lupus, lyme disease, lymphoma, meningitis, meningoencephalitis in greyhounds, miscellaneous meningitis / meningoencephalitis, microscopic polyangiitis, multifocal choroiditis, multifocal distemper encephalomyelitis in mature animals, multiple sclerosis, muscle tension dysphonias, mycotic (fungal) diseases, mycotic diseases of the CNS, necrotizing encephalitis, neosporosis, old dog encephalitis, onchocerciasis, parasitic encephalomyelitis, parasitic infections, pars planitis, parvovirus encephalitis, pediatric laryngitis, pollution and inhalant allergy, polymyositis, post-vaccinal canine distemper encephalitis, post-vaccinal rabies, prion protein induced diseases, protothecosis, protozoal encephalitis-encephalomyelitis, psoriasis, psoriatic arthritis, pug dog encephalitis, pyogranulomatous meningoencephalomyelitis, rabies, radiation injury, radiation laryngitis, radionecrosis, relapsing polychondritis, Reiters's syndrome, retinitis pigmentosa, retinoblastoma, rheumatoid arthritis, rickettsial disorders, rocky mountain spotted fever, salmon poisoning, sarcocystosis, sarcoidosis, schistosomiasis, scleroderma, scleroma, serpiginous choroiditis, shaker dog disease, Sjogren's syndrome, spasmodic croup, spirochetal (syphilis) diseases, spongiotic dermatitis, sporotrichosis, steroid responsive meningitis-arteritis, Stevens-Johnson syndrome (SJS,

EM major), supraglottitis (epiglottitis), sympathetic ophthalmia, syngamus laryngeus, syphilis, systemic lupus erythematosus, systemic vasculitis in sarcoidosis, Takayasu's arteritis, tendinitis (tendonitis), thromboangiitis obliterans (Buerger's Disease), tick-borne encephalitis in dogs, toxic epidermal necrolysis (TEN), toxocariasis, toxoplasmosis, trauma, traumatic laryngitis, trichinosis, trypanosomiasis, tuberculosis, tularemia, ulcerative colitis, urticaria (hives), vasculitis, vasculitis and malignancy, vasculitis and rheumatoid arthritis, vasculitis in systemic lupus erythematosus, vasculitis in the idiopathic inflammatory myopathies, vasculitis of the central nervous system, vasculitis secondary to bacterial, fungal, and parasitic infection, viral disorders, viral laryngitis, vitiligo, vocal abuse, vocal-cord hemorrhage, Vogt Koyanagi Harada syndrome, Wegener's granulomatosis, and Whipple's disease.

11. Use of a compound according to any one of claims 1 – 6 and/or pharmaceutically acceptable salts thereof for the manufacture of a pharmaceutical formulation for prophylaxis and/or treatment of neurodegenerative disorders, immunological diseases, neuroimmunological diseases, autoimmune diseases, diabetes, transplant rejection, infective diseases, prion diseases, cardiovascular diseases and disorders.

12. Use according to claim 11 wherein the cardiovascular diseases and disorders are selected from the group comprising: aneurysm, stable angina, unstable angina, angina pectoris, angioneurotic edema, aortic valve stenosis, aortic aneurysm, arrhythmia, arrhythmogenic right ventricular dysplasia, arteriosclerosis, arteriovenous malformations, atrial fibrillation, Behcet syndrome, bradycardia, cardiac tamponade, cardiomegaly, congestive cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, carotid stenosis, cerebral hemorrhage, Churg-Strauss syndrome, diabetes, Ebstein's Anomaly, Eisenmenger complex, cholesterol embolism, bacterial endocarditis, fibromuscular dysplasia, congenital heart defects, heart diseases, congestive heart failure, heart valve diseases, heart attack, epidural hematoma, hematoma, subdural, Hippel-Lindau disease, hyperemia, hypertension, pulmonary hypertension, cardiac hypertrophy, left ventricular hypertrophy, right ventricular hypertrophy, hypoplastic left heart syndrome, hypotension, intermittent claudication, ischemic heart disease, Klippel-Trenaunay-Weber syndrome, lateral medullary syndrome, long QT syndrome mitral valve prolapse, moyamoya

disease, mucocutaneous lymph node syndrome, myocardial infarction, myocardial ischemia, myocarditis, pericarditis, peripheral vascular diseases, phlebitis, polyarteritis nodosa, pulmonary atresia, Raynaud disease, Sneddon syndrome, superior vena cava syndrome, syndrome X, tachycardia, Takayasu's arteritis, hereditary hemorrhagic telangiectasia, telangiectasis, temporal arteritis, tetralogy of fallot, thromboangiitis obliterans, thrombosis, thromboembolism, tricuspid atresia, varicose veins, vascular diseases, vasculitis, vasospasm, ventricular fibrillation, Williams syndrome, peripheral vascular disease, varicose veins and leg ulcers, deep vein thrombosis, Wolff-Parkinson-White syndrome.

13. Use according to claim 12 wherein the cardiovascular diseases and disorders are selected from the group comprising: thombosis, cardiac hypertrophy, and myocardial ischemia.

14. Use according to claim 11 wherein the neurodegenerative disorders are selected from the group comprising: Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, AIDS-related dementia, retinitis pigmentosa, spinal muscular atrophy and cerebrellar degeneration, fragile X-associated tremor/ataxia syndrome (FXTAS), progressive supranuclear palsy (PSP), and striatonigral degeneration (SND), which is included with olivopontocerebellear degeneration (OPCD), and Shy Drager syndrome (SDS) in a syndrome known as multiple system atrophy (MSA).

15. Use according to claim 11 wherein the immunological disease, neuroimmunological disease, and/or autoimmune disease is selected from the group comprising: asthma, diabetes, rheumatic diseases, AIDS, rejection of transplanted organs and tissues, rhinitis, chronic obstructive pulmonary diseases, osteoporisis, ulcerative colitis, sinusitis, lupus erythematosus, recurrent infections, atopic dermatitis / eczema and occupational allergies, food allergies, drug allergies, severe anaphylactic reactions, anaphylaxis, manifestations of allergic diseases, primary immunodeficiencies, antibody deficiency states, cell mediated immunodeficiencies, severe combined immunodeficiency, DiGeorge syndrome, Hyper-IgE syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia, immune mediated cancers, white cell defects, autoimmune diseases, systemic lupus erythematosus, rheumatoid arthritis (RA), multiple

sclerosis (MS), immune-mediated or Type 1 Diabetes Mellitus, immune mediated glomerulonephritis, scleroderma, pernicious anemia, alopecia, pemphigus, pemphigus vulgaris, myasthenia gravis, inflammatory bowel diseases, Crohn's disease, psoriasis, autoimmune thyroid diseases, Hashimoto's disease, dermatomyositis, goodpastture syndrome, myasthenia gravis pseudoparalytica, ophtalmia sympatica, phakogene uveitis, chronical agressivce hepatitis, primary billiary cirrhosis, autoimunehemolytic anemy, Werlof disease.

16. Use according to claim 11 wherein the transplant rejection are selected from the group comprising: heart transplant rejection, heart-lung transplant rejection, lung transplant rejection, liver transplant rejection, kidney transplant rejection, pancreas transplant rejection, spleen transplant rejection, skin transplant rejection, tissue transplant rejection, bone marrow transplant rejection, spinal marrow transplant rejection, hormone producing glands transplant rejection, gonads and gonadal gland transplant rejection, graft-versus-host-diseases and host-versus-graft-diseases.

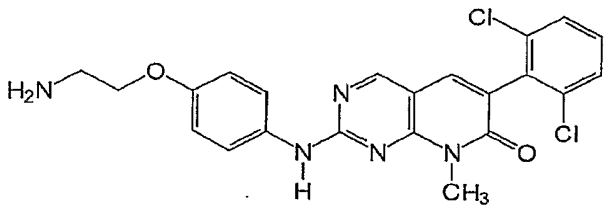
17. Use according to claim 11 wherein the infective diseases are selected from the group comprising: AIDS, Alveolar Hydatid Disease (AHD, Echinococcosis), Amebiasis (Entamoeba histolytica Infection), Angiostrongylus Infection, Anisakiasis, Anthrax, Babesiosis (Babesia Infection), Balantidium Infection (Balantidiasis), Baylisascaris Infection (Raccoon Roundworm), Bilharzia (Schistosomiasis), Blastocystis hominis Infection (Blastomycosis), Boreliosis, Botulism, Brainerd Diarrhea, Brucellosis, BSE (Bovine Spongiform Encephalopathy), Candidiasis, Capillariasis (Capillaria Infection), CFS (Chronic Fatigue Syndrome), Chagas Disease (American Trypanosomiasis), Chickenpox (Varicella-Zoster virus), Chlamydia pneumoniae Infection, Cholera, Chronic Fatigue Syndrome, CJD (Creutzfeldt-Jakob Disease), Clonorchiasis (Clonorchis Infection), CLM (Cutaneous Larva Migrans, Hookworm Infection), Coccidioidomycosis, Conjunctivitis, Coxsackievirus A16 (Hand, Foot and Mouth Disease), Cryptococcosis, Cryptosporidium Infection (Cryptosporidiosis), Culex mosquito (Vector of West Nile Virus), Cutaneous Larva Migrans (CLM), Cyclosporiasis (Cyclospora Infection), Cysticercosis (Neurocysticercosis), Cytomegalovirus Infection, Dengue / Dengue Fever, Dipylidium Infection (Dog and Cat Flea Tapeworm), Ebola Virus Hemorrhagic Fever, Echinococcosis (Alveolar Hydatid Disease),

Encephalitis, Entomoeba coli Infection, Entomoeba dispar Infection, Entomoeba hartmanni Infection, Entomoeba histolytica Infection (Amebiasis), Entomoeba polecki Infection, Enterobiasis (Pinworm Infection), Enterovirus Infection (Non-Polio), Epstein-Barr Virus Infection, Escherichia coli Infection, Foodborne Infection, Foot and mouth Disease, Fungal Dermatitis, Gastroenteritis, Group A streptococcal Disease, Group B streptococcal Disease, Hansen's Disease (Leprosy), Hantavirus Pulmonary Syndrome, Head Lice Infestation (Pediculosis), Helicobacter pylori Infection, Hematologic Disease, Hendra Virus Infection, Hepatitis (HCV, HBV), Herpes Zoster (Shingles), HIV Infection, Human Ehrlichiosis, Human Parainfluenza Virus Infection, Influenza, Isosporiasis (Isospora Infection), Lassa Fever, Leishmaniasis, Kala-azar (Kala-azar, Leishmania Infection), Leprosy, Lice (Body lice, Head lice, Pubic lice), Lyme Disease, Malaria, Marburg Hemorrhagic Fever, Measles, Meningitis, Mosquito-borne Diseases, Mycobacterium avium Complex (MAC) Infection, Naegleria Infection, Nosocomial Infections, Nonpathogenic Intestinal Amebae Infection, Onchocerciasis (River Blindness), Opisthorciasis (Opisthorcis Infection), Parvovirus Infection, Plague, PCP (Pneumocystis carinii Pneumonia), Polio, Q Fever, Rabies, Respiratory Syncytial Virus (RSV) Infection, Rheumatic Fever, Rift Valley Fever, River Blindness (Onchocerciasis), Rotavirus Infection, Roundworms Infection, Salmonellosis, Salmonella Enteritidis, Scabies, Shigellosis, Shingles, Sleeping Sickness, Smallpox, Streptococcal Infection, Tapeworm Infection (Taenia Infection), Tetanus, Toxic Shock Syndrome, Tuberculosis, Ulcers (Peptic Ulcer Disease), Valley Fever, Vibrio parahaemolyticus Infection, Vibrio vulnificus Infection, Viral Hemorrhagic Fever, Warts, Waterborne infectious Diseases, West Nile Virus Infection (West Nile Encephalitis), Whooping Cough, Yellow Fever.

18. Use according to claim 11 wherein the prion diseases are selected from the group comprising: Scrapie, TME, CWD, BSE, CJD, vCJD, GSS, FFI, Kuru, and Alpers Syndrome.

Figures

Figure 1



Compound A

Figure 2

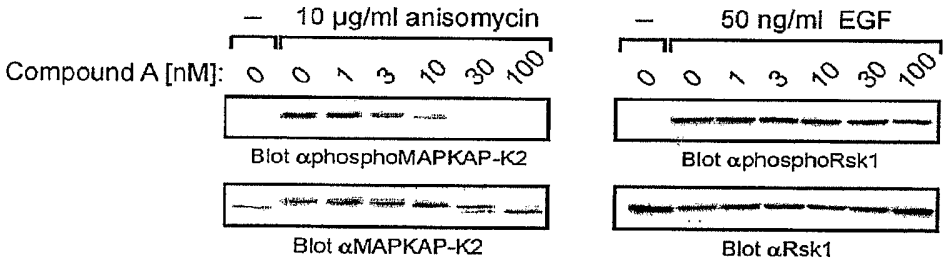


Figure 3

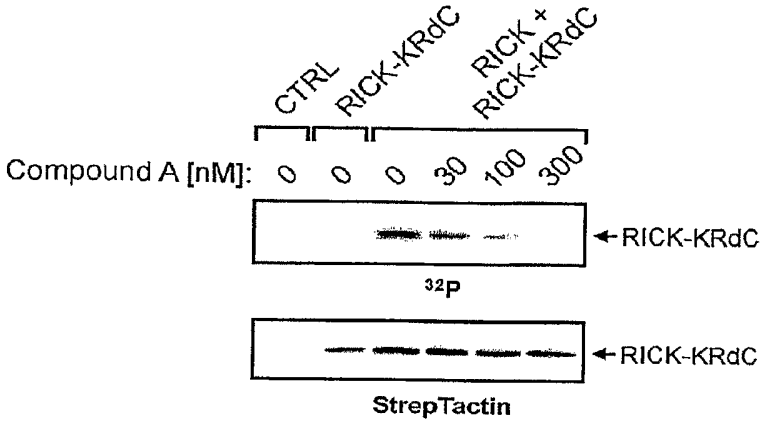


Figure 4

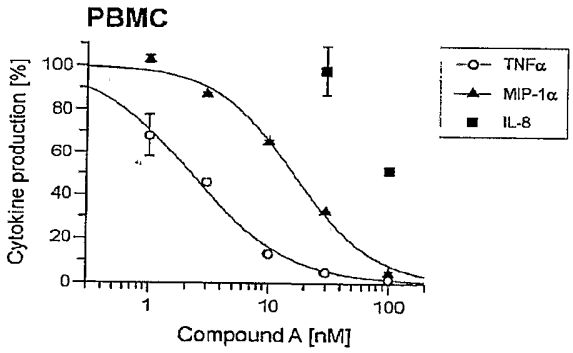


Figure 5

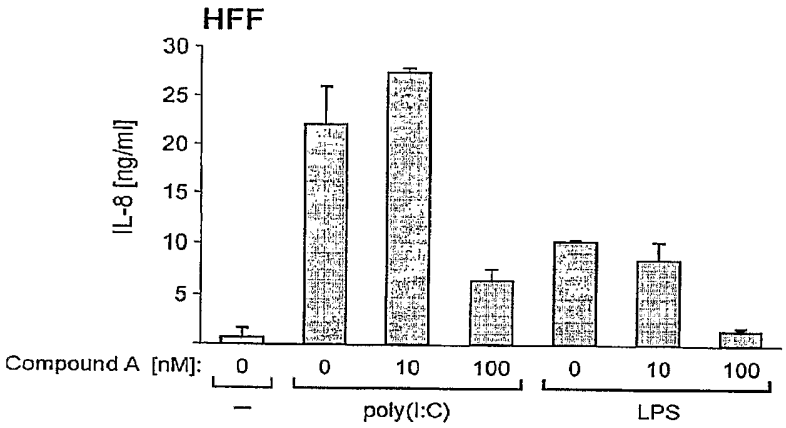


Figure 6

