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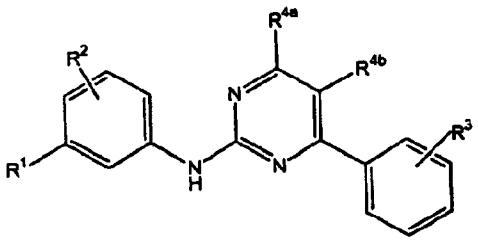

(I)

(57) Abstract: The present invention relates to inhibitors of cyclin-dependent kinases and therapeutic applications thereof. Furthermore, the invention relates to methods of preventing and/or treating any type of pain, inflammatory disorders, immunological diseases, proliferative diseases, infectious diseases, cardiovascular diseases and neurodegenerative diseases comprising the administration of an effective amount of at least one inhibitor of cyclin-dependent kinases.

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INHIBITORS OF PROTEIN KINASES

BACKGROUND OF THE INVENTION

Cyclin-dependent protein kinases ("CDKs"), constitute a family of well-conserved enzymes that play multiple roles within the cell, such as cell cycle regulation and transcriptional control (Science 1996, Vol. 274:1643-1677; Ann. Rev.Cell Dev. Biol., 1997, 13:261-291).

Some members of the family, such as CDK1, 2, 3, 4, and 6 regulate the transition between different phases of the cell cycle, such as the progression from a quiescent stage in G1 (the gap between mitosis and the onset of DNA replication for a new round of cell division) to S (the period of active DNA synthesis), or the progression from G2 to M phase, in which active mitosis and cell division occur. Other members of this family of proteins, including CDK7, 8, and 9 regulate key points in the transcription cycle, whereas CDK5 plays a role in neuronal and secretory cell function.

CDK complexes are formed through association of a regulatory cyclin subunit (e. g., cyclin A, B1, B2, D1, D2, D3, and E) and a catalytic kinase subunit (e. g., cdc2 (CDK1), CDK2, CDK4, CDK5, and CDK6). As the name implies, the CDKs display an absolute dependence on the cyclin subunit in order to phosphorylate their target substrates, and different kinase/cyclin pairs function to regulate progression through specific portions of the cell cycle.

CDK9 in association with its cyclin partners (cyclin T1, T2a, T2b, or K) constitutes the catalytic component of the positive P-TEFb protein kinase complex that functions during the elongation phase of transcription by phosphorylating the carboxyl-terminal domain (CTD) of the largest subunit of RNA polymerase II. P-TEFb acts in concert with positive transcription factor NfκB as well as negative transcription factors, thus overcoming a block of transcriptional elongation (Liu and Herrmann 2005).

It is known that cell-cycle dysregulation, which is one of the cardinal characteristics of neoplastic cells, is closely associated with genetic alteration and deregulation of CDKs and their regulators, suggesting that inhibitors of CDKs may be useful as therapeutics for proliferative diseases, such as cancer. Thus, small molecule inhibitors targeting CDKs have been the focus of extensive interest in cancer therapy (Current Opinion in Pharmacology, 2003(3): 362-370). The ability of inhibiting cell cycle progression

suggests a general role for small molecule inhibitors of CDKs as therapeutics for proliferative diseases, such as cancer. While inhibition of cell cycle-related CDKs is clearly relevant in oncology applications, this may not be the case for the inhibition of RNA polymerase-regulating CDKs. Recently, inhibition of CDK9/cyclin T function was linked to prevention of HIV replication and the discovery of new CDK biology thus continues to open up new therapeutic indications for CDK inhibitors (Sausville, E.A. Trends Molec. Med. 2002, 8, S32-S37), such as, for example, viral infections (WO 02/100401). CDK inhibitors could conceivably also be used to treat other conditions such as immunological diseases and neurodegenerative diseases, amongst others.

More than 50 pharmacological CDK inhibitors have been described, some of which have potent antitumor activity (Current Opinion in Pharmacology, 2003(3): 362-370). A comprehensive review about the known CDK inhibitors may be found in Angew. Chem. Int. Ed. Engl. 2003, 42(19):2122-2138.

The use of 2-anilino-4-phenylpyrimidine derivatives as cyclin-dependent kinase inhibitors for the treatment of e.g. cancer has been reported in WO 2005/012262. Furthermore, 2-pyridinylamino-4-thiazolyl-pyrimidine derivatives for the treatment of cancer etc. have been described in WO 2005/012298. The use of 4,5-dihydro-thiazolo, oxazolo and imidazolo[4,5-h]quinazolin-8-ylamines as protein kinase inhibitors is known from WO 2005/005438. Furthermore, indolinone derivatives and induribin derivatives, which are useful as cyclin-dependent kinase inhibitors have been disclosed in WO 02/081445 and WO 02/074742. Additionally, CDK inhibitors for various therapeutic applications have been described in WO2005/026129.

Known CDK inhibitors may be classified according to their ability to inhibit CDKs in general or according to their selectivity for a specific CDK. Flavopiridol, for example, acts as a “pan” CDK antagonist and is not particularly selective for a specific CDK (Current Opinion in Pharmacology, 2003(3): 362-370). Purine-based CDK inhibitors, such as olomoucine, roscovitine, purvanolols and CGP74514A are known to exhibit a greater selectivity for CDKs 1, 2 and 5, but show no inhibitory activity against CDKs 4 and 6 (Current Opinion in Pharmacology, 2003(3): 362-370). Furthermore, it has been demonstrated that purine-based CDK inhibitors such as roscovitine can exert anti-apoptotic effects in the nervous system (Pharmacol Ther 2002, 93:135-143) or prevent neuronal death in neurodegenerative diseases, such as Alzheimers’s disease (Biochem

Biophys Res Commun 2002 (297):1154-1158; Trends Pharmacol Sci 2002 (23):417-425).

Given the tremendous potential of targeting CDKs for the therapy of conditions such as proliferative, immunological, infectious, cardiovascular and neurodegenerative diseases, the development of small molecules as selective inhibitors of particular CDKs constitutes a desirable goal.

The present invention provides novel small molecule inhibitors of cyclin-dependent kinases. Preferably, said small molecule inhibitors show an increased potency to inhibit a particular CDK, in particular CDK9. Said small molecule inhibitors may have a therapeutic utility for the treatment of conditions such as proliferative, immunological, neurodegenerative, infectious and cardiovascular diseases. Furthermore, the small molecule inhibitors of the present invention have surprisingly been shown to exert a beneficial effect in the treatment of inflammatory diseases and of any type of pain.

Current treatments for pain are only partially effective, and many also cause debilitating or dangerous side effects. For example, many of the traditional analgesics used to treat severe pain induce debilitating side effects such as nausea, dizziness, constipation, respiratory depression, and cognitive dysfunction (Brower, 2000).

Although there is already a broad panel of approved pain medications like non-narcotic analgesics, opioid analgesics, calcium channel blockers, muscle relaxants, and systemic corticosteroids available, said treatments remain merely empirical and, while they may relieve the symptoms of pain, they do not lead to complete relief in most cases. This is also due to fact that the mechanisms underlying the development of the different types of pain are still only poorly understood. Researchers are only just beginning to appreciate the complexity and diversity of the signalling systems used to relay nerve impulses for each type of pain.

Generally, pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, according to the International Association for the Study of Pain (IASP). Specifically, pain may occur as acute or chronic pain.

Acute pain occurs for brief periods of time, typically less than 1 month and is associated with temporary disorders. It is a natural body response to let the host be aware of

physiological or biochemical alteration that could result in further damage within a short period of time. It is felt when noxious stimuli activate high threshold mechanical and/or thermal nociceptors in peripheral nerve endings and the evoked action potentials in thinly myelinated (Aδ) and/or unmyelinated (C) afferent fibres reach a conscious brain. Said noxious stimuli may be provided by injury, surgery, illness, trauma or painful medical procedures. Acute pain usually disappears when the underlying cause has been treated or has healed. Unrelieved acute pain, however, may lead to chronic pain problems that may result in long hospital stays, rehospitalizations, visits to outpatient clinics and emergency departments, and increased health care costs.

In contrast to acute pain, chronic pain persists long after the initial injury has healed and often spreads to other parts of the body, with diverse pathological and psychiatric consequences. Chronic somatic pain results from inflammatory responses to trauma in peripheral tissues (e.g., nerve entrapment, surgical procedures, cancer, or arthritis), which leads to oversensitization of nociceptors and intense searing pain responses to normally non-noxious stimuli (hyperalgesia). Chronic pain is continuous and recurrent and its intensity will vary from mild to severe disabling pain that may significantly reduce quality of life.

Chronic pain is currently treated with conventional analgesics such as NSAIDs (Ibuprofen, Naproxen), Cox-2 inhibitors (Celecoxib, Valdecoxib, Rofecoxib) and opiates (codeine, morphine, thebain, papaverin, noscapin). For a significant number of patients however, these drugs provide insufficient pain relief.

Another subtype of pain, inflammatory pain, can occur as acute as well as chronic pain. Resulting injuries of tissue and neurons must not but may develop into long-lasting chronic neuropathic pain effects in succession to such inflammatory events.

Inflammatory pain is mediated by noxious stimuli like e.g. inflammatory mediators (e.g. cytokines, such as TNF α, prostaglandins, substance P, bradykinin, purines, histamine, and serotonine), which are released following tissue injury, disease, or inflammation and other noxious stimuli (e.g. thermal, mechanical, or chemical stimuli). In addition, cytokines and growth factors can influence neuronal phenotype and function (Besson 1999). These mediators are detected by nociceptors (sensory receptors) that are distributed throughout the periphery of the tissue. Said nociceptors are sensitive to noxious stimuli (e.g. mechanical, thermal, or chemical), which would damage tissue if

prolonged (Koltzenburg 2000). A special class of so called C-nociceptors represent a class of "silent" nociceptors that do not respond to any level of mechanical or thermal stimuli but are activated in presence of inflammation only.

Current approaches for the treatment of especially inflammatory pain aim at cytokine inhibition (e.g. IL1ß) and suppression of pro-inflammatory TNFα. Current approved anticytokine / antiTNFalpha treatments are based on chimeric antibodies such as Infliximab and Etanercept which reduce TNFα circulation in the bloodstream. TNFα is one of the most important inflammatory mediators that induces synthesis of important enzymes such as COX-2, MMP, iNOS, $cPLa_2$ and others. The main drawbacks of these "biologicals", however, reside in their immunogenic potential with attendant loss of efficacy and their kinetics that lead to a more or less digital all-or-nothing reduction of circulating TNFα. The latter can result in severe immune suppressive side effects.

A distinct form of chronic pain, neuropathic (or neurogenic) pain, arises as a result of peripheral or central nerve dysfunction and includes a variety of conditions that differ in etiology as well as location. Generally, the causes of neuropathic pain are diverse, but share the common symptom of damage to the peripheral nerves or components of central pathways. The causative factors might be metabolic, viral or mechanical nerve lesion. Neuropathic pain is believed to be sustained by aberrant somatosensory processes in the peripheral nervous system, the CNS, or both. Neuropathic pain is not directly linked to stimulation of nociceptors, but instead, is thought to arise e.g. from oversensitization of glutamate receptors on postsynaptic neurons in the gray matter (dorsal horn) of the spinal cord.

Neuropathic pain is associated with conditions such as nerve degeneration in diabetes and postherpetic neuralgia (shingles). Neuropathic pain conditions are the consequence of a number of diseases and conditions, including diabetes, AIDS, multiple sclerosis, stump and phantom pain after amputation, cancer-related neuropathy, post-herpetic neuralgia, traumatic nerve injury, ischemic neuropathy, nerve compression, stroke, spinal cord injury.

Management of neuropathic pain remains a major clinical challenge, partly due to an inadequate understanding of the mechanisms involved in the development and maintenance of neuropathic pain. Many existing analgesics are ineffective in treating neuropathic pain and most of current narcotic and non-narcotic drugs do not control the

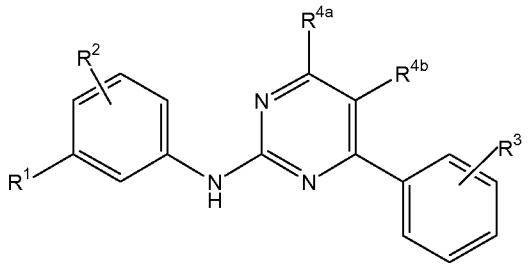
pain. Current clinical practice includes the use of a number of drug classes for the management of neuropathic pain, for example anticonvulsants, tricyclic antidepressants, and systemic local anaesthetics. However, the usual outcome of such treatment is partial or unsatisfactory pain relief, and in some cases the adverse effects of these drugs outweigh their clinical usefulness. Classic analgesics are widely believed to be poorly effective or ineffective in the treatment of neuropathic pain. Few clinical studies on the use of non steroidal anti-inflammatory drugs (NSAIDs) or opiates in the treatment of neuropathic pain have been conducted, but in those which have, the results appear to indicate that NSAIDs are poorly effective or ineffective and opiates only work at high doses. A review analysing the controlled clinical data for peripheral neuropathic pain (PNP) (Pain, November, 1997 73(2), 123-39) reported that NSAIDs were probably ineffective as analgesics for PNP and that there was no long-term data supporting the analgesic effectiveness of any drug.

Available analgesic drugs often produce insufficient pain relief. Although tricyclic antidepressants and some antiepileptic drugs, for example gabapentin, lamotrigine and carbamazepine, are efficient in some patients, there remains a large unmet need for efficient drugs for the treatment of these conditions.

In conclusion, there is a high unmet need for safe and effective methods of pain treatment, in particular of chronic inflammatory and neuropathic pain.

SUMMARY OF THE INVENTION

The present invention is directed to inhibitors of cyclin-dependent kinases and to methods and compositions for treating and/or preventing any type of pain, inflammatory disorders, immunological diseases, proliferative diseases, infectious diseases, cardiovascular diseases and neurodegenerative diseases comprising: administering an effective amount of at least one inhibitor of a cyclin-dependent kinase (cdk, CDK) to a subject in need thereof. The inhibitor is selected among compounds according to the general Formula I:



Formula I

wherein

R^1 is $-XSO_2NR^5R^6$ or $-XSO_2R^8$; wherein

X is a C_{1-4} alkylene (including branched alkylene), wherein said C_{1-4} alkylene can be bound to R^5 or R^6 to form a 5- or 6- membered heterocycle;

R^5 and R^6 independently of each other are hydrogen, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl or C_{3-4}alkenyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-4}alkyl or C_{4-7}-heterocycloalkyl-C_{0-4}alkyl, C_{4-7}-aryl-C_{0-4}alkyl, C_{4-7}-heteroaryl-C_{0-4}alkyl or

wherein R^5 and R^6 together with the N-atom to which they are bound also may form a 5- to 8-membered heterocycloalkyl,

wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl or alkyl is further optionally substituted by up to 2 radicals selected from the group consisting of halo, hydroxy, aminocarbonyl, C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{1-4} alkyl – O - C_{1-4} alkyl, C_{1-4} alkyl – O - and $-NR^5R^6$;

R^8 is C_{1-4} alkyl, hydroxy-C_{2-4}alkyl or C_{3-4}alkenyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-4}alkyl or C_{4-7}-heterocycloalkyl-C_{0-4} alkyl;

wherein said cycloalkyl, heterocycloalkyl or alkyl is further optionally substituted by up to 2 radicals selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{1-4} alkyl – O -C_{1-4} alkyl, C_{1-4} alkyl - O and $-NR^5R^6$;

R^2 is one or two substituents independently selected from halogen and hydrogen;

R^3 can be 1 to 3 substituents each independently selected from the group consisting of hydrogen, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4} alkyl -cycloalkyl, C_{1-4} alkyl –heterocycloalkyl, -O-heterocycloalkyl, C_{1-4} alkoxy, C_{2-4} alkenyloxy, $-OCF_3$, C_{2-4} alkanoyl, C_{1-4}alkylsulfonyl, mono- and di-(C_1-C_4alkyl)sulfonamido, aminocarbonyl, mono- and di-(C_1-C_4alkyl)aminocarbonyl, aryl-C_{1-4} alkoxy, heteroaryl-C_{1-4} alkoxy,

heterocycloalkyl –C1-4-alkoxy, heterocycloalkyl-C1-4-alkyl, heteroaryl-C1-4-alkyl, C_{1-4} alkyloxymethyl, hydroxy-C_{1-4}alkyloxymethyl, cyano, -COOH and C_1-C_4 alkoxycarbonyl, wherein the above mentioned substituents can be further substituted by radicals selected from the group of C_{1-4}-alkyl, hydroxyl-C_{0-4}-alkyl, C_{1-4}-alkoxy, aminocarbonyl, halo, and NR^5R^6;

R^{4a} and R^{4b} are the same or different and each is independently hydrogen, C_{1-4} alkyl or –NR´R´´, wherein R´and R´´ are each independently hydrogen or C_{1-4} alkyl;

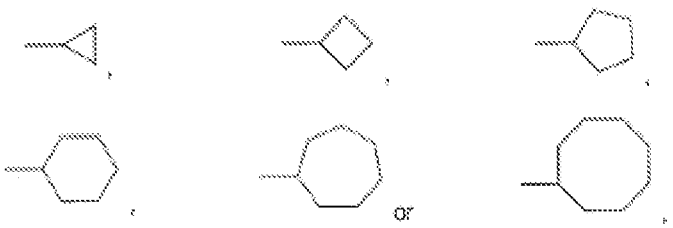
and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e. g., hydrates) of such compounds.

As disclosed herein, the term "C_{1-4} alkyl" is meant to include straight or branched chain saturated aliphatic hydrocarbon having 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl.

The term "lower alkenyl" refers to straight or branched chain alkene groups which have from 2 to 6 carbon atoms, such as, for example, vinyl, allyl, but-2-enyl, -but-3-enyl, or isopropenyl; the term "lower alkenyl" preferably represents allyl, -but-2-enyl, or –but-3-enyl.

As disclosed herein, the term "halo" is meant to include fluoro, chloro, bromo, and iodo.

The term C_3-C_8 cycloalkyl denotes the following cycloalkyls:



The term aryl denotes an aromatic mono- or bicyclic 6 to 10 membered ring system such as phenyl, naphthyl, 3-chlorophenyl, 2,6-dibromophenyl, 2,4,6 tribromophenyl, 4,7-dichloronaphthyl, and preferably phenyl or naphthyl.

The term heterocycloalkyl is meant to include a 5 to 10 membered mono- or bicyclic ring system, containing one to three heteroatoms independently selected from oxygen, sulfur or nitrogen and is preferably selected from the group comprising: Aziridinyl, azetidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperadizinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl or morpholinyl.

The term heterocycloalkyl further comprises all heteroaryls as defined below, wherein all double bonds of the correspondent heteroaryls are replaced by single bonds.

The term heteroaryl denotes a partially or fully unsaturated 5 to 10 membered mono- or bicyclic ringsystem, containing one to three heteroatoms independently selected from oxygen, sulfur or nitrogen and is preferably selected from the group consisting of :

Pyrrolyl, furanyl, thiophenyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrazinyl, pyrazyl, pyradizinyl, pyradizyl, 3-methylpyridyl, benzothienyl, 4-ethylbenzothienyl, 3,4-diethylfuranyl, pyrrolyl, tetrahydroquinolyl, quinolyl, tetrahydroisoquinolinyl, isoquinolinyl, benzoimidazolyl, benzothiazolyl, benzooxyzolyl, benzo [1, 3] dioxolyl, indolyl, benzofuranyl, benzothiophenyl, indazolyl or chrom-2-onyl.

It is to be understood, that the term heteroaryl also comprises partially unsaturated 5 to 10 membered mono- or bicyclic ringsystem, wherein one up to 4 double bonds of the ringsystem are replaced by a single bond and wherein the ringsystem contains at least one double bond.

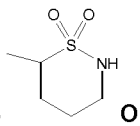
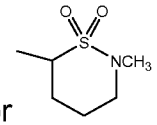
When any variable occurs more than once in Formula I or in any substituent, its definition on each occurrence is independent of its definition at every other occurrence. For example, when a compound comprises more than one R^5 and/or R^6 substituent, they can be the same or different.

In the compounds of formula I:

X is preferably methylene.

R^2 is preferably hydrogen.

Preferably R^6 is hydrogen or methyl and R^5 is ethyl, 2-hydroxyethyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, n-propyl, t-butyl, 3-methoxy-propyl, 2-

dimethylaminoethyl, 3-dimethylaminopropyl, piperidinyl and especially 4-piperidinyl, pyridinyl and especially pyridine-3-yl or pyridin-4-yl, pyrrolidinyl and especially pyrrolidin-3-yl, tetrahydrofuranyl and especially tetrahydro-furan-3-yl, tetrahydro-furan-2-ylmethyl, 4-chloro-benzyl, thiophen-2-yl-methyl, or R^5 and R^6 are both hydrogen, methyl, ethyl, or R^5 and R^6 together with the N-atom to which they are bound form morpholine, 4-aminocarbonyl-piperidine or azepane, or $-XSO_2NR^5R^6$ is  or  .

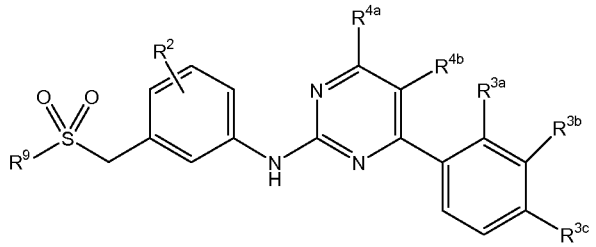
R^5 and R^6 are more preferably each independently selected from hydrogen, methyl, cyclopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and 2-hydroxyethyl. R^5 and R^6 are most preferably hydrogen.

R^8 is preferably C_{1-4} alkyl or hydroxy-C_{-2-4}-alkyl; R^8 is more preferably methyl or 2-hydroxyethyl.

R^3 is preferably 1 to 3 substituents independently selected from the group consisting of hydrogen, halo, hydroxy, C_{1-4}alkyl, C_{1-4} alkoxy, C_{2-4} alkenyloxy, $-OCF_3$, C_{2-4} alkanoyl, C_{1-4}alkylsulfonyl, mono- and di-(C_1-C_4alkyl)sulfonamido, aminocarbonyl, mono- and di-(C_1-C_4alkyl)aminocarbonyl, C_{1-4} alkyloxymethyl, hydroxy-C_{1-4}alkyloxymethyl, cyano, -COOH and C_1-C_4 alkoxycarbonyl; or one substituent selected from C_{3-7}cycloalkyl, C_{1-4} alkyl -cycloalkyl, C_{1-4} alkyl –heterocycloalkyl, -O-heterocycloalkyl, aryl-C_{1-4} alkoxy, heterocycloalkyl-C_{1-4} alkoxy, heterocycloalkyl-C_{1-4}- alkyl, heteroaryl-C_{1-4} alkoxy, heteroaryl-C_{1-4}-alkyl; wherein said substituents can be further substituted by one or more radicals selected from the group of C_{1-4}-alkyl, hydroxyl-C_{0-4}-alkyl, C_{1-4}-alkoxy, halo, aminocarbonyl, and NR^5R^6. R^3 is more preferably 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, hydroxymethyl, hydroxy, methoxy, ethoxy, isopropoxy, benzyloxy, hydrogen, fluoro, chloro, trifluoromethyl, 2-methoxy-ethoxy, methoxymethyl, 2-methoxy-ethyl, tetrahydro-furan-3-yloxy, tetrahydro-furan-2-yl-methoxy, -N(CH3)SO2CH3, piperidin-1-yl-methyl, 2-hydroxymethyl-piperidin-1-yl-methyl, 3-hydroxymethyl-piperidin-1-yl-methyl, 3-(2-hydroxy-ethyl)-piperidin-1-yl-methyl, 3-aminocarbonyl-piperidin-1-yl-methyl, dimethylaminomethyl, diethylaminomethyl, (ethyl-isopropyl-amino)-methyl, morpholin-4-ylmethyl, 4-methyl-piperazin-1-yl-methyl,

[1,2,4]triazol-1-yl-methyl, pyridine-3-yl-methoxy and pyridine-4-yl-methoxy. R^3 is most preferably methoxy, isopropoxy and/or fluoro.

Another preferred group of compounds of Formula I comprises those of Formula Ia



Formula Ia

wherein

R^2, R^{4a} and R^{4b} are as defined above;

R^{3a}, R^{3b} and R^{3c} are as defined above for R^3; and

R^9 is NR^5R^6 or R^8, wherein R^5, R^6 and R^8 are as defined above;

and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e. g., hydrates) of such compounds.

Within these compounds of Formula Ia:

R^2 is preferably hydrogen or halogen, more preferably hydrogen.

R^{3a} is preferably hydrogen, halo or C_{1-4} alkoxy; more preferably C_{1-4} alkoxy; most preferably methoxy or isopropoxy.

R^{3b} is preferably hydrogen.

R^{3c} is preferably hydrogen or halogen, especially fluoro.

R^{4a} is preferably C_{1-4} alkyl or hydrogen; more preferably hydrogen or methyl; most preferably hydrogen.

R^{4b} is preferably hydrogen or C_{1-4} alkyl; more preferably hydrogen or methyl; most preferably hydrogen.

R^5 and R^6 are preferably each independently hydrogen, cycloalkyl or C_{1-4} alkyl optionally substituted by hydroxyl or dialkylamino; most preferably R^5 and R^6 are each independently hydrogen, methyl, cyclopropyl, 2-hydroxyethyl, 2-dimethylaminoethyl or 3-dimethyl aminopropyl.

R^8 is preferably hydroxy-C_{2-4}-alkyl, more preferably 2-hydroxyethyl.

The following compounds are preferred:

{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 1);

{3-[4-(2-Isopropoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 2);

C-{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide (Compound 3);

C-{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide (Compound 4);

{3-[4-(4-Fluoro-2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 5);

N-Cyclopropyl-C-{3-[4-(2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 6);

N-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 7);

N-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide (Compound 8);

2-{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenylmethanesulfonyl}-ethanol (Compound 9);

{3-[4-(2-Methoxy-phenyl)-6-methyl-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 10);

-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-6-methyl-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide (Compound 11);

2-{3-[4-(2-Methoxy-phenyl)-6-methyl-pyrimidin-2-ylamino]-phenylmethanesulfonyl}-ethanol (Compound 12);

{3-[4-(2-Methoxy-phenyl)-5-methyl-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 13);

N-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-5-methyl-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide (Compound 14); and

2-{3-[4-(2-Methoxy-phenyl)-5-methyl-pyrimidin-2-ylamino]-phenylmethanesulfonyl}-ethanol (Compound 15).

In a further embodiment, the invention provides the above mentioned compounds according to Formula I, for medical use.

In a further embodiment, the invention provides pharmaceutical compositions containing a compound as outlined above, together with a pharmaceutically acceptable carrier.

In a further embodiment, the invention provides use of a compound as outlined above for preparing a pharmaceutical composition for treating inflammatory disorders, immunological diseases, proliferative diseases, infectious diseases, cardiovascular diseases and neurodegenerative diseases.

In a further embodiment, the invention provides use of a compound as outlined above for preparing a pharmaceutical composition for treating pain, chronic pain, and/or neuropathic pain.

In a further embodiment, the invention provides a method for treating inflammatory disorders, immunological diseases, proliferative diseases, infectious diseases, cardiovascular diseases and neurodegenerative diseases comprising the administration of an effective amount of at least one of the compounds as mentioned above to a subject in need thereof.

In a further embodiment, the invention provides a method for treating pain, chronic pain and/or neuropathic pain comprising the administration of an effective amount of at least one of the compounds as mentioned above to a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

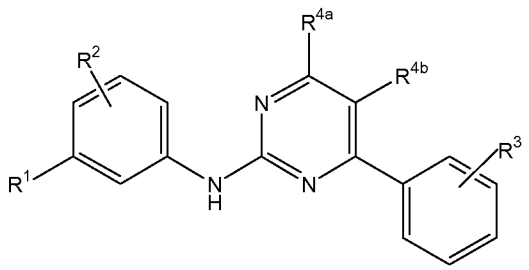
Figure 1 schematically depicts the spared nerve injury model (SNI model, as developed by Decosterd and Woolf (2000), which is characterized by ligation and section of two branches of the sciatic nerve (namely tibial and common peroneal nerves) leaving the sural nerve intact.

Figure 2 schematically depicts a possible role of CDK9 as a target in the development of pain.

Figure 3 depicts the results of cytokine measurements performed with LPS-induced THP-1 macrophages. TNF expression displayed as % inhibition compared to the DMSO control. Cells treated with compounds 1, 5, 6, 8, or 9 show a significant inhibition of TNF expression in the supernatant compared to the vehicle (DMSO). Compared to reference compounds SB203580 (p38-inhibitor) and BMS345541 (IKK-inhibitor) these compounds exhibit a similar or better inhibition of TNF expression in this assay.

DETAILLED DESCRIPTION OF THE INVENTION

The inhibitors of CDKs provided by the present invention are compounds according to the general Formula I:



Formula I

wherein

R^1 is $-XSO_2NR^5R^6$ or - XSO_2R^8 ; wherein

X is a C_{1-4} alkylene (including branched alkylene), wherein said C_{1-4} alkylene can be bound to R^5 or R^6 to form a 5- or 6- membered heterocycle;

R^5 and R^6 independently of each other are hydrogen, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl or C_{3-4}alkenyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-4}alkyl or C_{4-7}-heterocycloalkyl-C_{0-4}alkyl, C_{4-7}-aryl-C_{0-4}alkyl, C_{4-7}-heteroaryl-C_{0-4}alkyl or

wherein R^5 and R^6 together with the N-atom to which they are bound also may form a 5- to 8-membered heterocycloalkyl,

wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl or alkyl is further optionally substituted by up to 2 radicals selected from the group consisting of halo, hydroxy, aminocarbonyl, C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{1-4} alkyl – O - C_{1-4} alkyl, C_{1-4} alkyl – O - and -NR^5R^6;

R^8 is C_{1-4} alkyl, hydroxy-C_{2-4}alkyl or C_{3-4}alkenyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-4}alkyl or C_{4-7}-heterocycloalkyl-C_{0-4} alkyl;

wherein said cycloalkyl, heterocycloalkyl or alkyl is further optionally substituted by up to 2 radicals selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{1-4} alkyl – O -C_{1-4} alkyl, C_{1-4} alkyl - O and -NR^5R^6;

R^2 is one or two substituents independently selected from halogen and hydrogen;

R^3 can be 1 to 3 substituents each independently selected from the group consisting of hydrogen, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4} alkyl -cycloalkyl, C_{1-4} alkyl –heterocycloalkyl, -O-heterocycloalkyl, C_{1-4} alkoxy, C_{2-4} alkenyloxy, -OCF_3, C_{2-4} alkanoyl, C_{1-4}alkylsulfonyl, mono- and di-(C_1-C_4alkyl)sulfonamido, aminocarbonyl, mono- and di-(C_1-C_4alkyl)aminocarbonyl, aryl-C_{1-4} alkoxy, heteroaryl-C_{1-4} alkoxy, heterocycloalkyl –C1-4-alkoxy, heterocycloalkyl-C1-4-alkyl, heteroaryl-C1-4-alkyl, C_{1-4} alkyloxymethyl, hydroxy-C_{1-4}alkyloxymethyl, cyano, -COOH and C_1-C_4 alkoxycarbonyl, wherein the above mentioned substituents can be further substituted by radicals selected from the group of C_{1-4}-alkyl, hydroxyl-C_{0-4}-alkyl, C_{1-4}-alkoxy, aminocarbonyl, halo, and NR^5R^6;

R^{4a} and R^{4b} are the same or different and each is independently hydrogen, C_{1-4} alkyl or –NR´R´´, wherein R´and R´´ are each independently hydrogen or C_{1-4} alkyl;

and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e. g., hydrates) of such compounds.

In a preferred embodiment of this invention, the cyclin-dependent kinase inhibitor according to Formula I inhibits a CDK selected from the group consisting of CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, CDK11, CrkRS (Crk7, CDC2-related protein kinase 7), CDKL1 (cyclin-dependent kinase- like 1); KKIALRE, CDKL2 (cyclin-dependent kinase-like 2), KKIAMRE, CDKL3 (cyclin-dependent kinase-like 3), NKIAMRE, CDKL4, similar to cyclin-dependent kinase-like 1, CDC2L1 (cell division cycle 2-like 1), PITSLRE B, CDC2L1 (cell division cycle 2-like 1), PITSLRE A, CDC2L5 (cell division cycle 2-like 5), PCTK1 (PCTAIRE protein kinase 1), PCTK2 (PCTAIRE protein kinase 2), PCTK3 (PCTAIRE protein kinase 3) or PFTK1 (PFTAIRE protein kinase 1).

The inhibitor may also inhibit more than one cyclin-dependent kinase selected from the above-recited group.

In a particular preferred embodiment of this invention, the compound according to Formula I inhibits CDK9.

In a further embodiment of this invention, the compound according to Formula I selectively inhibits one or more CDKs without having a substantial inhibitory effect on other enzymes or proteins.

In a preferred embodiment, such inhibitory compounds display an increased selectivity for a particular CDK. “Increased selectivity” as used herein means that the inhibitory compound is at least 10-100 x more selective for a particular CDK selected from the group of CDKs as recited herein, *supra*. In a preferred embodiment of the present invention, the inhibitory compound is 20-90 x more selective for a particular CDK. In a particular preferred embodiment, the inhibitory compound is 30-80 x more selective for a particular CDK.

In a particular preferred embodiment, the compound according to Formula I displays an increased selectivity for CDK9 than for other CDKs.

As used herein, the term "inhibiting" or "inhibition" refers to the ability of a compound to downregulate, decrease, reduce, suppress, inactivate, or inhibit at least partially the cellular function of a cyclin-dependent kinase, i.e. its activity or the expression of the cyclin-dependent kinase.

Furthermore, the term “cyclin-dependent kinase inhibitor" refers to any compound or group of compounds capable of downregulating, decreasing, suppressing or otherwise regulating the amount and/or activity of a cyclin-dependent kinase. Inhibition of said kinases can be achieved by any of a variety of mechanisms known in the art, including, but not limited to binding directly to the kinase polypeptide, denaturing or otherwise inactivating the kinase, or inhibiting the expression of the gene (e.g., transcription to mRNA, translation to a nascent polypeptide, and/or final polypeptide modifications to a mature protein), which encodes the kinase. Furthermore, a cyclin-dependent kinase inhibitor may also interfere with expression, modification, regulation or activation of a molecule acting downstream of a CDK in a CDK-dependent pathway. Generally, kinase inhibitors may be proteins, polypeptides, nucleic acids, small molecules, or other chemical moieties. Specifically, kinase inhibitors also include monoclonal or polyclonal antibodies directed against cyclin-dependent kinases.

In a preferred embodiment, the cyclin-dependent kinase inhibitor is selected from the compounds as represented by Formula I as disclosed herein.

Therapeutic use

The compounds of Formula I are inhibitors of cyclin-dependent kinases. Thus, they are expected to have the ability to arrest, or to recover control of the cell cycle in abnormally dividing cells. Consequently, it is suggested that the compounds according to Formula I will prove useful in treating and/or preventing proliferative disorders such as cancers.

It is known that CDKs play a role in apoptosis, proliferation, differentiation and transcription and therefore, the compounds according to Formula I may also be useful in the treatment of diseases other than proliferative diseases, such as infectious diseases, immunological diseases, neurodegenerative diseases and cardiovascular diseases.

Furthermore, the compounds according to Formula I also display an unexpected antinociceptive and anti-inflammatory effect.

Thus, in a preferred embodiment, the compounds of Formula I may be used in methods and/or pharmaceutical compositions for the treatment of any type of pain, including chronic pain, neuropathic and/or inflammatory pain.

In a further preferred embodiment, the compounds of Formula I may be used in methods and/or pharmaceutical compositions for the treatment of inflammatory disorders.

In a particular preferred embodiment, the compounds of Formula I for use in the treatment of any type of pain or in the treatment of inflammatory disorders display an increased selectivity for CDK9 than for other CDKs.

Pain

It has turned out that administration of CDK inhibitors according to Formula I to mice suffering from nerve lesion exerts a hypoalgesic effect, in particular in murine models of inflammatory and neuropathic pain.

The discovery that inhibition of a cyclin-dependent kinase is involved in mediating a hypoalgesic effect was unexpected.

Thus, in a preferred embodiment, this invention relates to a method of treating any type of pain comprising administering an effective amount of an inhibitor of cyclin-dependent kinase according to Formula I. Specifically, the compounds of Formula I may be used for the treatment of chronic, neuropathic and/or inflammatory pain. In a particular preferred embodiment, the compounds of Formula I for use in the treatment of any type of pain display an increased selectivity for CDK9 than for other CDKs.

The role of CDK9 in the development of pain could be based on the following mechanism of action: Both cyclin T1 and CDK9 stimulate the basal promoter activity of TNFα. TNFα is a pro-inflammatory cytokine and pain mediator that controls expression of inflammatory genetic networks. For mediation of cellular TNF receptor responses, the nuclear factor-κB (NFκB) pathway is crucial. TNFα triggers its recruitment to cytokine genes while NfκB interacts with p-TEFb complex for stimulation of gene transcription (Barboric M et al., 2001).

Additionally, it has been shown that CDK9 is a binding partner of TRAF2, a member of the TNFα receptor complex (MacLachlan et al, 1998), while GP130, a subunit of the pro-inflammatory IL6 receptor complex has recently been identified as another potential

binding partner of CDK9 (Falco et al, 2002). As a key player in TNFα and interleukin signaling as well as in NfκB mediated expression of several genes (e.g. cytokines as pain mediators), CDK9 can thus be considered as a central target for the treatment of any type of pain, such as inflammatory pain (see Figure 2).

For the treatment of neuropathic pain, pharmacological action has to take place beyond the blood-brain-barrier (BBB) in the central nervous system (CNS). Microglial cells as the principal immune cells in the CNS, for example, release, upon activation, a variety of noxious factors such as cytokines (TNFα, IL1ß, IL6) and other pro-inflammatory molecules (Huwe 2003). Microglia are activated by stimulation of TNFα receptor or Toll-like receptor and signal is mediated via Iκ kinase (IKK) and NfκB leading to transcriptional activation of the cytokines described above. Microglial contribution has been discussed as instrumental in chronic CNS diseases and may contribute to pain perception (Watkins et al, 2003).

Recently it has been shown that the transcription factor NfκB regulates expression of Cyclooxygenase-2 (COX-2) via Interleukin 1ß (IL1ß) in the spinal cord (Lee et al. 2004). As the major contributor to elevation of spinal prostaglandin E2, the pain mediator COX-2 is already known as a target for a variety of anti-nociceptive/anti-inflammatory drugs. NfκB inhibitors have proven their ability to significantly reduce COX-2 levels and mechanical allodynia as well as thermal hyperalgesia in animal models.

In contrast to COX-2, inhibition of CDK9 action would lead to suppression of a variety of pain mediators instead of just a single one. Thus, anti-nociceptive action of CDK9 inhibitors may be superior compared to e.g. COX-2 inhibitors.

Due to its relevance for NfκB mediated gene transcription, the inhibitory interaction with CDK9 may therefore be a reasonable approach not only for the treatment of acute inflammatory pain, but also for the treatment of chronic pain.

The term “pain” as used herein generally relates to any type of pain and broadly encompasses types of pain such as acute pain, chronic pain, inflammatory and neuropathic pain. In a preferred embodiment of the present invention, “pain” comprises neuropathic pain and associated conditions. The pain may be chronic, allodynia (the perception of pain from a normally innocuous stimulus), hyperalgesia (an exaggerated response to any given pain stimulus) and an expansion of the receptive field (i.e. the area that is "painful" when a stimulus is applied), phantom pain or inflammatory pain.

Acute pain types comprise, but are not limited to pain associated with tissue damage, postoperative pain, pain after trauma, pain caused by burns, pain caused by local or systemic infection, visceral pain associated with diseases comprising: pancreatits, intestinal cystitis, dysmenorrhea, Irritable Bowel syndrome, Crohn's disease, ureteral colic and myocardial infarction

Furthermore, the term “pain” comprises pain associated with CNS disorders comprising: multiple sclerosis, spinal cord injury, traumatic brain injury, Parkinson's disease and stroke

In a preferred embodiment, “pain” relates to chronic pain types comprising headache (for example migraine disorders, episodic and chronic tension-type headache, tension-type like headache, cluster headache, and chronic paroxysmal hemicrania), low back pain, cancer pain, osteoarthritis pain and neuropathic pain, but is not limited thereto.

Inflammatory pain (pain in response to tissue injury and the resulting inflammatory process) as defined herein relates to imflammatory pain associated with diseases comprising connective tissue diseases, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and arthritis, but is not limited thereto.

Neuropathic pain (pain resulting from damage to the peripheral nerves or to the central nervous system itself) includes conditions comprising, but not limited to metabolic neuropathies (e.g., diabetic neuropathy), post-herpetic neuralgia, trigeminal neuralgia, cranial neuralgia, post-stroke neuropathic pain, multiple sclerosis-associated neuropathic pain, HIV/AIDS-associated neuropathic pain, cancer-associated neuropathic pain, carpal tunnel-associated neuropathic pain, spinal cord injury-associated neuropathic pain, complex regional pain syndrome, fibromyalgia-associated neuropathic pain, reflex sympathic dystrophy, phantom limb syndrome or peripheral nerve or spinal cord trauma, nerve transection including surgery, limb amputation and stump pain, pain caused by the side effects of anti-cancer and anti-AIDS therapies, post-surgical neuropathic pain, neuropathy-associated pain such as in idiopathic or post-traumatic neuropathy and mononeuritis, and neuropathic pain caused by connective tissue disease such as rheumatoid arthritis, Wallenberg's syndrome, systemic lupus erythematosus, multiple sclerosis, or polyarteritis nodosa. The

neuropathy can be classified as radiculopathy, mononeuropathy, mononeuropathy multiplex, polyneuropathy or plexopathy.

The term “allodynia” denotes pain arising from stimuli which are not normally painful. Allodynic pain may occur other than in the area stimulated.

The term “hyperalgesia” denotes an increased sensitivity to a painful stimulus.

The term “hypoalgesia” denotes a decreased sensitivity to a painful stimulus.

Inflammatory diseases Surprisingly, it could be shown that the CDK inhibiting compounds according to Formula I as disclosed herein exert an anti-inflammatory effect in *in vitro* and *in vivo* inflammatory assays.

Thus, in a preferred embodiment, this invention relates to a method of treating inflammatory diseases comprising administering an effective amount of an inhibitor of cyclin-dependent kinase according to Formula I. In a particular preferred embodiment, the compounds of Formula I for use in the treatment of inflammatory diseases display an increased selectivity for CDK9 than for other CDKs.

The role of CDK9 in the development of inflammatory diseases could be based on the following mechanism of action: inflammatory diseases such as rheumatoid arthritis (RA); atherosclerosis; asthma; inflammatory bowel disease, systemic lupus erythematosus and several other autoimmune diseases are mediated by tumor necrosis factor α (TNFα), a key regulator of inflammatory and tissue obstructive pathways in said diseases. It is known that the TNFα signal is mediated via several transducers such as IκB Kinase (IKK), which phosphorylates the IκB protein which dissociates from NfκB upon its phosphorylation. Dissociated NfκB, a positive regulator of cytokine transcription, translocates into the cell nucleus where it binds to its recognition sites.

Activated NfκB has been found in the synovium of RA patients [Han et al.; 2003, Autoimmunity, 28, 197-208]. It regulates pro-inflammatory genes such as TNFα, IL-6, IL-8, NOS and COX2. Targeting NfκB and its upstream signalling partner IKK has already proven to be an efficient therapeutic strategy in many animal models of arthritis [Firestein, 2003, Nature 423, 356-361].

Bound NfκB associates with a coactivator complex containing histone acetyltransferases (CBP, p300, p/CAF, SRC-1, and SRC-1-related proteins) that recruits and activates CDK9 which catalyzes the phosphorylation of the CTD of RNA

Pol II [West et al.; 2001, Journal of Virology 75(18), 8524–8537]. Resulting hyperphosphorylation of the RNA Pol II CTD leads to transcriptional activation of pro-inflammatory cytokines such as IL-1ß, IL-6 and IL-8 that are also known as being regulated by TNFα.

Several studies showed that TNFα is a ´master regulator´ of an autologous signalling cascade that regulates pro-inflammatory cytokine expression. To interrupt this pro-inflammatory cascade, specific antibodies (Abs) can be used successfully to block the TNFα signal. Anti-TNFα treatment of RA with Abs has already proven its therapeutic efficacy in several clinical studies and FDA approved drugs such as Infliximab and Etanercept have entered the market [Feldmann and Maini, NatMed, 2003, 9 (10); 356-61]. However, disadvantages of Ab based therapies include their immunogenic potential, attendant loss of efficacy during progressive treatment and high treatment costs. Additionally, the Ab kinetics permits a more or less all-or-nothing reduction of circulating TNFα. As a result, physiologic functions of the immune response are also suppressed [Laufer et al., Inflammation and Rheumatic Diseases, 2003; Thieme, pp. 104-5].

Therapeutic interventions into the TNFα-mediated signalling cascade.with kinase inhibitors aiming at targets such as p38 MAPK or IKK have shown severe adverse effects – in most cases due to a lack of specificity against the respective target.

In contrast thereto, CDK specific inhibitors according to Formula I as presented herein may intervene at the very bottom end of the TNFα signalling pathways reducing the interaction with physiological functions. Additionally, said compounds will allow interruption of the autologous TNFα mediated inflammatory network by avoidance of adverse effects via superior specificity. Therefore, treatment of with CDK specific inhibitors of Formula I constitutes a promising strategy for the treatment of inflammatory and autoimmune diseases.

Thus, the compounds according to Formula I as presented herein may be used for the treatment and/or prevention of inflammatory diseases.

The term “inflammatory diseases” as used herein relates to diseases triggered by cellular or non-cellular mediators of the immune system or tissues causing the inflammation of body tissues and subsequently producing an acute or chronic inflammatory condition.

Examples for such inflammatory diseases are hypersensitivity reactions of type I-IV, for example but not limited to hypersensitivity diseases of the lung including asthma, atopic diseases, allergic rhinitis or conjunctivitis, angioedema of the lids, hereditary angioedema, antireceptor hypersensitivity reactions and autoimmune diseases, Hashimoto's thyroiditis, systemic lupus erythematosus, Goodpasture's syndrome, pemphigus, myasthenia gravis, Grave's and Raynaud's disease, type B insulin-resistant diabetes, rheumatoid arthritis, psoriasis, Crohn's disease, scleroderma, mixed connective tissue disease, polymyositis, sarcoidosis, Wegener's granulomatosis, glomerulonephritis, acute or chronic host versus graft reactions.

Furthermore, the term “inflammatory diseases” includes but is not limited to abdominal cavity inflammation, dermatitis, gastrointestinal inflammation (including inflammatory bowel disease, ulcerative colitis), fibrosis, ocular and orbital inflammation, dry eye disease and severe dry eye disease resulting from Sjörgen’s syndrome, mastitis, otitis, mouth inflammation, musculoskeletal system inflammation (including gout, osteoarthritis), inflammatory diseases of the central nervous system (including multiple sclerosis, bacterial meningitis, meningitis), genitourinary tract inflammation (incl prostatitis, glomerulonephritis), cardiovascular inflammation (including atherosclerosis, heart failure), respiratory tract inflammation (including chronic bronchitis, chronic obstructive pulmonary disease), thyroiditis, diabetes mellitus, osteitis, myositis, multiple organ failure (including. sepsis), polymyositis and psoriatic arthritis.

Immunological diseases

The compounds according to Formula I are also envisaged to be useful in the treatment and/or prevention of immunological diseases, such as, for example, autoimmune diseases.

Accordingly, the present invention provides a method for the treatment and/or prevention of immunological diseases comprising the administration of an effective amount of at least one CDK inhibitor according to Formula I to a subject in need thereof.

The term “immunological diseases” as used herein relates to diseases including but not limited to allergy, asthma, graft-versus-host disease, immune deficiencies and autoimmune diseases.

Specifically, immunological diseases include diabetes, rheumatic diseases, AIDS, chronic granulomatosis disease, rejection of transplanted organs and tissues, rhinitis, chronic obstructive pulmonary diseases, osteoporosis, ulcerative colitis, Crohn's disease, sinusitis, lupus erythematosus, psoriasis, multiple sclerosis, myasthenia gravis, alopecia, recurrent infections, atopic dermatitis, eczema and severe anaphylactic reactions, but are not limited thereto. Furthermore, "immunological diseases" also include allergies such as contact allergies, food allergies or drug allergies.

Proliferative diseases

The compounds of Formula I are inhibitors of cyclin-dependent kinases, which represent key molecules involved in regulation of the cell cycle. Cell-cycle disregulation is one of the cardinal characteristics of neoplastic cells. Thus, said compounds are expected to prove useful in arresting or recovering control of the cell cycle in abnormally dividing cells. It is thus expected that the compounds according to Formula I are useful in the treatment and/or prevention of proliferative diseases such as cancer.

Accordingly, the invention provides a method for the treatment and/or prevention of proliferative diseases comprising administering an effective amount of at least one inhibitor of a cyclin-dependent kinase according to Formula I.

As used herein, the term "proliferative disease" relates to cancer disorders, including, but not limited to benign neoplasms, dysplasias, hyperplasias as well as neoplasms showing metastatic growth or any other transformations.

The term "cancer" includes but is not limited to benign and malign neoplasia like carcinoma, sarcoma, carcinosarcoma, cancers of the blood-forming tissues, tumors of nerve tissues including the brain and cancer of skin cells.

Examples of cancers which may be treated include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e. g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall bladder, ovary, pancreas e. g. exocrine pancreatic carcinoma, stomach, cervix, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's

lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumor of myeloid lineage, for example acute and chronicmyelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma,; a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentoum; keratoctanthoma; thyroid follicular cancer; Kaposi's sarcoma, astrocytoma, basal cell carcinoma, small intestine cancer, small intestinal tumors, gastrointestinal tumors, glioblastomas, liposarcoma, germ cell tumor, head and neck tumors (tumors of the ear, nose and throat area), cancer of the mouth, throat, larynx, and the esophagus, cancer of the bone and its supportive and connective tissues like malignant or benign bone tumour, e.g. malignant osteogenic sarcoma, benign osteoma, cartilage tumors; like malignant chondrosarcoma or benign chondroma, osteosarcomas; tumors of the urinary bladder and the internal and external organs and structures of the urogenital system of male and female, soft tissue tumors, soft tissue sarcoma, Wilm's tumor or cancers of the endocrine and exocrine glands like e.g. thyroid, parathyroid, pituitary, adrenal glands, salivary glands.

Infectious diseases

Furthermore, the invention relates to a method of treating and/or preventing infectious diseases comprising administering an effective amount of at least one inhibitor of a cyclin-dependent kinase according to Formula I.

It is known that certain host cell CDKs are involved in viral replication, i.e. CDK2, CDK7, CDK8 and CDK9 (J. Virol. 2001; 75: 7266-7279). Specifically, the role of CDK9 kinase activity in regulation of HIV-1 transcription elongation and histone methylation has been described (J. Virol 2004, 78(24):13522-13533.

In a preferred embodiment, the invention thus relates to a method of treating and/or preventing infectious diseases comprising administering an effective amount of at least one inhibitor of a cyclin-dependent kinase according to Formula I, wherein said compound displays an increased selectivity for CDK9 than for other CDKs.

The term “infectious diseases” as used herein comprises infections caused by pathogens such as viruses, bacteria, fungi and/or parasites.

Virus-induced infectious diseases include diseases caused by infection with retroviruses, human endogenous retroviruses, hepadnaviruses, herpesviruses, flaviviruses, adenoviruses, togaviruses and poxviruses. Specifically, infectious diseases are caused by viruses comprising, but not limited to viruses such as HIV-1, HIV-2, HTLV-I and HTLV-II, hepadnaviruses such as HBV, herpesviruses such as Herpes simplex virus I (HSV I), herpes simplex virus 11 (HSV II), Epstein-Barr virus (EBV), varicella zoster virus (VZV), human cytomegalovirus (HCMV) or human herpesvirus 8 (HHV-8), flaviviruses such as HCV, West nile or Yellow Fever virus, human papilloma virus, poxviruses, Sindbis virus or adenoviruses.

Examples of infectious diseases include, but are not limited to AIDS, borreliosis, botulism, diarrhea, BSE (Bovine Spongiform Encephalopathy), chikungunya, cholera, CJD (Creutzfeldt-Jakob Disease), conjunctivitis, cytomegalovirus cnfection, dengue/dengue Fever, encephalitis, eastern equine encephalitis, western equine encephalitis, Epstein-Barr Virus Infection, Escherichia coli Infection, foodborne infection, foot and mouth disease, fungal dermatitis, gastroenteritis, Helicobacter pylori Infection, Hepatitis (HCV, HBV), Herpes Zoster (Shingles), HIV Infection, Influenza, malaria, measles, meningitis, meningoencephalitis, molluscum contagiosum, mosquito-borne Diseases, Parvovirus Infection, plague, PCP (Pneumocystis carinii Pneumonia), polio, primary gastroenteritis, Q Fever, Rabies, Respiratory Syncytial Virus (RSV) Infection, rheumatic fever, rhinitis, Rift Valley Fever, Rotavirus Infection, salmonellosis, salmonella enteritidis, scabies, shigellosis, smallpox, streptococcal infection, tetanus, Toxic Shock Syndrome, tuberculosis, ulcers (peptic ulcer disease), hemorrhagic fever, variola, warts, West Nile Virus Infection (West Nile Encephalitis), whooping cough, yellow fever.

Cardiovascular diseases

Furthermore, the invention relates to the treatment and/or prevention of cardiovascular diseases comprising administering an effective amount of at least one inhibitor of a cyclin-dependent kinase according to Formula I.

It has been reported that the field of cariodvascular diseases constitutes a possible clinical application for CDK inhibitors (Pharmacol Ther 1999, 82(2-3):279-284). Furthermore, it is known that inhibition of the cyclin T/CDK9 complex and more specifically, inhibition of CDK9 may play a beneficial role in the treatment of cardiovascular diseases such as heart failure (WO2005/027902).

Thus, in a preferred embodiment, the invention relates to a method of treating and/or preventing cardiovascular diseases comprising administering an effective amount of at least one inhibitor of a cyclin-dependent kinase according to Formula I, wherein said compound displays an increased selectivity for CDK9 than for other CDKs.

The term “cardiovascular diseases” includes but is not limited to disorders of the heart and the vascular system like congestive heart failure, myocardial infarction, ischemic diseases of the heart, such as stable angina, unstable angina and asymptomatic ischemia, all kinds of atrial and ventricular arrhythmias, hypertensive vascular diseases, peripheral vascular diseases, coronary heart disease and atherosclerosis. Furthermore, as used herein, the term includes, but is not limited to adult congenital heart disease, aneurysm, angina pectoris, angioneurotic edema, aortic valve stenosis, aortic aneurysm, aortic regurgitation, arrhythmogenic right ventricular dysplasia, arteriovenous malformations, atrial fibrillation, Behcet syndrome, bradycardia, cardiomegaly, cardiomyopathies such as congestive, hypertrophic and restrictive cardiomyopathy, carotid stenosis, cerebral hemorrhage, Churg-Strauss syndrome, cholesterol embolism, bacterial endocarditis, fibromuscular dysplasia, congestive heart failure, heart valve diseases such as incompetent valves or stenosed valves, heart attack, epidural or subdural hematoma, von Hippel-Lindau disease, hyperemia, hypertension, pulmonary hypertension, hypertrophic growth, left ventricular hypertrophy, right ventricular hypertrophy, hypoplastic left heart syndrome, hypotension, intermittent claudication, ischemic heart disease, Klippel-Trenaunay-Weber syndrome, lateral medullary syndrome, mitral valve prolapse, long QT syndrome mitral valve prolapse, myocardial ischemia, myocarditis, disorders of the pericardium, pericarditis, peripheral vascular diseases, phlebitis, polyarteritis nodosa, pulmonary atresia, Raynaud disease, restenosis, rheumatic heart disease, Sneddon syndrome, stenosis, superior vena cava syndrome, syndrome X, tachycardia, hereditary hemorrhagic telangiectasia, telangiectasis, temporal arteritis, thromboangiitis obliterans, thrombosis, thromboembolism, varicose veins, vascular diseases, vasculitis, vasospasm, ventricular fibrillation, Williams syndrome, peripheral vascular disease, varicose veins and leg ulcers, deep vein thrombosis and Wolff-Parkinson-White syndrome.

Furthermore, the term cardiovascular diseases includes diseases resulting from congenital defects, genetic defects, environmental influences (i. e., dietary influences, lifestyle, stress, etc.), and other defects or influences.

Neurodegenerative diseases

CDK inhibitors have been described to exert neuroprotective effects. Specifically, it has been reported that CDK inhibitors prevent neuronal death in neurodegenerative diseases such as Alzheimer's disease (Biochem Biophys Res Commun 2002 (297):1154-1158; Trends Pharmacol Sci 2002 (23):417-425; Pharmacol Ther 1999, 82(2-3):279-284).

Thus, the compounds according to Formula I, which are CDK inhibitors, are expected to provide beneficial effects in the therapeutic management of neurodegenerative diseases.

Accordingly, the invention relates a method of treating and/or preventing neurodegenerative diseases comprising administering an effective amount of at least one inhibitor of a cyclin-dependent kinase according to Formula I.

The term "neurodegenerative diseases" as used herein includes disorders of the central nervous system as well as disorders of the peripheral nervous system, including, but not limited to brain injuries, cerebrovascular diseases and their consequences, Parkinson's disease, corticobasal degeneration, motor neuron disease, dementia, including ALS, multiple sclerosis, traumatic brain injury, stroke, post-stroke, post-traumatic brain injury, and small-vessel cerebrovascular disease, dementias, such as Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia and Parkinsonism linked to chromosome 17, frontotemporal dementias, including Pick's disease, progressive nuclear palsy, corticobasal degeneration, Huntington's disease, thalamic degeneration, Creutzfeld-Jakob dementia, HIV dementia, schizophrenia with dementia, Korsakoff's psychosis and AIDS-related dementia.

Similarly, cognitive-related disorders, such as mild cognitive impairment, age-associated memory impairment, age-related cognitive decline, vascular cognitive impairment, attention deficit disorders, attention deficit hyperactivity disorders, and memory disturbances in children with learning disabilities are also considered to be neurodegenerative disorders.

Specifically, the present invention relates to a method for treating the above-referenced types of pain and associated conditions and inflammatory disorders, immunological diseases, proliferative diseases, infectious diseases, cardiovascular diseases and

neurodegenerative diseases, wherein the term “treating” comprises the prevention, amelioration or treating of pain and associated conditions and inflammatory disorders, immunological diseases, proliferative diseases, infectious diseases, cardiovascular diseases and neurodegenerative diseases

Pharmaceutical compositions

Preferred embodiments of the present invention include the administration of compositions comprising at least one cyclin-dependent kinase inhibitor according to Formula I as an active ingredient together with at least one pharmaceutically acceptable (i. e. non-toxic) carrier, excipient and/or diluent.

Preferably, the composition comprises at least one cyclin-dependent kinase inhibitor according to Formula I as an active ingredient, wherein said at least one cyclin-dependent kinase inhibitor has an increased selectivity for CDK9 than for other CDKs.

Furthermore, the invention also comprises compositions combining at least two inhibitors of CDK and/or pharmaceutically acceptable salts thereof. Said at least two inhibitors may inhibit the same cyclin-dependent kinase or may also inhibit different types of cylin-dependent kinases, e.g. one inhibitor in the composition may inhibit CDK9 while the other inhibitor is capable of inhibiting CDK2, for example.

Having regard to pain treatment, an individual pain medication often provides only partially effective pain alleviation because it interferes with just one pain-transducing pathway out of many. Thus, it is also intended to administer CDK inhibitors according to Formula I in combination with a pain-reducing (analgesic) agent that acts at a different point in the pain perception process.

An "analgesic agent" comprises a molecule or combination of molecules that causes a reduction in pain perception. An analgesic agent employs a mechanism of action other than inhibition of CDK.

One class of analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), down-regulates the chemical messengers of the stimuli that are detected by the nociceptors and another class of drugs, such as opioids, alters the processing of nociceptive information in the CNS. Other analgesics are local anesthetics, anticonvulsants and antidepressants such as tricyclic antidepressants. Administering one or more classes of drug in addition to CDK inhibitors can provide more effective amelioration of pain.

Preferred NSAIDs for use in the methods and compositions of the present invention are aspirin, acetaminophen, ibuprofen, and indomethacin. Furthermore, cyclooxygenase-2 (COX-2) inhibitors, such as specific COX-2 inhibitors (e.g. celecoxib, COX189, and rofecoxib) may also be used as an analgesic agent in the methods or compositions of the present invention.

Preferred tricyclic antidepressants are selected from the group consisting of Clomipramine, Amoxapine, Nortriptyline, Amitriptyline, Imipramine, Desipramine, Doxepin, Trimipramine, Protriptylin, and Imipramine pamoate.

Furthermore, the use of anticonvulsants (e.g. gabapentin), GABAB agonists (e.g. L-baclofen), opioids, vanniloid receptor antagonists and cannabinoid (CB) receptor agonists, e.g. CB1 receptor agonists as analgesic is also preferred in the methods and compositions in the present invention.

In preparing cyclin-dependent kinase inhibitor compositions of this invention, one can follow the standard recommendations of well-known pharmaceutical sources such as Remington: The Science and Practice of Pharmacy, ^{19th} ed. (Mack Publishing, 1995).

The pharmaceutical compositions of the present invention can be prepared in a conventional solid or liquid carrier or diluent and a conventional pharmaceutically-made adjuvant at suitable dosage level in a known way. The preferred preparations are adapted for oral application. These administration forms include, for example, pills, tablets, film tablets, coated tablets, capsules, powders and deposits.

Furthermore, the present invention also includes pharmaceutical preparations for parenteral application, including dermal, intradermal, intragastral, intracutan, intravasal, intravenous, intramuscular, intraperitoneal, intranasal, intravaginal, intrabuccal, percutan, rectal, subcutaneous, sublingual, topical, or transdermal application, wherein said preparations in addition to typical vehicles and/or diluents contain at least one inhibitor according to the present invention and/or a pharmaceutical acceptable salt thereof as active ingredient.

The pharmaceutical compositions according to the present invention containing at least one inhibitor according to the present invention and/or a pharmaceutical acceptable salt thereof as active ingredient will typically be administered together with suitable carrier materials selected with respect to the intended form of administration, i. e. for oral

administration in the form of tablets, capsules (either solid filled, semi-solid filled or liquid filled), powders for constitution, gels, elixirs, dispersable granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable carrier, preferably with an inert carrier like lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid filled capsules) and the like.

Moreover, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated into the tablet or capsule. Powders and tablets may contain about 5 to about 95 % by weight of a cyclin-dependent kinase inhibitor according to the Formula I as recited herein or analogues thereof or the respective pharmaceutical active salt as active ingredient.

Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among suitable lubricants there may be mentioned boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like.

Suitable disintegrants include starch, methylcellulose, guar gum, and the like.

Sweetening and flavoring agents as well as preservatives may also be included, where appropriate. The disintegrants, diluents, lubricants, binders etc. are discussed in more detail below.

Moreover, the pharmaceutical compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimise the therapeutic effect (s), e. g. antihistaminic activity and the like. Suitable dosage forms for sustained release include tablets having layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions, and emulsions. As an example, there may be mentioned water or water/propylene glycol solutions for parenteral injections or addition of sweeteners and opacifiers for oral solutions,

suspensions, and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be present in combination with a pharmaceutically acceptable carrier such as an inert, compressed gas, e. g. nitrogen.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides like cocoa butter is melted first, and the active ingredient is then dispersed homogeneously therein e. g. by stirring. The molten, homogeneous mixture is then poured into conveniently sized moulds, allowed to cool, and thereby solidified.

Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions, and emulsions.

The compounds according to the present invention may also be delivered transdermally. The transdermal compositions may have the form of a cream, a lotion, an aerosol and/or an emulsion and may be included in a transdermal patch of the matrix or reservoir type as is known in the art for this purpose.

The term capsule as recited herein refers to a specific container or enclosure made e. g. of methylcellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredient(s). Capsules with hard shells are typically made of blended or relatively high gel strength gelatins from bones or pork skin. The capsule itself may contain small amounts of dyes, opaquing agents, plasticisers and/or preservatives. Under tablet a compressed or moulded solid dosage form is understood which comprises the active ingredients with suitable diluents. The tablet may be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation, or by compaction well known to a person of ordinary skill in the art.

Oral gels refer to the active ingredients dispersed or solubilised in a hydrophilic semi-solid matrix.

Powders for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended e. g. in water or in juice.

Suitable diluents are substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol, and sorbitol, starches derived from wheat, corn rice, and potato, and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 5 to about 95 % by weight of the total composition, preferably from about 25 to about 75 % by weight, and more preferably from about 30 to about 60 % by weight.

The term disintegrants refers to materials added to the composition to support disintegration and release of the pharmaceutically active ingredients of a medicament. Suitable disintegrants include starches, "cold water soluble" modified starches such as sodium carboxymethyl starch, natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar, cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose, microcrystalline celluloses, and cross-linked microcrystalline celluloses such as sodiumcroscaramellose, alginates such as alginic acid and sodium alginate, clays such as bentonites, and effervescent mixtures. The amount of disintegrant in the composition may range from about 2 to about 20 % by weight of the composition, more preferably from about 5 to about 10 % by weight.

Binders are substances which bind or "glue" together powder particles and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose, starches derived from wheat corn rice and potato, natural gums such as acacia, gelatin and tragacanth, derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate, cellulose materials such as methylcellulose, sodium carboxymethylcellulose and hydroxypropylmethylcellulose, polyvinylpyrrolidone, and inorganic compounds such as magnesium aluminum silicate. The amount of binder in the composition may range from about 2 to about 20 % by weight of the composition, preferably from about 3 to about 10 % by weight, and more preferably from about 3 to about 6 % by weight.

Lubricants refer to a class of substances which are added to the dosage form to enable the tablet granules etc. after being compressed to release from the mould or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate, or potassium stearate, stearic acid, high melting

point waxes, and other water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and D,L-leucine. Lubricants are usually added at the very last step before compression, since they must be present at the surface of the granules. The amount of lubricant in the composition may range from about 0.2 to about 5 % by weight of the composition, preferably from about 0.5 to about 2 % by weight, and more preferably from about 0.3 to about 1.5 % by weight of the composition.

Glidents are materials that prevent baking of the components of the pharmaceutical composition together and improve the flow characteristics of granulate so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc.

The amount of glident in the composition may range from about 0.1 to about 5 % by weight of the final composition, preferably from about 0.5 to about 2 % by weight.

Coloring agents are excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent may vary from about 0.1 to about 5 % by weight of the composition, preferably from about 0.1 to about 1 % by weight.

The present invention relates to the administration of compositions containing as active ingredient a cyclin-dependent kinase inhibitor to a subject in need thereof for the treatment of any type of pain, inflammatory disorders, immunological diseases, proliferative diseases, cardiovascular diseases or neurodegenerative diseases.

"A subject in need thereof "comprises an animal, preferably a mammal, and most preferably a human, expected to experience any type of pain, inflammatory disorders, immunological diseases, proliferative diseases, cardiovascular diseases or neurodegenerative diseases in the near future or which has ongoing experience of said conditions. For example, such animal or human may have a ongoing condition that is causing pain currently and is likely to continue to cause pain, or the animal or human has been, is or will be enduring a procedure or event that usually has painful consequences. Chronic painful conditions such as diabetic neuropathic hyperalgesia and collagen vascular diseases are examples of the first type; dental work, particularly in an area of inflammation or nerve damage, and toxin exposure (including exposure to chemotherapeutic agents) are examples of the latter type.

In order to achieve the desired therapeutic effect, the respective cyclin-dependent kinase inhibitor has to be administered in a therapeutically effective amount.

The term "therapeutically effective amount" is used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. This response may occur in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, and includes alleviation of the symptoms of the disease being treated. In the context of the present invention, a therapeutically effective amount comprises, e.g., an amount that reduces pain, in particular inflammatory or neuropathic pain. Specifically, a therapeutically effective amount denotes an amount which exerts a hypoalgesic effect in the subject to be treated.

Such effective amount will vary from subject to subject depending on the subject's normal sensitivity to, e.g., pain, its height, weight, age, and health, the source of the pain, the mode of administering the inhibitor of CDKs, the particular inhibitor administered, and other factors. As a result, it is advisable to empirically determine an effective amount for a particular subject under a particular set of circumstances.

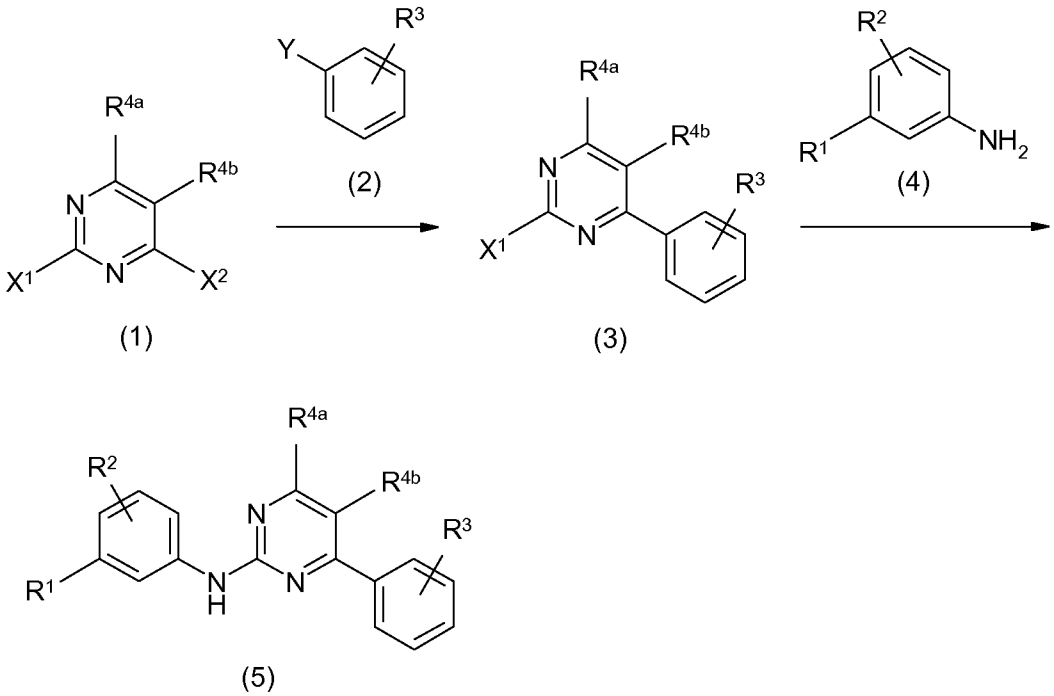
The invention is further illustrated by the following non-limiting examples.

EXAMPLES

All reagents were purchased from ACROS Organics, Aldrich, Lancaster, Maybridge and Boron Molecular.

The LC/MS analyses for the compounds were done at Surveyor MSQ (Thermo Finnigan, USA) with APCI ionization.

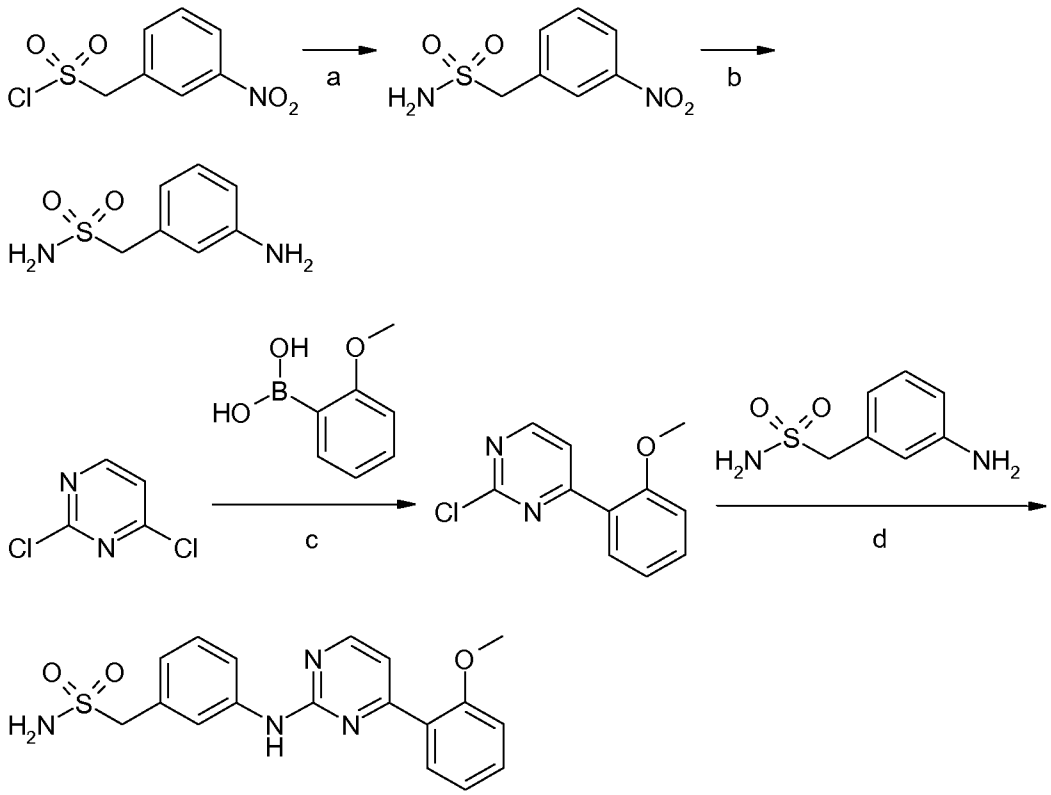
The compounds of the invention can be prepared by any method known in the art. One convenient synthetic route is shown below in Scheme 1:



Scheme 1

Palladium-catalyzed cross-coupling of phenyl boronic acids (2, Y = $B(OH)_2$) or their derivatives with 2,4-dihalogenated pyrimidines (1, e.g. $X^1 = X^2 = Cl$) affords 4-arylated 2-halogenopyrimidines (3), which are aminated with anilines (4).

Example 1: Synthesis of {3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 1)



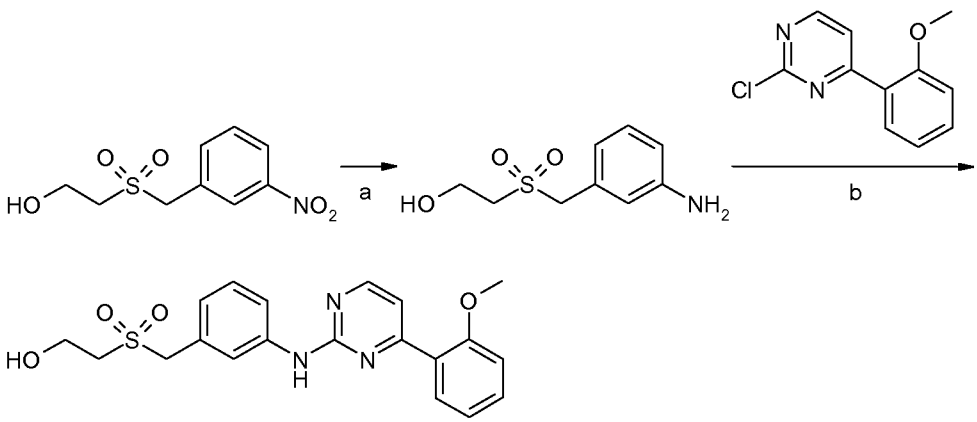
a. (Nitrophenyl)methanesulfonyl chloride (4.17 g, 20 mM) (Ziegler, Carl and Sprague, James M., J. of Org. Chem. (1951), 16, 621-5) was dissolved in acetonitrile (20 mL), concentrated aqueous ammonia (20 mL), saturated with ammonium carbonate, was added and the mixture was vigorously stirred for 1 h at room temperature. Then acetonitrile was evaporated, the residue was diluted with cold water (20 mL) leading to the formation of a precipitate which was filtered off and washed with water (2x5 mL) and ether and dried under reduced pressure. Yield of (3-nitro-phenyl)methanesulfonamide: 3.5 g (80 %).

b. (3-Nitrophenyl) methanesulfonyl amide (3,5 g, 16 mM) was hydrogenated over Raney-Ni (0.5 g) in methanol at 50°C and 70 psi for 4 hours. Then the catalyst was filtered off and washed with warm methanol. The combined filtrates were evaporated to give 2.83 g (95 %) of (3-amino-phenyl)-methanesulfonamide.

c. 4,6-Dichloro-pyrimidine (6 g, 0.04 mol) (Ranganathan, Subramania et al., Proceedings - Indian Academy of Sciences, Chemical Sciences (1994), 106(5), 1051-70. Maggiali, C. et al., Farmaco, Edizione Scientifica (1988), 43(3), 277-91. Gershon, Herman et al., J. of Med. Chem. (1963), 6, 87-9) and (2-methoxy-phenyl)-boronic acid (4.37 g, 0.029 mol) were dissolved in dimethoxyethane (120 mL) and water (18 mL). To this solution were added $NaHCO_3$ (6.72g, 0.08 mol), $PdCl_2(PPh_3)_2$ (0.84 g) and allowed to reflux for 7 hrs (TLC control). Then the mixture was cooled down to room temperature and the solvents removed under reduced pressure. The obtained crude solid was dissolved in dichloromethane (100 mL), washed with water (1 x 100 mL), the organic layer was separated, dried over K_2CO_3, filtered and the solvent removed under reduced pressure. The obtained solid was further purified by flash-chromatography (eluent dichloromethane) to afford a crude product that was crystallized from hexane to yield 2-chloro-4-(2-methoxy-phenyl)-pyrimidine (4.7 g, 73%).

d. A solution of 2-chloro-4-(2-methoxy-phenyl)-pyrimidine (0.882 g, 0.004 mol), and (3-amino-phenyl)-methanesulfonamide (0.865 g, 0.005 mol) in DMF (12 ml) was stirred for 2 hours at 80°C (TLC control). The solvent was removed under reduced pressure to afford {3-[4-(2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide.

Example 2: Synthesis of 2-{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenylmethanesulfonyl}-ethanol (Compound 9)

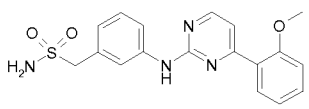
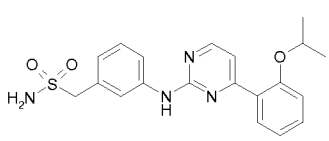
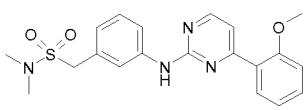


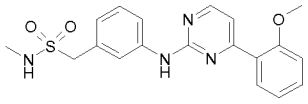
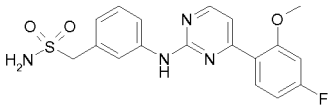
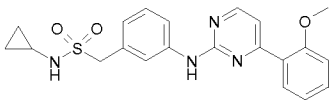
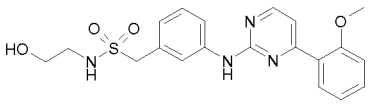
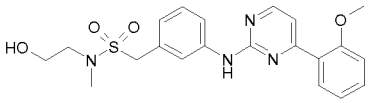
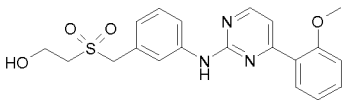
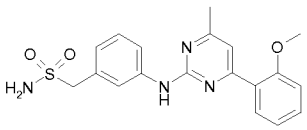
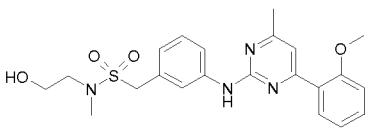
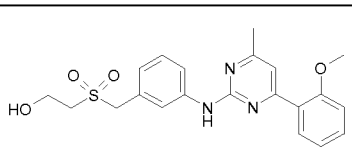
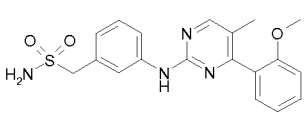
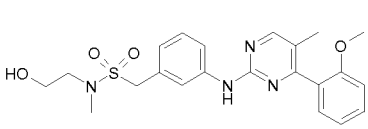
a. 2-(3-Nitro-phenylmethanesulfonyl)-ethanol (0.8 g, 3.3 mmol) (Harms, Wolfgang et al., Ger. Offen. (1995), DE 4402189 A1, 19950727) was placed in a hydrogenation flask

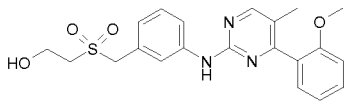
and dissolved in methanol (100 mL). After the addition of Raney-Ni (200 mg) the mixture was allowed to shake at a hydrogen pressure of 70 psi at 50 °C for 4 hours. Then the catalyst was removed by filtration and washed with methanol. The methanol solutions were combined and the solvent evaporated under reduced pressure. The crude product was purified by flash-chromatography (eluent system: dichloromethane / methanol - 10/1), the desired fractions were combined, dried and evaporated. The residue was washed with diethylether to afford 2-(3-amino-phenylmethanesulfonyl)-ethanol (0.51g, yield 73%).

b. A solution of 2-(3-amino-phenylmethanesulfonyl)-ethanol (0.215 g, 1 mmol) and 2-chloro-4-(2-methoxy-phenyl)-pyrimidine (0.22 g, 1mmol) in DMF (3 mL) was stirred for 2 hours at 80°C (TLC control). The solvent was removed under reduced pressure to afford an oily residue which was crystallized from isopropanol yielding 2-{3-[4-(2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenylmethanesulfonyl}-ethanol (0.3 g, 75%).

In analogy, the following compounds have been synthesized using the correspondingly substituted starting materials.

Compound No.	Structure	IUPAC name	MS m/z
1		{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide	371 (M+1)
2		{3-[4-(2-Isopropoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide	399 (M+1)
3		C-{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide	399 (M+1)

4		C-{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide	385 (M+1)
5		{3-[4-(4-Fluoro-2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide	389 (M+1)
6		N-Cyclopropyl-C-{3-[4-(2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide	411 (M+1)
7		N-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide	415 (M+1)
8		N-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide	429 (M+1)
9		2-{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenylmethanesulfonyl}-ethanol	400 (M+1)
10		{3-[4-(2-Methoxy-phenyl)-6-methyl-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide	367.9 (M+1) 365.6 (-MS)
11		N-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-6-methyl-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide	444 (M+1)
12		2-{3-[4-(2-Methoxy-phenyl)-6-methyl-pyrimidin-2-ylamino]-phenylmethanesulfonyl}-ethanol	413.9 (M+1)
13		{3-[4-(2-Methoxy-phenyl)-5-methyl-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide	384.9 (M+1)
14		N-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-5-methyl-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide	444 (M+1)

15		2-{3-[4-(2-Methoxy-phenyl)-5-methyl-pyrimidin-2-ylamino]-phenylmethanesulfonyl}-ethanol	414, 416 (M+1)

Example 3

I. Behavioral animal models for the analysis of inflammatory and neuropathic pain

Several animal models for the analysis of inflammatory and neuropathic pain are known. Said models share the common feature that after e.g., induction of a nerve lesion (e.g., spared nerve injury, SNI) or after exposing experimental animals to a noxious stimulus (e.g., injection of formalin or carrageenan), the signs of pain as induced by said interventions are measured by quantifiable behavioral components such as, e.g., paw withdrawal threshold to mechanical stimulation with von Frey hairs (or to thermal stimulation using a laser source or licking behaviour). These reactions are interpreted as being equivalent to mechanical and thermal allodynia (hypersensitivity to mechanical stimuli) or hyperalgesia in humans.

The spared nerve injury model (SNI model, as developed by Decosterd and Woolf (2000), see Figure 1) is characterized by the induction of clinically relevant nerve lesions and after surgical intervention, subsequent behavioral experiments (e.g., von Frey Assay). Said model constitutes a common nerve injury model which consists of ligation and section of two branches of the sciatic nerve (namely tibial and common peroneal nerves) leaving the sural nerve intact. The SNI model results in early (less than 24 hours), prolonged and substantial changes in mechanical and cold sensitivity that closely mimic the features of clinical neuropathic pain. Animals with these types of nerve injury have been shown to develop abnormal pain sensations and hypersensitivity to mechanical stimuli (allodynia) similar to those reported by neuropathic pain patients.

Alternatively, the formalin assay in mice is a valid and reliable behavioral model of nociception in inflammatory and neuropathic pain. It is sensitive to various classes of analgesic drugs (Hunskaar S, Hole K, Pain. 1987 Jul;30(1):103-14.) The noxious stimulus consists of an injection of 10 µl diluted formalin (2% in saline) under the skin of the dorsal surface of the left hindpaw (subcutaneous or interplantar into the left hindpaw). The response is licking and flinching of the injected paw.

For the carrageenan assay a subcutaneous injection of 25 µl of 1% carrageenan (in saline) into a single hind paw (ipsi-lateral paw) of mice is applied. Subsequent inflammation results in long lasting swelling and hypersensitivity (against mechanical and thermal stimuli) of the paw. The carrageenan assay is a standard laboratory assay used to predict anti-inflammatory activity of test compounds. Paw edema measurements and Hargreaves Assay (withdrawal of paws due to thermal stimulation via a light source) are used for read out.

Regarding the present invention, the effect of administration of cyclin-dependent kinase (CDK)-inhibiting compounds according to Formula I on the development of inflammatory and neuropathic pain is assayed in a SNI model, in a carrageenan and in a formalin assay. The experimental procedure and results are described in detail below.

Example 4

A. *Spared nerve injury (SNI) – Model of chronic neuropathic pain*

As outlined above, the spared nerve injury (SNI) model (see Figure 1) involves a lesion of two of the three terminal branches of the sciatic nerve (tibial and common peroneal nerves) of experimental animals, leaving the sural nerve intact. SNI results in mechanical and thermal allodynia in the non-injured sural nerve skin territory (Decosterd and Woolf, Pain 2000; 87:149-158. (2) Tsujino et al., Mol. Cel. Neurosci. 2000; 15:170-182).

1. Induction of spared nerve injury (nerve lesion) in wildtype mice

Wildtype mice (strain C3HeB/FeJ) (age, sex and weight matched) were anesthetized with Hypnorm (0.315 mg/ml fentanyl citrate + 10 mg/ml fluanisone; Janssen)/Hypnovel (5 mg/ml midazolam; Roche Applied Sciences)/water at a ratio of 1:1:2 at 4 µl/g prior to surgical preparation.

Subsequently, an incision was made under aseptic precautions in the ipsi-lateral right hind leg of all mice just above the level of the knee, exposing the three terminal branches of the sciatic nerve: the common peroneal, tibial, and sural nerves. The common peroneal and tibial nerves were ligated tightly with 7/0 silk and sectioned distal to the ligation removing ≈2 mm of distal nerve stump. The sural branch remained untouched during the procedure (denoted herein “SNI ipsi”). The overlying muscle and

skin was sutured, and the animals were allowed to recover and to permit wound healing. In the same mice the sciatic nerve branches of the contra-lateral left hind leg were exposed but not lesioned (denoted herein "SNI contra-lateral"). Mice that underwent spared nerve injury are hereinafter denoted "SNI mice".

2. Administration of CDK-inhibiting compounds to SNI mice

After recovery from surgery and wound healing, SNI mice received per oral (p.o.) injections of CDK-inhibiting compounds.

30mg/kg of a CDK inhibitor, dissolved in 400 µl of 2 % Hydroxprolylcellulose; 0.25 % Lactic Acid (85 % solution) was administered via per oral application 30 min prior to von Frey measurements (mechanical allodynia). As a negative control, the same amount (400µl) of 2 % Hydroxprolylcellulose; 0.25 % Lactic Acid (85 % solution) vehicle was administered by a single per oral application 30 min prior to von Frey measurements.

Injection of inhibitor or vehicle, and subsequent measurements of paw withdrawal threshold to mechanical stimulation in von Frey assays were performed at day 107 post SNI. Reflex nociceptive responses to mechanical stimulation were measured in a von Frey assay 30 min after each injection.

The effect of administration of CDK inhibitors to SNI mice on the development of mechanical allodynia was analyzed in a von Frey assay, as described below.

3. Behavioral testing of SNI mice after administration of CDK-inhibiting compounds (von Frey assay)

Mice that underwent SNI and subsequent administration of the compounds of the present invention were tested for signs of mechanical allodynia post nerve injury and post administration in a von Frey assay (Decosterd and Woolf, Pain 2000; 87:149-158). This assay determines the mechanical threshold upon which a stimulus, which normally is not painful, is recognized by an animal as uncomfortable or painful. SNI ipsi and SNI contra baselines, respectively, were established.

Mechanical thresholds of SNI mice were quantified using the up-down method based on Chaplan et al. (1994) and Malmberg and Basbaum (1998).

Mice were placed in plexiglass cylinders of about 9.5 cm in diameter, 14 cm high with four vent holes toward the top and a plexiglass lid. The cylinders were placed on an elevated mesh surface (7x7mm squares). Prior to the day of testing, the mice were

acclimated to the testing cylinders for 1-2 hours. On the day of testing the mice were acclimated to the cylinders for about an hour, wherein the acclimation time depends on factors such as the strain of the mouse and the number of times they have been tested previously. In general, testing may begin once the mice are calm and stop exploring the new environment.

For testing mice, filaments 2.44, 2.83, 3.22, 3.61, 3,84, 4,08, and 4.31 (force range = 0.04 to 2.0 g) were used. The 3,61 mN filament was applied first. Said filament was gently applied to the plantar surface of one paw, allowed to bend, and held in position for 2 – 4 seconds. Whenever a positive response to the stimulus (flexion reaction) occurred the next weaker von Frey hair was applied; whenever a negative response (no reaction) occurred the next stronger force was applied. The test was continued until the response to 4 more stimuli after the first change in response had been obtained. The highest force tested was 4.31. The cut-off threshold was 2g.

The series of scores (i.e, “flexion reaction” and “no reaction”) and the force of the last filament applied were used to determine the mechanical threshold as described in Chaplan et al., Journal of Neuroscience Methods. 53(1):55-63, 1994 Jul. The threshold determined is that to which the animal would be expected to respond to 50% of the time. Mice were sacrificed after von Frey measurements were accomplished.

4. Effects of administration of CDK-inhibiting compounds on the development of neuropathic pain

CDK-inhibiting compounds were administered to SNI mice as described above. Von Frey measurements were performed at ipsi-lateral and contra-lateral paws of the animals at day 107 after surgery as described above. Without pharmacological treatment SNI mice show a stable allodynia after SNI surgery. Animals treated with compound display a significant increase of threshold values indicating reduced sensitivity to mechanical stimuli (reduced allodynia). The observation of reduced allodynia signify that a CDK-inhibiting compound is effective as a hypoalgesic drug in models of chronic neuropathic pain.

Example 5

Formalin Assay – Model of inflammatory processes/ inflammatory and chronic neuropathic pain

The formalin assay in mice is a valid and reliable behavioral model of nociception and is sensitive to various classes of analgesic drugs (Hunskaar S, Hole K, Pain. 1987 Jul;30(1):103-14.) The noxious stimulus is an injection of 10 µl diluted formalin (2% in saline) subcutaneous or intraplantar into the left hind paw. The response is licking and flinching of the injected paw. The response shows two phases, which reflect different parts of the inflammatory process (Abbott et al 1995), an early/acute phase 0-5 min post-injection, and a late/chronic phase 5-30 min post-injection. The following protocol describes one possible way to conduct the experiment:

1. *Injection of formalin and administration of CDK-inhibiting compound*

Age, sex and weight matched wildtype mice (C3HeB/FeJ) are used in this assay. Prior to formalin injection the animals are randomly subdivided into experimental groups of 10 animals each. Thirty minutes prior to formalin injection, a suitable dose of a CDK inhibitor dissolved in (400µl) of 2 % Hydroxprolylcellulose; 0.25 % Lactic Acid (85 % solution)) can be administered by i.p. injection. Similarly, Iκ Kinase (IKK) inhibitor (30 mg/kg) in (400µl) of 2 % Hydroxprolylcellulose; 0.25 % Lactic Acid (85 % solution) (positive control), or vehicle alone ((400µl) of 2 % Hydroxprolylcellulose; 0.25 % Lactic Acid (85 % solution)) (negative control) can be administered by i.p. injection 30 min before formalin injection.

For formalin injection the mouse is held with a paper towel, in order to avoid disturbance of the injection by movements. The injected hind paw is held between thumb and forefinger and 10µl of Formalin (2%) is injected subcutaneously (s.c.) between the two front tori into the plantar hind paw using a Hamilton syringe. The behavior of the formalin- and inhibitor-treated mice is analyzed as described below.

2. *Behavioral analysis of mice after injection of formalin and administration of CDK-inhibiting compound*

The behaviour of the formalin-treated mice, i.e. licking and flinching, is monitored by an automated tracking system (Ethovision 3.0 Color Pro, Noldus, Wageningen,

Netherlands) over a defined period of time: measurement is initiated 5 min after formalin injection and terminated 30 min after formalin injection. This time frame covers phase II of formalin-induced nociception (pain), which is hyperalgesia.

Two different fluorescent dyes are used for topically marking the injected hind paw (yellow dye) (Lumogenyellow; BASF Pigment, Cologne, Germany) and the contralateral paw (blue dye) (Lumogenviolet; Kremer Pigmente, Aichstetten, Germany) respectively. To determine licking behaviour, mice are monitored with a CCD camera. After monitoring and recording, the video is analyzed using the EthoVision software (Ethovision 3.0 Color Pro, Noldus, Wageningen, Netherlands) or by manual analysis. Fluorescent dot sizes and fluorescence intensities were measured and reduction of fluorescent dot size through licking and biting was calculated. The overall licking time intensity was automatically calculated by comparison of dot size reduction of treated versus untreated paws.

As another variant of assay read out the licking behaviour of the individual animals was tracked manually based on video files. Licking times were recorded over 30 minutes after formalin injection and subdivided for three different licking zones (dorsum, plantar, toes). Overall licking times can be calculated for each animal as well as each experimental group and be used as a parameter for determination of compound efficacy.

As a result it was found that mice receiving vehicle treatment prior to formalin injection (negative control) displayed a prolonged licking time and a significant reduction of fluorescent dot size at the formalin-treated paw.

In contrast, a reduction in licking time and in consequence no significant reduction of fluorescent dot size of the formalin-treated paw could be observed in test compound/formalin-treated mice. The same effect, i.e. a reduction in licking time and a minor change in fluorescent dot size, was observed in control mice treated with Ikappa kinase inhibitor (IKK; for function of IKK see Figure 2, positive control).

This observation is indicative for reduced inflammatory/chronic inflammatory pain perception in CDK9 inhibitor-treated mice and for a hypoalgesic effect of the tested compound.

Example 6

Carrageenan Assay in mice – Model of Inflammation and Inflammatory Pain

The model of carrageenan induced paw edema is a standard laboratory assay used to predict anti-inflammatory activity and reduction of inflammation-induced pain perception of respective compounds. The following protocol describes one possible way to conduct the experiment.

The basic measurement constitutes in the measurement of edema and mechanical as well as thermal hypersensitivity in response to irritants, such as carrageenan.

Inflammation and resulting inflammatory pain is induced by subcutaneous injection of 25 µl of 1% carrageenan (in saline) into mice hind paw (ipsi-lateral paw). Each group of 10 mice receives administration of a compound according to Formula I, 30 mg/kg body weight, vehicle ((400µl) of 2 % Hydroxprolylcellulose; 0.25 % Lactic Acid (85 % solution)) and saline (physiol. NaCl) by i.p. injection 30min prior to carrageenan injection. Contra-lateral paws do not receive carrageenan injection.

1.1 Effects of administration of a CDK-inhibiting compound on carrageenan-treated mice

Paw edema induced by carrageenan injection are detected by increased paw size measured from dorsal to plantar at the metatarsus region of the injected (ipsi-lateral) paws. Sizes of ipsi- and contra-lateral paws serve as surrogate markers for inflammation and are measured at several time points after carrageenan injection: before injection (-1), 2h (2),3h (3) 4h (4), 5h (5), 6h (6), 24h (24) after injection.

The paw size of all mice may increase, e.g., by 2 to 3mm (+10%) within the first hour after carrageenan injection, independent of the type of treatment substance injected 30 minutes prior to carrageenan. During the time course, mice which received treatment with a CDK-inhibiting compound prior to carrageenan injection may display a reduction of the edema until 24h after carrageenan injection: the increase in paw size could drop e.g. from 10% down to 8%. In contrast, the paw size of the control mice could increase by 30% in average at this time point. After 24h post carrageenan injection, the size of all paws treated with carrageenan may increase to reach its maximum at 96h after injection.

As a read-out of the carrageenan assay, a Hargreaves Assay may be performed, wherein said assay allows the measuring of thermal sensitivity to radiant heat. The Hargreaves assay (Hargreaves et al., 1988) measures nociceptive sensitivity in a freely moving animal by focusing a radiant heat source on the plantar surface of an animal's hindpaw as it stands in a plexiglass chamber. Specifically, the lower side of a paw is exposed to a luminous source, generating a temperature of, e. g. 55°C. Thermal sensitivity is measured as latency between start of exposure and lifting/pulling the exposed paw.

Mice treated with a CDK9 inhibitor as disclosed herein and carrageenan, or with Naproxen and carrageenan, or with solvent and carrageenan, respectively, are subjected to a Hargreaves assay. Mice treated with a CDK inhibitor and carrageenan could display a longer latency, compared to negative control mice. This observation would be indicative for a hypoalgesic effect of the CDK inhibitors as disclosed herein.

Example 7

Carrageenan Assay in rats – Model of Inflammation and Inflammatory Pain

The following depicts one possible way of performing the carrageenan assay in rats.

Said assay detects analgesic/anti-inflammatory activity in rats with inflammatory pain, following the protocol as described by Winter et al (Proc. Soc. Exp. Biol. Med., 111, 544-547, 1962).

Rats (200 – 250 g) are injected with a suspension of carrageenan into the lower surface of the right hindpaw (0.75 mg per paw in 0.05 ml physiological saline). Two hours later rats are submitted consecutively to tactile and thermal stimulation of both hindpaws.

For tactile stimulation, the animal is placed under an inverted acrylic plastic box (18 x 11.5 x 13 cm) on a grid floor. The tip of an electronic Von Frey probe (Bioseb, Model 1610) is then applied with increasing force first to the non-inflamed and then the inflamed hindpaw and the force required to induce paw-withdrawal is automatically recorded. This procedure is carried out 3 times and the mean force per paw is calculated.

For thermal stimulation, the apparatus (Ugo Basile, Reference: 7371) consists of individual acrylic plastic boxes (17 x 11 x 13 cm) placed upon an elevated glass floor. A rat is placed in the box and left free to habituate for 10 minutes. A mobile infrared radiant source (96 ± 10 mW/cm²) is then focused first under the non-inflamed and then the inflamed hindpaw and the paw-withdrawal latency is automatically recorded. In order to prevent tissue damage the heat source is automatically turned off after 45 seconds.

After the behavioral measures, the paw edema is evaluated by measuring the volume of each hindpaw using a digital plethysmometer (Letica, Model 7500), which indicates water displacement (in ml) induced by paw immersion.

10 rats are studied per group. The test is performed blind.

The test substance, such as a CDK inhibitor according to Formula I as presented herein, will be evaluated at 2 doses (10 and 30 mg/kg), administered p.o. 60 minutes before the test, and compared with a vehicle control group.

Morphine (128 mg/kg p.o.) and acetylsalicylic acid (512 mg/kg p.o.), administered under the same experimental conditions, will be used as reference substances.

The experiment will therefore include 6 groups. Data will be analyzed by comparing treated groups with vehicle control using unpaired Student's t tests.

Rats treated with a CDK9 inhibitor as disclosed herein and carrageenan, or with Naproxen and carrageenan, or with solvent and carrageenan, respectively, are subjected to a Hargreaves assay. Rats treated with a CDK inhibitor and carrageenan should display a longer latency, compared to negative control rats. This observation would be indicative for a hypoalgesic effect of the CDK inhibitors as disclosed herein.

Example 8

A. LPS In Vivo Assay (LPS) – Model of Cytokine Repression In Vivo

For the LPS induced model of septic shock, mice receive an intraperitoneal (i.p.) injection of 30 µg bacterial Lipopolysaccharide (LPS; L2630 SIGMA) in saline. Said LPS-mediated initiation of the inflammatory signalling cascade results in increasing blood serum concentrations of cytokines such as e.g. TNFα, IL-6 and IL1ß. Blood can

be taken from these animals at defined time points. Thereafter, serum will be separated and the samples can be stored at –80°C until cytokine concentrations are measured using commercial ELISA assays. (AL Moreira et al., Braz J Med Biol Res 1997; 30:1199-1207).

It has been recognized that inflammatory mediators such as the cytokines TNFα, IL6 and IL1ß can contribute to persistent pain states as well as inflammatory disorders. After being released from immune cells like macrophages in peripheral and microglia in CNS tissues, these mediators seem to play a pivotal role not only in inflammatory and neuropathic pain but also in inflammatory disorders such as rheumatoid arthritis (F Marchand et al., Nat Rev Neurosci 2005; 6 (7); 521-532). Thus, inhibition of tumor necrosis factor α (TNFα) represents a relevant target for the treatment of inflammatory diseases as well [Lavagno et al., Eur J Pharmacol 2004; 501, 199-208].

The LPS in vivo assay can be used as a powerful model to address repression of cytokine expression by pharmacological treatments.

1. Induction of cytokine expression in wildtype mice

Wildtype mice (strain C3HeB/FeJ) (age, sex and weight matched) were injected with 30 µg LPS (SIGMA) intraperitoneally. 90 minutes after LPS administration these animals were anaesthetized with 0.1 ml/10 g bodyweight Ketamine-Rompun (50/20 mg/ml) and blood for serum preparation was taken via cardiac puncture.

2. Administration of CDK-inhibiting compounds to LPS mice

Pharmacological treatment groups (n=4) of LPS mice received per os (p.o.) injections of CDK-inhibiting compounds or the vehicle (negative control), respectively.

10 or 30 mg/kg (compound per bodyweight) of a CDK inhibitor, dissolved in 1% carboxy-Methylcellulose (SIGMA) was administered as a single p.o. dosage 30 min prior to LPS stimulation. Vehicle control was administered in the same manner.

90 minutes (min) after LPS stimulation, blood samples were taken from the mice. Previously, the 90 min time point had been identified as the peak of TNF alpha expression in this animal model by a time course experiment.

The effect of pharmacological treatment with CDK inhibitors on cytokine levels in LPS mice was analyzed in commercial ELISA assays as described below.

3. Determination of cytokine blood serum concentrations in LPS mice after administration of CDK-inhibiting compounds

Blood samples (~500 µl/animal) from the LPS animals were incubated on wet ice for 30 min after cardiac puncture. Afterwards the samples were centrifuged for 15 min at 13.000 rpm. Serum was separated from the clot and stored frozen at –80°C.

Serum concentrations of TNF alpha and IL6 within the samples were measured by using commercial ELISA Kits (Natutec) according to the manufacturers instructions.

4. Effects of administration of CDK inhibiting compounds on the protein expression of cytokines

Compounds were administered to LPS mice as described above. ELISA based determinations of cytokine serum concentrations were performed as described above. Comparison of CDK inhibiting compounds treated versus vehicle treated control animals displayed a significant repressive effect on TNFα and IL6 protein concentration in the blood serum. indicating that CDK inhibiting compounds are effective as suppressive drugs of cytokines TNF alpha and IL6 in models of cytokine expression.

Example 9

A. In Vitro *THP-1 Assay* – In Vitro *Model of Cytokine Inhibition*

The human THP-1 cell line can be utilized as an in vitro model of cytokine expression as mediated by Lipopolysaccharide (LPS) or Tumor Necrosis Factorα [TNFα].

Monocytic THP-1 cells (ATCC; TIB-202) can be differentiated into macrophage-like cells expressing pro-inflammatory cytokines like TNFα, IL6 and IL1ß upon induction with LPS or by TNFα (autocrine induction) itself.

It has been recognized that inflammatory mediators such as the cytokines TNFα, IL6 and IL1ß can contribute to persistent pain states as well as to inflammatory disorders. After being released from immune cells like macrophages in peripheral and microglia in CNS tissues, these mediators seem to play a pivotal role not only in inflammatory and neuropathic pain but also in inflammatory disorders such as rheumatoid arthritis (F Marchand et al., Nat Rev Neurosci 2005; 6 (7); 521-532). Hence inhibition of tumor

necrosis factor α (TNFα) represents a relevant target in the treatment of inflammatory disorders as well [Lavagno et al., Eur J Pharmacol 2004; 501, 199-208].

Therefore, the THP-1 in vitro assay can be used as a powerful screening model to address pharmacological inhibition of cytokine expression (U Singh et al, Clin Chem 2005; 51 (12); 2252-6], K Rutault et al., J Biol Chem 2001; 276 (9); 6666-74].

1. Growth and differentiation of THP-1 cells

THP-1 cells are grown in modified RPMI-1640 medium (ATCC, Cat. No. 30-2001) supplemented with 10% FCS and 1% Pen/Strep. For cytokine inhibition assays, cells are seeded at a density of 5 x 10^5 cells/ml into 6-well plates in standard growth medium supplemented with 100 ng/ml PMA (Sigma, P1585) to induce differentiation into macrophage-like cells. After 24 hours, the medium is replaced with standard growth medium (without PMA) and the cells are incubated for another 48 hours to complete differentiation.

2. Treatment of differentiated THP-1 cells with CDK-inhibiting compounds and LPS stimulation

After 72 h of differentiation, the medium is replaced with serum free growth medium , and CDK-inhibiting compounds as well as reference compounds such as positive and negative controls, each dissolved in DMSO are added at concentrations ranging from 0.5 to 5 µM (final concentration of DMSO in the well is 0.1%). Cells are incubated for 60 min with compounds prior to stimulation with 100 ng/ml LPS (Sigma, L2630) for another 4-48 hours. Supernatants are collected and assayed immediately for cytokine expression, e.g. for TNFα, IL-6 and IL-1b using commercially available sandwich ELISA assays (eBioscience, Cat. No 88-7346, 88-7066, 88-7010) or kept frozen at 20°C until evaluation.

3. Determination of cytokine concentrations in THP-1 supernatant after administration of CDK-inhibiting compounds

Concentrations of TNFα, IL6 and IL1ß within the cell culture supernatants are measured by using commercial ELISA Kits (eBioscience) according to the manufacturers' instructions.

4. Effects of treatment with CDK-inhibiting compounds on the protein expression of cytokines in THP-1 cell supernatants

CDK-inhibitory compounds # 1, 5, 6, 8, and 9 were administeredat to differentiated THP-1 cells in triplicates as described above (see section 2.). After 60 min of pre-incubation with test or reference compound (SB203580, a p38 inhibitor and BMS345541, an IKK-inhibitor) alone, cells were stimulated with LPS. After incubation for 4-48 h, supernatants were collected and ELISA based determinations of cytokine supernatant concentrations were performed as described in section 3, *supra*.

Comparison of cells treated with compounds # 1, 5, 6, 8, and 9 and reference compounds versus cells treated with vehicle (DMSO) displayed a significant inhibitory effect of compound # 1, 5, 6, 8, and 9 on TNFα and IL6 protein concentration in the cell supernatant. Compared to reference compounds SB203580 or BMS3455541, these compounds exhibited a similar or better inhibition of TNFα/Il-6 expression.

The effects of administration of compounds # 1, 5, 6, 8, and 9 on expression of TNFα in LPS induced THP-1 macrophages is shown in Figure 3.

These findings indicate that CDK-inhibitory compounds # 1, 5, 6, 8, and 9 are effective suppressors of expression of cytokines TNFα.

Example 10

A. In Vitro *Kinase Inhibition Assays*

IC50 profiles of compounds 1-15 were determined for cyclin-dependent kinases CDK2/CycA, CDK4/CycD1, CDK5/p35NCK, CDK6/CycD1 and CDK9/CycT in enzymatic kinase inhibition assays *in vitro*. IC50 values as obtained in these assays were used for evaluating the specific selectivity and potency of the compounds with respect to CDK9 inhibition.

Results obtained in these assays were used to select compounds displaying specificity for CDK9. Specifically, it was intended to distinguish the CDK9-specific compounds from other compounds having significant inhibitory potency also with regard to other CDKs, i.e. on some or all of CDKs 2, 4, 5, and 6. This separation is essential in order to avoid adverse (cytostatic/cytotoxic) effects, which may occur upon inhibition of cell cycle relevant CDKs 2, 4,5, and 6.

Furthermore, these data were used to establish structure activity relationships (SAR) supporting the design of new and even improved structures/compounds with respect to potency and selectivity.

1. Test compounds

Compounds were used as 1 x 10^{-02} M stock solutions in 100 % DMSO, 100 µl each in column 2 of three 96-well V-shaped microtiterplates (in the following, said plates are referred to as "master plates").

Subsequently, the 1 x 10^{-02} M stock solutions in column 2 of the master plates were subjected to a serial, semi-logarithmic dilution using 100 % DMSO as a solvent, resulting in 10 different concentrations, the dilution endpoint being 3 x 10^{-07} M/100 % DMSO in column 12. Column 1 and 7 were filled with 100 % DMSO as controls. Subsequently, 2 x 5 µl of each well of the serial diluted copy plates were aliquoted in 2 identical sets of "compound dilution plates", using a 96-channel pipettor.

On the day of the kinase inhibition assay, 45 µl H_2O were added to each well of a set of compound dilution plates. To minimize precipitation, the H_2O was added to the plates only a few minutes before the transfer of the compound solutions into the assay plates. The plates were shaken thoroughly, resulting in "compound dilution plates/ 10 % DMSO" with a concentration of 1 x 10^{-03} M/10 % DMSO to 3 x 10^{-08} M/10% DMSO in semilog steps. These plates were used for the transfer of 5 µl compound solution into the "assay plates". The compound dilution plates were discarded at the end of the working day. For the assays (see below), 5 µl solution from each well of the compound dilution plates were transferred into the assay plates. The final volume of the assay was 50 µl. All compounds were tested at 10 final assay concentrations in the range from 1 x 10^{-04} M to 3 x 10^{-09} M. The final DMSO concentration in the reaction mixtures was 1 % in all cases.

2. Recombinant Protein Kinases

For the determination of inhibitory profiles, the following 5 protein kinases were used: CDK2/CycA, CDK4/CycD1, CDK5/p35NCK, CDK6/CycD1 and CDK9/CycT. Said protein kinases were expressed in Sf9 insect cells as human recombinant GST-fusion proteins or His-tagged proteins by means of the baculovirus expression system. Kinases were purified by affinity chromatography using either GSH-agarose (Sigma) or

Ni-NTH-agarose (Qiagen). The purity of each kinase was determined by SDS-PAGE/silver staining and the identity of each kinase was verified by western blot analysis with kinase specific antibodies or by mass spectroscopy.

3. Protein Kinase Assay

All kinase assays were performed in 96-well FlashPlates™ from Perkin Elmer/NEN (Boston, MA, USA) in a 50 µl reaction volume. The reaction mixture was pipetted in four steps in the following order:

- 20 µl of assay buffer (standard buffer)
- 5 µl of ATP solution (in H_2O)
- 5 µl of test compound (in 10 % DMSO)
- 10 µl of substrate / 10 µl of enzyme solution (premixed)

The assay for all enzymes contained 60 mM HEPES-NaOH, pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 µM Na-Orthovanadate, 1.2 mM DTT, 50 µg/ml PEG20000, 1 µM [-^{33}P]-ATP (approx. 5 x 1005 cpm per well).

The following amounts of enzyme and substrate were used per well:

#	Kinase	Kinase Lot #	Kinase ng/50 µl	Substrate	Substrate ng/50 µl
1	CDK2/CycA	SP005	100	Histone H1	250
2	CDK4/CycD1	SP005	50	Rb-CTF (Lot 009)	500
3.	CDK5/p35NCK	SP001	50	Rb-CTF (Lot 009)	1000
3	CDK6/CycD1	SP003	400	Rb-CTF (Lot 009)	500
4	CDK9/CycT	003	100	Rb-CTF (Lot 009)	1000

Reaction mixtures were incubated at 30° C for 80 minutes. The reaction was stopped with 50 µl of 2 % (v/v) H_3PO_4, plates were aspirated and washed two times with 200 µl H_2O or 200 µl 0.9 % (w/v) NaCl. Incorporation of ^{33}P was determined with a microplate scintillation counter (Microbeta, Wallac).

All assays were performed with a BeckmanCoulter/Sagian robotic system.

4. Evaluation of Raw Data

The median value of the counts in column 1 (n=8) of each assay plate was defined as "low control". This value reflects unspecific binding of radioactivity to the plate in the absence of a protein kinase but in the presence of the substrate. The median value of the counts in column 7 of each assay plate (n=8) was taken as the "high control", i.e. full activity in the absence of any inhibitor. The difference between high and low control was referred to as 100 % activity. As part of the data evaluation, the low control value from a particular plate was subtracted from the high control value as well as from all 80 "compound values" of the corresponding plate. The residual activity (in %) for each well of a particular plate was calculated by using the following formula:

Res. Activity (%) = 100 X [(cpm of compound – low control) / (high control – low control)]

The residual activities for each concentration and the compound IC50 values were calculated using *Quattro Workflow V2.0.1.3* (Quattro Research GmbH, Munich, Germany; www.quattro-research.com). The model used was "Sigmoidal response (variable slope)" with parameters "top" fixed at 100% and "bottom" at 0 %.

It turns out that the IC50 values of compounds 1-15 are all comprised between 1nM and 10μM.

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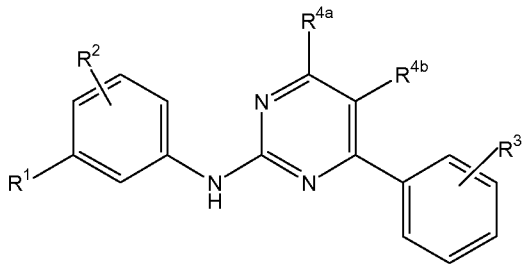
CLAIMS:

1. A compound according to the general Formula I



Formula I

wherein

R^1 is $-XSO_2NR^5R^6$ or - XSO_2R^8 ;

X is a C_{1-4} alkylene (including branched alkylene), wherein said C_{1-4} alkylene can be bound to R^5 or R^6 to form a 5- or 6- membered heterocycle;

R^5 and R^6 independently of each other are hydrogen, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl or C_{3-4}alkenyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-4}alkyl or C_{4-7}-heterocycloalkyl-C_{0-4}alkyl, C_{4-7}-aryl-C_{0-4}alkyl, C_{4-7}-heteroaryl-C_{0-4}alkyl or

wherein R^5 and R^6 together with the N-atom to which they are bound also may form a 5- to 8-membered heterocycloalkyl,

wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl or alkyl is further optionally substituted by up to 2 radicals selected from the group consisting of halo, hydroxy, aminocarbonyl, C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{1-4} alkyl – O - C_{1-4} alkyl, C_{1-4} alkyl – O - and $-NR^5R^6$;

R^8 is C_{1-4} alkyl, hydroxy-C_{2-4}alkyl or C_{3-4}alkenyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-4}alkyl or C_{4-7}-heterocycloalkyl-C_{0-4} alkyl;

wherein said cycloalkyl, heterocycloalkyl or alkyl is further optionally substituted by up to 2 radicals selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{1-4} alkyl – O -C_{1-4} alkyl, C_{1-4} alkyl - O and $-NR^5R^6$;

R^2 is one or two substituents independently selected from halogen and hydrogen;

R^3 can be 1 to 3 substituents each independently selected from the group consisting of hydrogen, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4} alkyl -cycloalkyl, C_{1-4} alkyl –heterocycloalkyl, -O-heterocycloalkyl, C_{1-4} alkoxy, C_{2-4} alkenyloxy, $-OCF_3$, C_{2-4} alkanoyl, C_{1-4}alkylsulfonyl, mono- and di-(C_1-C_4alkyl)sulfonamido, aminocarbonyl, mono- and di-(C_1-C_4alkyl)aminocarbonyl, aryl-C_{1-4} alkoxy, heteroaryl-C_{1-4} alkoxy,

heterocycloalkyl –C1-4-alkoxy, heterocycloalkyl-C1-4-alkyl, heteroaryl-C1-4-alkyl, C_{1-4} alkyloxymethyl, hydroxy-C_{1-4}alkyloxymethyl, cyano, -COOH and C_1-C_4 alkoxycarbonyl, wherein the above mentioned substituents can be further substituted by radicals selected from the group of C_{1-4}-alkyl, hydroxyl-C_{0-4}-alkyl, C_{1-4}-alkoxy, aminocarbonyl, halo, and NR^5R^6;

R^{4a} and R^{4b} are the same or different and each is independently hydrogen, C_{1-4} alkyl or –NR´R´´, wherein R´and R´´ are each independently hydrogen or C_{1-4} alkyl;

and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e. g., hydrates) of such compounds.

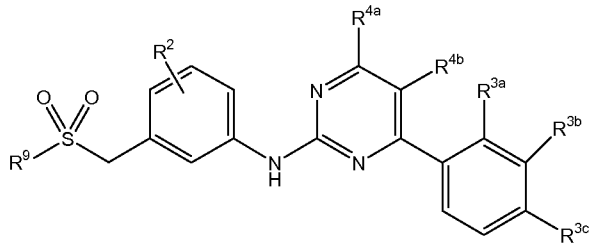
2. A compound according to claim 1, **characterised** in that R^3 is 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, hydroxymethyl, hydroxy, methoxy, ethoxy, isopropoxy, benzyloxy, hydrogen, fluoro, chloro, trifluoromethyl, 2-methoxy-ethoxy, methoxymethyl, 2-methoxy-ethyl, tetrahydro-furan-3-yloxy, tetrahydro-furan-2-yl-methoxy, $-N(CH_3)SO_2CH_3$, piperidin-1-yl-methyl, 2-hydroxymethyl-piperidin-1-yl-methyl, 3-hydroxymethyl-piperidin-1-yl-methyl, 3-(2-hydroxy-ethyl)-piperidin-1-yl-methyl, 3-aminocarbonyl-piperidin-1-yl-methyl, dimethylaminomethyl, diethylaminomethyl, (ethyl-isopropyl-amino)-methyl, morpholin-4-ylmethyl, 4-methyl-piperazin-1-yl-methyl, [1,2,4]triazol-1-yl-methyl, pyridine-3-yl-methoxy and pyridine-4-yl-methoxy.

3. A compound according to claim 1 or claim 2, **characterized** in that R^1 is –$XSO_2NR^5R^6$, and R^5 and R^6 are each independently selected from the group consisting of hydrogen, methyl, cyclopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and 2-hydroxyethyl.

4. A compound according to claim 1 or claim 2, **characterized** in that R^1 is –XSO_2R^8 and R^8 is C_{1-4} alkyl or hydroxy-C_{2-4}-alkyl.

5. A comnpound according to any of the preceding claims **characterized** in that X is methylene.

6. A compound according to claim 1, **characterized** in that the compound has a structure according to Formula Ia



wherein

R^9 is $-NR^5R^6$ or R^8,

R^2 is hydrogen or halogen,

R^{3a} is hydrogen, halogen or C_{1-4}-alkoxy,

R^{3b} is hydrogen,

R^{3c} is hydrogen or halogen,

R^{4a} and R^{4b} are each independently hydrogen or C_{1-4} alkyl,

R^5 and R^6 are each independently hydrogen, cycloalkyl or C_{1-4} alkyl optionally substituted by hydroxyl or dialkylamino,

and R^8 is hydroxy-C_{2-4}-alkyl,

and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e. g., hydrates) of such compounds.

7. A compound according to claim 1, which is chosen from the group consisting of:

{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 1);

{3-[4-(2-Isopropoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 2);

C-{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide (Compound 3);

C-{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide (Compound 4);

{3-[4-(4-Fluoro-2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 5);

N-Cyclopropyl-C-{3-[4-(2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 6);
N-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 7);
N-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide (Compound 8);
2-{3-[4-(2-Methoxy-phenyl)-pyrimidin-2-ylamino]-phenylmethanesulfonyl}-ethanol (Compound 9);
{3-[4-(2-Methoxy-phenyl)-6-methyl-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 10);
-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-6-methyl-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide (Compound 11);
2-{3-[4-(2-Methoxy-phenyl)-6-methyl-pyrimidin-2-ylamino]-phenylmethanesulfonyl}-ethanol (Compound 12);
{3-[4-(2-Methoxy-phenyl)-5-methyl-pyrimidin-2-ylamino]-phenyl}-methanesulfonamide (Compound 13);
N-(2-Hydroxy-ethyl)-C-{3-[4-(2-methoxy-phenyl)-5-methyl-pyrimidin-2-ylamino]-phenyl}-N-methyl-methanesulfonamide (Compound 14); and
2-{3-[4-(2-Methoxy-phenyl)-5-methyl-pyrimidin-2-ylamino]-phenylmethanesulfonyl}-ethanol (Compound 15).

8. A compound according to anyone of claims 1-7, for medical use.

9. A pharmaceutical composition containing a compound according to anyone of claims 1-7, together with a pharmaceutically acceptable carrier.

10. A method for the treatment of a disease selected from the group of any type of pain, inflammatory disorders, immunological diseases, proliferative diseases, infectious diseases, cardiovascular diseases and neurodegenerative diseases, comprising administering a therapeutically effective amount of at least one of the compounds according to claims 1-7.

11. A method according to claim 10, wherein any type of pain comprises chronic pain, inflammatory and/or neuropathic pain.

12. Use of a compound according to any one of claims 1-7 for preparing a pharmaceutical composition for treating any type of pain, inflammatory disorders, immunological diseases, proliferative diseases, infectious diseases, cardiovascular diseases and neurodegenerative diseases.

13. Use according to claim 12, wherein any type of pain comprises chronic pain, inflammatory and/or neuropathic pain.

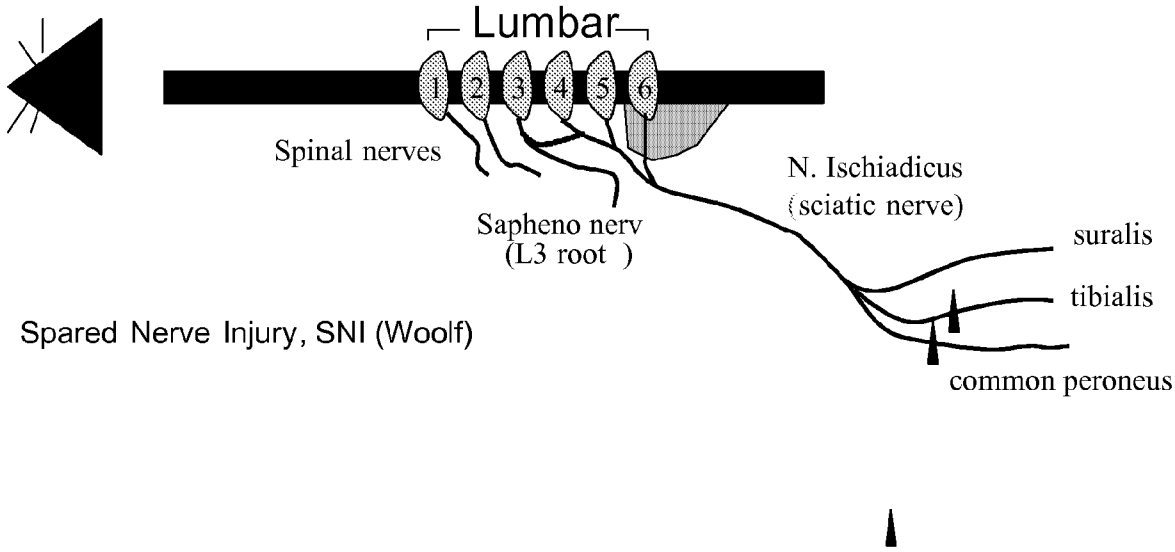

Lumbar
1
2
3
4
5
6
Spinal nerves
Sapheno nerv
(L3 root)
N. Ischiadicus
(sciatic nerve)
suralis
tibialis
common peroneus
Spared Nerve Injury, SNI (Woolf)

Figure 1

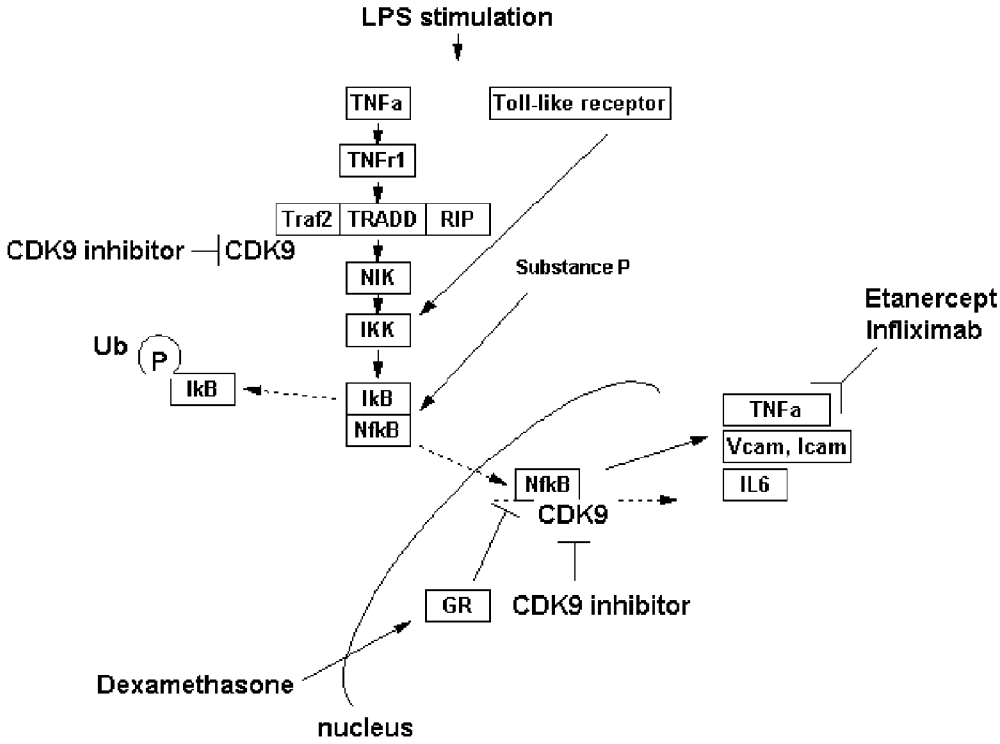

LPS stimulation
TNFa
Toll-like receptor
TNFr1
Traf2
TRADD
RIP
CDK9 inhibitor
CDK9
NIK
Substance P
Etanercept
Infliximab
IKK
Ub
P
IkB
IkB
NfkB
TNFa
Vcam, Icam
IL6
NfkB
CDK9
GR
CDK9 inhibitor
Dexamethasone
nucleus

Figure 2

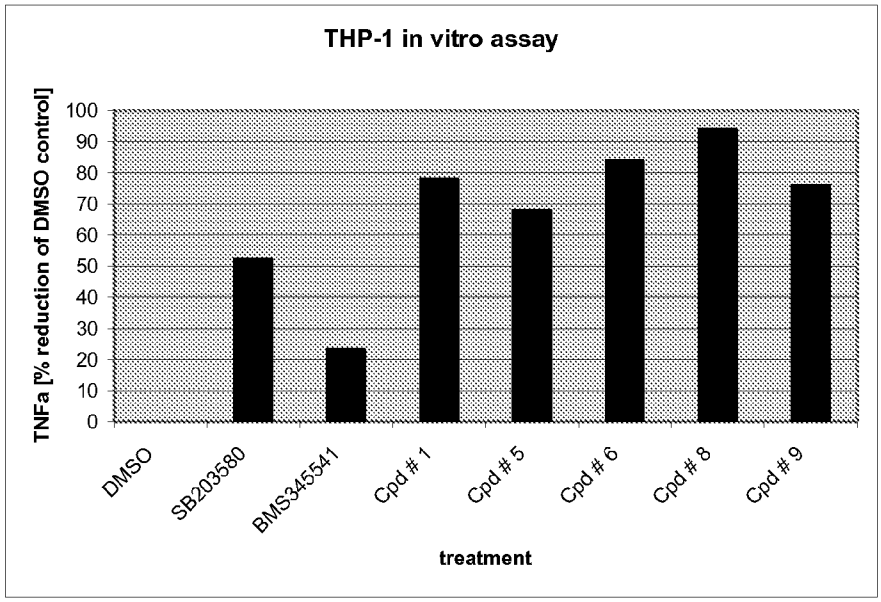

THP-1 in vitro assay
TNFa [% reduction of DMSO control]
100
90
80
70
60
50
40
30
20
10
0
DMSO
SB203580
BMS345541
Cpd # 1
Cpd # 5
Cpd # 6
Cpd # 8
Cpd # 9
treatment

Figure 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/054975

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/42 A61K31/505 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/012262 A (CYCLACEL LTD [GB]; WANG SHUDONG [GB]; MCLACHLAN JANICE [GB]; GIBSON DA) 10 February 2005 (2005-02-10) example 25	1-13
A	WO 01/72745 A (CYCLACEL LTD [GB]; FISCHER PETER MARTIN [GB]; WANG SHUDONG [GB]) 4 October 2001 (2001-10-04) claims 1,21	1-13
A	WO 03/076436 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; NEWCOMBE NICHOLAS JOHN [ ]) 18 September 2003 (2003-09-18) claims 1,24	1-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 2008	02/09/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bakboord, Joan

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/054975

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005012262 A	10-02-2005	AU 2004261484 A1	10-02-2005
		BR PI0412347 A	05-09-2006
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		MX PA04008807 A	26-11-2004
		UA 78292 C2	15-03-2007
		US 2005131000 A1	16-06-2005
		UY 27705 A1	31-10-2003
		ZA 200406937 A	22-02-2006