Title: VANILLOID RECEPTOR LIGANDS AND THEIR USE IN TREATMENTS

Abstract: Compounds having the general structure formula (1) and compositions containing them, for the treatment of acute, inflammatory and neuropathic pain, dental pain, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rhematic diseases, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, causalgia, sympathetically maintained pain, deafferentation syndromes, asthma, epitelial tissue damage or dysfunction, herpes simplex, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritus, vitiligo, general gastrointestinal disorders, gastric ulceration, duodenal ulcers, diarrhea, gastric lesions induced by necroizing agents, hair growth, vasomotor or allergic rhinitis, bronchial disorders or bladder disorders.
VANILLOID RECEPTOR LIGANDS AND THEIR USE IN TREATMENTS

This application claims the benefit of U.S. Provisional Application No. 60/538,702, filed January 23, 2004, which is hereby incorporated by reference.

Background

The vanilloid receptor 1 (VR1) is the molecular target of capsaicin, the active ingredient in hot peppers. Julius et al. reported the molecular cloning of VR1 (Caterina et al., 1997). VR1 is a non-selective cation channel which is activated or sensitized by a series of different stimuli including capsaicin and resiniferatoxin (exogenous activators), heat & acid stimulation and products of lipid bilayer metabolism, anandamide (Premkumar et al., 2000, Szabo et al., 2000, Gauldie et al., 2001, Olah et al., 2001) and lipoxygenase metabolites (Hwang et al., 2000). VR1 is highly expressed in primary sensory neurons (Caterina et al., 1997) in rats, mice and humans (Onozawa et al., 2000, Mezey et al., 2000, Helliiwell et al., 1998, Cortright et al., 2001). These sensory neurons innervate many visceral organs including the dermis, bones, bladder, gastrointestinal tract and lungs; VR1 is also expressed in other neuronal and non-neuronal tissues including but not limited to, CNS nuclei, kidney, stomach and T-cells (Nozawa et al., 2001, Yangou et al., 2001, Birder et al., 2001). Presumably expression in these various cells and organs may contribute to their basic properties such as cellular signaling and cell division.

Prior to the molecular cloning of VR1, experimentation with capsaicin indicated the presence of a capsaicin sensitive receptor, which could increase the activity of sensory neurons in humans, rats and mice (Holzer, 1991; Dray, 1992, Szallasi and Blumberg 1996, 1999). The result of acute activation by capsaicin in humans was pain at injection site and in other species increased behavioral sensitivity to sensory stimuli (Szallasi and Blumberg, 1999). Capsaicin application to the skin in humans causes a painful reaction characterized not only by the perception of heat and pain at the site of administration but also by a wider area of hyperalgesia and allodynia, two characteristic symptoms of the human condition of neuropathic pain (Holzer, 1991). Taken together, it seems likely that
increased activity of VR1 plays a significant role in the establishment and maintenance of pain conditions. Topical or intradermal injection of capsaicin has also been shown to produce localized vasodilation and edema production (Szallasi and Blumberg 1999, Singh et al., 2001). This evidence indicates that capsaicin through its activation of VR1 can regulate afferent and efferent function of sensory nerves. Sensory nerve involvement in diseases could therefore be modified by molecules, which affect the function of the vanilloid receptor to increase or decrease the activity of sensory nerves.

VR1 gene knockout mice have been shown to reduce sensory sensitivity to thermal and acid stimuli (Caterina et al., 2000). This supports the concept that VR1 contributes not only to generation of pain responses (i.e. via thermal, acid or capsaicin stimuli) but also to the maintenance of basal activity of sensory nerves. This evidence agrees with studies demonstrating capsaicin sensitive nerve involvement in disease. Primary sensory nerves in humans and other species can be made inactive by continued capsaicin stimulation. This paradigm causes receptor activation induced desensitization of the primary sensory nerve - such reduction in sensory nerve activity in vivo makes subjects less sensitive to subsequent painful stimuli. In this regard both capsaicin and resiniferatoxin (exogenous activators of VR1), produce desensitization and they have been used for many proof of concept studies in in vivo models of disease (Holzer, 1991, Dray 1992, Szallasi and Blumberg 1999).

Bibliography


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30
Summary
The present invention comprises a new class of compounds useful in the treatment of diseases, such as vanilloid-receptor-mediated diseases and other maladies, such as inflammatory or neuropathic pain and diseases involving sensory nerve function such as asthma, rheumatoid arthritis, osteoarthritis, inflammatory bowel disorders, urinary incontinence, migraine and psoriasis. In particular, the compounds of the invention are useful for the treatment of acute, inflammatory and neuropathic pain, dental pain, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, causalgia, sympathetically maintained pain, deafferentation syndromes, asthma, epithelial tissue damage or dysfunction, herpes simplex, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritus, vitiligo, general gastrointestinal disorders, gastric ulceration, duodenal ulcers, diarrhea, gastric lesions induced by necrotising agents, hair growth, vasomotor or allergic rhinitis, bronchial disorders or bladder disorders. Accordingly, the invention also comprises pharmaceutical compositions comprising the compounds, methods for the treatment of vanilloid-receptor-mediated diseases, such as inflammatory or neuropathic pain, asthma, rheumatoid arthritis, osteoarthritis, inflammatory bowel disorders, urinary incontinence, migraine and psoriasis diseases, using the compounds and compositions of the invention, and intermediates and processes useful for the preparation of the compounds of the invention.

The compounds of the invention are represented by the following general structure:
or a pharmaceutically acceptable salt thereof, wherein $R^1$, $R^2$, $R^4$, $R^5$, $J$, $m$, $X$, $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are defined below.

The foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way. All patents, patent applications and other publications recited herein are hereby incorporated by reference in their entirety.

**Detailed Description**

One aspect of the current invention relates to compounds having the general structure:

or any pharmaceutically-acceptable salt or hydrate thereof, wherein:

- $J$ is O, NH, S, S=O or S(=O)$_2$;
- $X$ is independently in each instance N or C;
- $Y^1$, $Y^2$, $Y^3$ and $Y^4$ together are selected from -X=C-X=X-, -X-C-X-, -X-N-X- and -X-N-X=X-;
- $m$ is independently at each instance, 0, 1, 2 or 3;

(a) $R^1$ is

(b) $R^2$ is
(b) $R^1$ is a saturated, partially saturated or unsaturated 9- or 10-membered bicyclic ring containing 1, 2 or 3 N atoms and 0, 1 or 2 atoms selected from O and S, wherein the bicyclic ring is substituted by 0, 1 or 2 oxo groups and is also substituted by 0, 1, 2 or 3 substituents selected from $R^6$, $C_{1-4}$ haloalkyl, halo, cyano, nitro, -C(=O)R, -C(=O)OR, -C(=O)NR$^a$R$^b$, -C(=O)NR$^a$R$^b$, -OR$^a$, -OC(=O)R, -OC(=O)NR$^a$R$^b$, -OC(=O)N(R$^a$)S(=O)$_2$R$^b$, -OC$\text{_{2-6}alkyl}$NR$^a$R$^b$, -OC$\text{_{2-6}alkyl}$OR$^a$, -SR$^a$, -S(=O)R$^b$, -S(=O)$_2$R$^b$, -S(=O)$_2$NR$^a$R$^b$, -S(=O)$_2$N(R$^a$)C(=O)R$^b$, -S(=O)$_2$N(R$^a$)C(=O)OR$^b$, -S(=O)$_2$N(R$^a$)C(=O)NR$^a$R$^b$, -NR$^a$R$^b$, -N(R$^a$)C(=O)R$^b$, -N(R$^a$)C(=O)OR$^b$, -N(R$^a$)C(=O)NR$^a$R$^b$, -N(R$^a$)C(=O)NR$^a$R$^b$, -N(R$^a$)S(=O)$_2$R$^b$, -N(R$^a$)S(=O)$_2$NR$^a$R$^b$, -NR$^a$C$_{2-6}$alkylNR$^a$R$^b$ or -NR$^a$C$_{2-6}$alkylOR$^a$; and

$R^2$ is $R^7$; and

$R^3$ is, independently, in each instance, selected from $C_{1-8}$alkyl,

$C_{1-4}$ haloalkyl, halo, cyano, nitro, -C(=O)R, -C(=O)OR, -C(=O)NR$^a$R$^b$, -C(=O)NR$^a$R$^b$, -OR$^a$, -OC(=O)R, -OC(=O)NR$^a$R$^b$, -OC(=O)N(R$^a$)S(=O)$_2$R$^b$, -OC$_{2-6}$alkylNR$^a$R$^b$, -OC$_{2-6}$alkylOR$^a$, -SR$^a$, -S(=O)R$^b$, -S(=O)$_2$R$^b$, -S(=O)$_2$NR$^a$R$^b$, -S(=O)$_2$N(R$^a$)C(=O)R$^b$, -S(=O)$_2$N(R$^a$)C(=O)OR$^b$, -S(=O)$_2$N(R$^a$)C(=O)NR$^a$R$^b$, -NR$^a$R$^b$, -N(R$^a$)C(=O)R$^b$, -N(R$^a$)C(=O)OR$^b$, -N(R$^a$)C(=O)NR$^a$R$^b$, -N(R$^a$)C(=O)NR$^a$R$^b$, -N(R$^a$)S(=O)$_2$R$^b$, -N(R$^a$)S(=O)$_2$NR$^a$R$^b$, -NR$^a$C$_{2-6}$alkylNR$^a$R$^b$ or -NR$^a$C$_{2-6}$alkylOR$^a$;

$R^4$ is selected from $C_{1-8}$alkyl, $C_{1-4}$ haloalkyl, halo, cyano, nitro, -C(=O)R, -C(=O)OR, -C(=O)NR$^a$R$^b$, -C(=O)NR$^a$R$^b$, -OR$^a$, -OC(=O)R, -OC(=O)NR$^a$R$^b$, -OC(=O)N(R$^a$)S(=O)$_2$R$^b$, -OC$_{2-6}$alkylNR$^a$R$^b$, -OC$_{2-6}$alkylOR$^a$, -SR$^a$, -S(=O)R$^b$, -S(=O)$_2$R$^b$, -S(=O)$_2$NR$^a$R$^b$, -S(=O)$_2$N(R$^a$)C(=O)R$^b$, -S(=O)$_2$N(R$^a$)C(=O)OR$^b$, -S(=O)$_2$N(R$^a$)C(=O)NR$^a$R$^b$, -NR$^a$R$^b$, -N(R$^a$)C(=O)R$^b$, -N(R$^a$)C(=O)OR$^b$, -N(R$^a$)C(=O)NR$^a$R$^b$, -N(R$^a$)C(=O)NR$^a$R$^b$, -N(R$^a$)S(=O)$_2$R$^b$, -N(R$^a$)S(=O)$_2$NR$^a$R$^b$, -NR$^a$C$_{2-6}$alkylNR$^a$R$^b$ or -NR$^a$C$_{2-6}$alkylOR$^a$;

$R^5$ is, independently, in each instance, selected from $C_{1-8}$alkyl,

$C_{1-4}$ haloalkyl, halo, cyano, nitro, oxo, -C(=O)R, -C(=O)OR, -C(=O)NR$^a$R$^b$,
-C(=NR^a)NR^bR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)R^b,
-OC_2-alkylNR^aR^a, -OC_2-alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)_2R^b, -S(=O)_2NR^aR^a,
-S(=O)_2N(R^a)C(=O)R^b, -S(=O)_2N(R^a)C(=O)OR^b, -S(=O)_2N(R^a)C(=O)NR^aR^a,
-NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a;

R^6 is, independently, in each instance, selected from C_1-8alkyl,
C_1-4haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a,
-C(=NR^a)NR^bR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)R^b,
-OC_2-alkylNR^aR^a, -OC_2-alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)_2R^b, -S(=O)_2NR^aR^a,
-S(=O)_2N(R^a)C(=O)R^b, -S(=O)_2N(R^a)C(=O)OR^b, -S(=O)_2N(R^a)C(=O)NR^aR^a,
-NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a;

R^7 is selected from R^6, R^6, C_1-4haloalkyl, halo, cyano, -C(=O)R^b,
-C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^bR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
-OC(=O)N(R^a)S(=O)_2R^b, -OC_2-alkylNR^aR^a, -OC_2-alkylOR^a, -SR^a, -S(=O)R^b,
-S(=O)_2R^b, -S(=O)_2NR^aR^a, -S(=O)_2N(R^a)C(=O)R^b, -S(=O)_2N(R^a)C(=O)OR^b,
-S(=O)_2N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b;

N(R^a)C(=O)NR^aR^a, -N(R^a)S(=O)_2R^b, -N(R^a)S(=O)_2NR^aR^a, -NR^aC_2-alkylNR^aR^a or -NR^aC_2-alkylOR^a;

R^8 is independently, at each instance, H or R^b;

R^b is independently, at each instance, phenyl, benzyl or C_1-4alkyl, the
phenyl, benzyl and C_1-4alkyl being substituted by 0, 1, 2 or 3 substituents selected
from halo, C_1-4alkyl, C_1-3haloalkyl, -OC_1-4alkyl, -NH_2, -NHC_1-4alkyl,
-N(C_1-4alkyl)C_1-4alkyl;

R^d is independently at each instance C_1-4alkyl, C_1-4haloalkyl, halo, cyano,
nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^bR^a, -OR^a, -OC(=O)R^b,
-OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)_2R^b, -OC_2-alkylNR^aR^a, -OC_2-alkylOR^a,
-SR^a, -S(=O)R^b, -S(=O)_2R^b, -S(=O)_2NR^aR^a, -S(=O)_2N(R^a)C(=O)R^b,
-S(=O)_2N(R^a)C(=O)OR^b, -S(=O)_2N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
-N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)R^b,
-N(R^a)S(=O)NR^aR^a, -NR^aC_2=alkylNR^aR^a or -NR^aC_2=alkylOR^a;

R^a is independently at each instance C_1=alkyl substituted by 0, 1, 2 or 3
substituents independently selected from R^d and additionally substituted by 0 or 1
substituents selected from R^e; and

R^e is independently at each instance a saturated, partially saturated or
unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or
11-membered bicyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O
and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo
groups and the ring is substituted by 0, 1, 2 or 3 substituents selected from
C_1=alkyl, C_1=haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a,
-C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)R^b,
-OC_2=alkylNR^aR^a, -OC_2=alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)NR^aR^a,
-S(=O)NR^aC(=O)R^b, -S(=O)NR^aC(=O)OR^b, -S(=O)NR^aC(=O)NR^aR^a,
-NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a,
-N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)R^b, -N(R^a)S(=O)NR^aR^a,
-NR^aC_2=alkylNR^aR^a and -NR^aC_2=alkylOR^a.

In another embodiment, in conjunction with any of the above and below
embodiments, J is S, S=O or S(=O)2.

In another embodiment, in conjunction with any of the above and below
embodiments, J is O.

In another embodiment, in conjunction with any of the above and below
embodiments, J is NH.

In another embodiment, in conjunction with any of the above and below
embodiments, Y^1, Y^2, Y^3 and Y^4 together are -X=C-X=X-.

In another embodiment, in conjunction with any of the above and below
embodiments, Y^1, Y^2, Y^3 and Y^4 together are -X=C-X-X-.

In another embodiment, in conjunction with any of the above and below
embodiments, Y^1, Y^2, Y^3 and Y^4 together are -X=N-X-X-.

In another embodiment, in conjunction with any of the above and below
embodiments, Y^1, Y^2, Y^3 and Y^4 together are -X=N-X=X-.
In another embodiment, in conjunction with any of the above and below embodiments, Y¹, Y², Y³ and Y⁴ together are -C=C=C=C-.

In another embodiment, in conjunction with any of the above and below embodiments, Y¹, Y², Y³ and Y⁴ together are -C-C-C=C-.

In another embodiment, in conjunction with any of the above and below embodiments, Y¹, Y², Y³ and Y⁴ together are -C-N-C=C-.

In another embodiment, in conjunction with any of the above and below embodiments, Y¹, Y², Y³ and Y⁴ together are -C-N-C=C-.

In another embodiment, in conjunction with any of the above and below embodiments, m is 0.

In another embodiment, in conjunction with any of the above and below embodiments, m is independently at each instance, 0 or 1.

In another embodiment, in conjunction with any of the above and below embodiments, R¹ is

\[ \begin{align*}
&= \text{Diagram of molecule}
&= \text{Diagram of molecule}
&= \text{Diagram of molecule}
\end{align*} \]

R² is

\[ \begin{align*}
&= \text{Diagram of molecule}
&= \text{Diagram of molecule}
&= \text{Diagram of molecule}
\end{align*} \]

In another embodiment, in conjunction with any of the above and below embodiments,

R¹ is R⁷; and

R² is a saturated, partially saturated or unsaturated 9- or 10-membered bicyclic ring containing 1, 2 or 3 N atoms and 0, 1 or 2 atoms selected from O and S, wherein the bicyclic ring is substituted by 0, 1 or 2 oxo groups and is also substituted by 0, 1, 2 or 3 substituents selected from R⁵, C₁₋₄ haloalkyl, halo, cyano, nitro, -C(=O)R⁵, -C(=O)OR⁵, -C(=O)NR²R⁶, -C(=NR²)NR²R⁶, -OR², -OC(=O)R⁵, -OC(=O)NR²R⁶, -OC(=O)N(R⁵)S(=O)₂R⁵, -OC₂₋₆alkylNR²R⁶, -OC₂₋₆alkylOR², -SR², -S(=O)R⁵, -S(=O)₂R⁵, -S(=O)₂NR²R⁶, -S(=O)₂N(R⁵)C(=O)R³, -S(=O)₂N(R⁵)C(=O)OR⁵, -S(=O)₂N(R⁵)C(=O)NR²R⁶,
-NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a,
-N(R^a)C(NR^a)NR^aR^a, -N(R^a)S(=O)_{2}R^b, -N(R^a)S(=O)_{2}NR^aR^a,
-NR^aC_{2-6}alkylNR^aR^a or -NR^aC_{2-6}alkylOR^a.

In another embodiment, in conjunction with any of the above and below embodiments, R^7 is selected from R^5.

In another embodiment, in conjunction with any of the above and below embodiments, R^7 is selected from R^5.

In another embodiment, in conjunction with any of the above and below embodiments, R^7 is selected from C_{1-6}alkyl, C_{1-4}haloalkyl, halo and -OR^a.

In another embodiment, in conjunction with any of the above and below embodiments, R^7 is selected from C_{1-6}alkyl, C_{1-4}haloalkyl, and halo.

In another embodiment, in conjunction with any of the above and below embodiments, R^7 is selected from C_{1-6}alkyl and C_{1-4}haloalkyl.

Another aspect of the invention relates to a method of treating acute, inflammatory and neuropathic pain, dental pain, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases, osteoarthritis, inflammatory bowel disorders, depression, anxiety, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, causalgia, sympathetically maintained pain, deafferentation syndromes, asthma, epithelial tissue damage or dysfunction, herpes simplex, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritus, vitiligo, general gastrointestinal disorders, gastric ulceration, duodenal ulcers, diarrhea, gastric lesions induced by necrotising agents, hair growth, vasomotor or allergic rhinitis, bronchial disorders or bladder disorders, comprising the step of administering a compound according to any of the above embodiments.
Another aspect of the invention relates to a pharmaceutical composition comprising a compound according to any of the above embodiments and a pharmaceutically-acceptable diluent or carrier.

Another aspect of the invention relates to the use of a compound according to any of the above embodiments as a medicament.

Another aspect of the invention relates to the use of a compound according to any of the above embodiments in the manufacture of a medicament for the treatment of acute, inflammatory and neuropathic pain, dental pain, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases, osteoarthritis, inflammatory bowel disorders, depression, anxiety, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, causalgia, sympathetically maintained pain, deafferentation syndromes, asthma, epithelial tissue damage or dysfunction, herpes simplex, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritus, vitiligo, general gastrointestinal disorders, gastric ulceration, duodenal ulcers, diarrhea, gastric lesions induced by necrotising agents, hair growth, vasomotor or allergic rhinitis, bronchial disorders or bladder disorders.

The compounds of this invention may have in general several asymmetric centers and are typically depicted in the form of racemic mixtures. This invention is intended to encompass racemic mixtures, partially racemic mixtures and separate enantiomers and diasteromers.

Unless otherwise specified, the following definitions apply to terms found in the specification and claims:

"C_α-alkyl" means an alkyl group comprising a minimum of α and a maximum of β carbon atoms in a branched, cyclical or linear relationship or any combination of the three, wherein α and β represent integers. The alkyl groups described in
this section may also contain one or two double or triple bonds. Examples of C₅₆ alkyl include, but are not limited to the following:

"Benzo group", alone or in combination, means the divalent radical C₄H₄=, one representation of which is -CH=CH-CH=CH-, that when vicinally attached to another ring forms a benzene-like ring—for example tetrahydronaphthalene, indole and the like.
The terms “oxo” and “thioxo” represent the groups =O (as in carbonyl) and =S (as in thiocarbonyl), respectively.

“Halo” or “halogen” means a halogen atoms selected from F, Cl, Br and I.
“Cₓ-haloalkyl” means an alkyl group, as described above, wherein any number—at least one—of the hydrogen atoms attached to the alkyl chain are replaced by F, Cl, Br or I.
“Heterocycle” means a ring comprising at least one carbon atom and at least one other atom selected from N, O and S. Examples of heterocycles that may be found in the claims include, but are not limited to, the following:
“Available nitrogen atoms” are those nitrogen atoms that are part of a heterocycle and are joined by two single bonds (e.g. piperidine), leaving an external bond available for substitution by, for example, H or CH₃. "Pharmaceutically-acceptable salt" means a salt prepared by conventional means, and are well known by those skilled in the art. The "pharmacologically acceptable salts" include basic salts of inorganic and organic acids, including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, malic acid, acetic acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, succinic acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," see infra and Berge et al., J. Pharm. Sci. 66:1 (1977).

“Saturated or unsaturated” includes substituents saturated with hydrogens, substituents completely unsaturated with hydrogens and substituents partially saturated with hydrogens.
"Leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

"Protecting group" generally refers to groups well known in the art which are used to prevent selected reactive groups, such as carboxy, amino, hydroxy, mercapto and the like, from undergoing undesired reactions, such as nucleophilic, electrophilic, oxidation, reduction and the like. Preferred protecting groups are indicated herein where appropriate. Examples of amino protecting groups include, but are not limited to, aralkyl, substituted aralkyl, cycloalkenylalkyl and substituted cycloalkenyl alkyl, allyl, substituted allyl, acyl, alkoxy carbonyl, aralkoxy carbonyl, silyl and the like. Examples of aralkyl include, but are not limited to, benzyl, ortho-methyl benzyl, trityl and benzydryl, which can be optionally substituted with halogen, alkyl, alkoxy, hydroxy, nitro, acylamino, acyl and the like, and salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthyl, indanyl, anthracenyl, 9-(9-phenylfluorenyl), phenanthrenyl, durenyl and the like. Examples of cycloalkenylalkyl or substituted cycloalkylalkyl radicals, preferably have 6-10 carbon atoms, include, but are not limited to, cyclohexenyl methyl and the like. Suitable acyl, alkoxy carbonyl and aralkoxy carbonyl groups include benzyl oxy carbonyl, t-butoxy carbonyl, iso-butoxy carbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, trifluoroacetyl, trichloro acetyl, phthaloyl and the like. A mixture of protecting groups can be used to protect the same amino group, such as a primary amino group can be protected by both an aralkyl group and an aralkoxy carbonyl group. Amino protecting groups can also form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, such as nitrophthalimidyl. Amino groups may also be protected against undesired reactions, such as oxidation, through the formation of an addition salt, such as hydrochloride, toluenesulfonic acid, trifluoroacetic acid and the like. Many
of the amino protecting groups are also suitable for protecting carboxyl, hydroxy and mercaptop groups. For example, aralkyl groups. Alkyl groups are also suitable groups for protecting hydroxy and mercapto groups, such as tert-butyl.

Silyl protecting groups are silicon atoms optionally substituted by one or more alkyl, aryl and aralkyl groups. Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of an amino groups provide mono- or di-silylamino groups. Silylation of aminoalcohol compounds can lead to a N,N,O-trisilyl derivative. Removal of the silyl function from a silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during a reaction with the alcohol group. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyl-dimethylsilyl chloride, phenyltrimethylsilyl chloride, diphenylmethyl silyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

Protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of a protecting group, such as removal of a benzylxyoxycarbonyl group by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. A tert-butoxycarbonyl protecting group can be removed utilizing an inorganic or organic acid, such as HCl or trifluoroacetic acid, in a suitable solvent system, such as dioxane or methylene chloride. The resulting amino salt can readily be neutralized to yield the free amine. Carboxy protecting group, such as methyl, ethyl, benzyl, tert-butyl, 4-methoxyphenylmethyl and the like, can be removed
under hydrolysis and hydrogenolysis conditions well known to those skilled in the art.

It should be noted that compounds of the invention may contain groups that may exist in tautomeric forms, such as cyclic and acyclic amidine and guanidine groups, heteroatom substituted heteroaryl groups (Y' = O, S, NR), and the like, which are illustrated in the following examples:

![Chemical structures](image)

and though one form is named, described, displayed and/or claimed herein, all the tautomeric forms are intended to be inherently included in such name, description, display and/or claim.

Prodrugs of the compounds of this invention are also contemplated by this invention. A prodrug is an active or inactive compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxyethyl).
Amines have been masked as aryl carbamoyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bunngaard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with Nacyloxyloxymethyl groups (Bunngaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

The specification and claims contain listing of species using the language “selected from . . . and . . .” and “is . . . or . . .” (sometimes referred to as Markush groups). When this language is used in this application, unless otherwise stated it is meant to include the group as a whole, or any single members thereof, or any subgroups thereof. The use of this language is merely for shorthand purposes and is not meant in any way to limit the removal of individual elements or subgroups as needed.
**Experimental**

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All parts are by weight and temperatures are in degrees centigrade unless otherwise indicated. All microwave-assisted reactions were conducted with a Smith Synthesizer from Personal Chemistry, Uppsala, Sweden. All compounds showed NMR spectra consistent with their assigned structures. Melting points were determined on a Buchi apparatus and are uncorrected. Mass spectral data was determined by electrospray ionization technique. All examples were purified to >90% purity as determined by high-performance liquid chromatography. Unless otherwise stated, reactions were run at room temperature.

The following abbreviations are used:

- DMSO - dimethyl sulfoxide
- DMF - \( N,N \)-dimethylformamide
- THF - tetrahydrofuran
- \( \text{Et}_2\text{O} \) - diethyl ether
- \( \text{EtOAc} \) - ethyl acetate
- MeOH - methyl alcohol
- EtOH - ethyl alcohol
- MeCN - acetonitrile
- MeI - iodomethane
- NMP - 1-methyl-2-pyrrolidinone
- DCM - dichloromethane
- TFA - trifluoroacetic acid
- Sat. - saturated
- h - hour
- min - minutes
Generic Schemes

Scheme 1

![Chemical reaction scheme with labels and arrows indicating steps involving protective groups, heat, and deprotection.]

Scheme 2

![Chemical reaction scheme with labels and arrows indicating steps involving heat and reagents.]

Example 1

(a) 7-Chloro-3H-quinazolin-4-one. A mixture of 2-amino-4-chloro-benzoic acid (17.16 g, 100 mmol, Aldrich) and formamide (55 mL, Kodak) was heated at 140 °C with stirring for 16 h. The reaction mixture was cooled to room
temperature and diluted with acetone (100 mL). The solid precipitate was filtered, washed with acetone, and dried in vacuo to give the title compound as a pale-yellow powder. MS (ESI, pos. ion) m/z: 180.9 (M+1).

(b) 4,7-Dichloro-quinazoline hydrochloride. A mixture of 7-chloro-3H-quinazolin-4-one, Example 1(a), (7.22 g, 40 mmol) and SOCl₂ (84 mL) was heated at reflux with stirring for 3 h. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The solid residue was dried in vacuo to give the title compound as a white solid, which was used in the next step without purification.

(c) (7-Chloro-quinazolin-4-yl)-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-amine hydrochloride. A mixture of 4,7-dichloro-quinazoline hydrochloride, Example 1(b), (4.71 g, 20 mmol) and 2,3-dihydro-benzo[1,4]dioxin-6-ylamine (3.325 g, 22 mmol, Aldrich) in 2-propanol (100 mL) was heated at reflux with stirring for 2 h. The reaction mixture was filtered while hot, and the filter cake was washed with acetone and dried in vacuo to give the title compound as an yellow solid. Mp 304-306 °C. MS (ESI, pos. ion) m/z: 314.3 (M+1).

**Example 2**

N-[4-(7-Chloro-quinazolin-4-ylamino)-benzothiazol-2-yl]-acetamide. To a mixture of 4,7-dichloro-quinazoline hydrochloride, Example 1(b), 0.235 g, 1 mmol) and N-(4-amino-benzothiazol-2-yl)-acetamide (0.250 g, 1.2 mmol, prepared according to the procedure described in WO03099284) in DMF (2 mL) was added sodium hydride (0.065 g, 2.7 mmol, 60% suspension in mineral oil,
Aldrich) in small portions with stirring at room temperature. The reaction mixture was stirred at room temperature for 18 h and diluted with EtOAc (100 mL). The mixture was washed with 1 N NaOH and water, dried over MgSO₄, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl₃) to give the title compound as a white solid. Mp 229.8 °C. MS (ESI, pos. ion) m/z: 371.1 (M⁺)

**Example 3**

(7-Benzyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-trifluoromethyl-phenyl)-amine. A mixture of 7-benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine (233 mg, 0.9 mmol, prepared according to the procedure described in WO2003076427), 4-trifluoromethyl-phenylamine (188 mg, 1.17 mmol, Aldrich) and 2-methoxyethanol (0.5 mL) was heated at 150 °C in a sealed glass tube with stirring for 3 h. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient, 60 to 90% EtOAc/hexane) to provide the title compound as a brown amorphous solid. MS (ESI, pos. ion.) m/z: 385 (M⁺)

**Example 4**

(a) (5,6,7,8-Tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-trifluoromethyl-phenyl)-amine. To a solution of (7-benzyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-trifluoromethyl-phenyl)-amine, Example 3, (300 mg, 0.78 mmol) in methanol (5 mL) under nitrogen was added sequentially 10 % Pd/C (200 mg, Aldrich) and ammonium formate (491 mg, 7.8 mmol, Aldrich). The resulting mixture was heated at reflux for 1 h with stirring under nitrogen atmosphere. The reaction mixture was cooled to room temperature, filtered through a pad of Celite®, and the filter cake was washed with MeOH (2 x 5 mL). The filtrates were
combined and evaporated in vacuo to provide the title compound as a brown amorphous solid (MS (ESI, pos. ion.) m/z: 295 (M+1).

(b) (4-Trifluoromethyl-phenyl)-[7-(3-trifluoromethyl-pyridin-2-yl)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl]-amine. A mixture of 2-chloro-3-trifluoromethyl-pyridine (93 mg, 0.51 mmol, TCI America), (5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-trifluoromethyl-phenyl)-amine, Example 4(a), (125 mg, 0.42 mmol) and 2-methoxyethanol (0.3 mL) was heated in a sealed glass tube at 150 °C with stirring for 24 h. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient, 50 to 90% EtOAc/hexane) to provide the title compound as a brown amorphous solid. MS (ESI, pos. ion.) m/z: 440 (M+1).

Example 5

7-(3,5-Difluoropyridin-2-yl)-N-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine. A mixture of 2,3,5-trifluoropyridine (134 mg, 1.0 mmol, Oakwood) and 5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-trifluoromethyl-phenyl)-amine, Example 4(a), (100 mg, 0.34 mmol) in 2-methoxyethanol (0.5 mL) was heated in a microwave synthesizer at 185 °C for 45 min. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient, 30 to 70% EtOAc/hexane) to provide the title compound as a light-yellow amorphous solid. MS (ESI, pos. ion.) m/z: 408 (M+1).
Example 6

7-(3,5-Dichloropyridin-2-yl)-N-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine. This material was prepared analogously to the procedure described in Example 5. 2,3,5-Trichloropyridine (141 mg, 0.77 mmol, Aldrich) reacted with 5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-trifluoromethyl-phenyl)-amine, Example 4(a), (150 mg, 0.51 mmol) in 2-methoxyethanol (0.5 mL) to give after purification by silica gel column chromatography (gradient, 50 to 90% EtOAc/hexane) the title compound as an off-white crystalline solid. MS (ESI, pos. ion.) m/z: 441 (M+1).

Example 7

[7-(3-Chloro-pyridin-2-yl)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl]-(4-trifluoromethyl-phenyl)-amine. This material was prepared analogously to the procedure described in Example 4(b). 2,3-Dichloro-pyridine (23 mg, 0.22 mmol, Aldrich) reacted with (5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-trifluoromethyl-phenyl)-amine, Example 4(a), (50 mg, 0.17 mmol) to give after purification by silica gel column chromatography (gradient, 50 to 90% EtOAc/hexane) the title compound as an off-white amorphous solid. MS (ESI, pos. ion.) m/z: 406 (M+1).

Example 8
{5-Chloro-6-[4-(4-trifluoromethyl-phenylamino)-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl]-pyridin-3-yl}-methanol. This material was prepared analogously to the procedure described in Example 4(b). (5,6-Dichloro-pyridin-3-yl)-methanol (81 mg, 0.455 mmol, TCI America) reacted with (5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-trifluoromethyl-phenyl)-amine, Example 4(a), (103 mg, 0.35 mmol) to give after purification by silica gel column chromatography (gradient, 70 to 100% EtOAc/hexane) the title compound as an off-white amorphous solid. MS (ESI, pos. ion.) m/z: 436 (M+1).

Example 9

(7-Benzyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(6-trifluoromethyl-pyridin-3-yl)-amine. This material was prepared analogously to the procedure described in Example 3. 7-Benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine, (300 mg, 1.15 mmol, prepared according to the procedure described in WO2003076427) reacted with 6-trifluoromethyl-pyridin-3-ylamine (243 mg, 1.5 mmol, Oakwood) to give after purification by silica gel column chromatography (gradient, 50 to 80% EtOAc/hexane) the title compound as a brown amorphous solid. MS (ESI, pos. ion.) m/z: 386 (M+1).

Example 10

(a) (5,6,7,8-Tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(6-trifluoromethyl-pyridin-3-yl)-amine. This material was prepared analogously to the procedure described in Example 4(a). (7-Benzyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(6-trifluoromethyl-pyridin-3-yl)-amine, Example 9, (250 mg, 0.65 mmol) reacted with 10% Pd/C (150 mg, Aldrich) and ammonium formate (410 mg, 6.5 mmol, Aldrich) to give the title compound. MS (ESI, pos. ion.) m/z: 296 (M+1).
(b) (6-Trifluoromethyl-pyridin-3-yl)-(7-(3-trifluoromethyl-pyridin-2-yl)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-amine. This material was prepared analogously to the procedure described in Example 4(b). (5,6,7,8-Tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(6-trifluoromethyl-pyridin-3-yl)-amine, Example 10(a), (86 mg, 0.29 mmol) reacted with 2-chloro-3-trifluoromethyl-pyridine (69 mg, 0.38 mmol, TCI America) to give after purification by silica gel column chromatography (gradient, 50 to 100% EtOAc/hexanes) the title compound as a tan crystalline solid. Mp 144.5-150.0 °C. MS (ESI, pos. ion.) m/z: 441 (M+1).

Example 11

(7-Benzyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-tert-butyl-cyclohexyl)-amine. A mixture of 7-benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine (260 mg, 1.0 mmol, prepared according to the procedure described in WO2003076427) and 4-tert-butyl-cyclohexylamine (186 mg, 1.2 mmol, TCI-America) in isopropanol (2 mL) was heated in a microwave synthesizer at 185 °C for 30 min. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient, 25 to 80% EtOAc/hexane) to provide the title compound as a light-yellow amorphous solid. MS (ESI, pos. ion.) m/z: 379 (M+1).

Example 12
a) (4-tert-Butyl-cyclohexyl)-(5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-amine. This material was prepared analogously to the procedure described in Example 4(a). (7-Benzyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-tert-butyl-cyclohexyl)-amine, Example 11, (150 mg, 0.4 mmol) reacted with 10% Pd/C (43 mg, Aldrich) and ammonium formate (252 mg, 4 mmol, Aldrich) to give the title compound. MS (ESI, pos. ion.) m/z: 289 (M+1).

(b) (4-tert-Butyl-cyclohexyl)-(7-(3-chloro-pyridin-2-yl)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-amine. A mixture of (4-tert-butyl-cyclohexyl)-(5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-amine, Example 12(a), (80 mg, 0.28 mmol), 2,3-dichloro-pyridine (63 mg, 0.42 mmol, Aldrich) and NaHCO₃ (29 mg, 0.34 mmol) in isopropanol (2 mL) was heated in a microwave synthesizer at 185 °C for 25 min. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient, 25 to 90% EtOAc/hexane) to provide the title compound as an yellow amorphous solid. MS (ESI, pos. ion.) m/z: 400 (M+1).

Example 13

(4-tert-Butyl-cyclohexyl)-(7-(3-trifluoromethyl-pyridin-2-yl)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-amine. A mixture of (4-tert-butyl-cyclohexyl)-(5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-amine, Example 12(a), (100 mg, 0.35 mmol), 2-chloro-3-trifluoromethyl-pyridine (82 mg, 0.46 mmol, TCI America) and K₂CO₃ (97 mg, 0.7 mmol) in DMF (3 mL) was heated at 90 °C in a sealed glass tube with stirring for 3 h. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by
silica gel column chromatography (gradient, 30 to 90% EtOAc/hexane) to provide the title compound as a light-yellow amorphous solid. MS (ESI, pos. ion.) m/z: 434 (M+1).

**Example 14**

(7-Benzyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-tert-butyl-phenyl)-amine. This material was prepared according to the method described in Example 11. 7-Benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine (240 mg, 0.92 mmol, prepared according to the procedure described in WO2003076427) reacted with 4-tert-butyl-phenylaniline (208 mg, 1.4 mmol, Aldrich) in isopropanol (1.0 mL) and dioxane (1.0 mL) to give after purification by silica gel column chromatography (gradient, 50 to 100% EtOAc/hexanes) the title compound as a light-yellow amorphous solid. MS (ESI, pos. ion.) m/z: 373 (M+1).

**Example 15**

a) (4-tert-Butyl-phenyl)-(5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-amine. This material was prepared analogously to the procedure described in Example 4(a). (7-Benzyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-(4-tert-butyl-phenyl)-amine, Example 14, (240 mg, 0.64 mmol) reacted with 10% Pd/C (240 mg, Aldrich) and ammonium formate (412 mg, 6.4 mmol, Aldrich) to give the title compound. MS (ESI, pos. ion.) m/z: 283 (M+1).
(b) (4-tert-Butyl-phenyl)\text{-}[7-(3-trifluoromethyl-pyridin-2-yl)-5,6,7,8-tetrahydro-
pyrido[3,4-d]pyrimidin-4-yl]-amine. To a mixture of (4-tert-butyl-phenyl)-
(5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-amine, Example 15(a), (100 mg,
0.35 mmol) and 2-chloro3-trifluoromethyl-pyridine (63 mg, 0.42 mmol, TCI
America) in DMF (3 mL) was added NaH (18 mg, 0.7 mmol, 95%, Aldrich) at 0
°C. The mixture was stirred at 0 °C for 30 min, and then at 50 °C for 2 h. The
reaction mixture was cooled to room temperature, quenched with saturated NH₄Cl
(5 mL), and extracted with EtOAc (2 x 10 mL). The combined EtOAc layers
were dried over MgSO₄, filtered, and evaporated under reduced pressure. The
residue was purified by silica gel column chromatography (gradient, 20 to 95%
EtOAc/hexane) to give the title compound as a brown amorphous solid. MS (ESI,
pos. ion.) m/z: 428 (M+1).

Example 16

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(a) 7-Benzyl-4-(4-tert-butyl-phenoxy)-5,6,7,8-tetrahydro-pyrido[3,4-
d]pyrimidine. To a solution of 4-tert-butyl-phenol (225 mg, 1.5 mmol, Aldrich)
in DMF (3 mL) was added NaH (38 mg, 1.5 mmol, 95%, Aldrich), and the
mixture was stirred at 0 °C for 10 min. A solution of 7-benzyl-4-chloro-5,6,7,8-
tetrahydro-pyrido[3,4-d]pyrimidine (260 mg, 1.0 mmol, prepared according to the
procedure described in WO2003076427) in DMF (2 mL) was then added, and the
resulting mixture was heated at 60 °C with stirring for 3 h. The reaction mixture
was cooled to room temperature and partitioned between EtOAc (50 mL) and 1 N
NaOH (5 mL). The EtOAc layer was separated, dried over MgSO₄, filtered, and
concentrated under reduced pressure. Purification of the residue by silica gel
column chromatography (gradient, 20 to 80% EtOAc/hexane) provided the title
compound as a white solid. MS (ESI, pos. ion.) m/z: 374 (M+1).
(b) 4-(4-tert-Butyl-phenoxy)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine. This material was prepared analogously to the procedure described in Example 4(a). 7-Benzyl-4-(4-tert-butyl-phenoxy)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine, Example 16(a), (150 mg, 0.4 mmol) reacted with 10% Pd/C (100 mg, Aldrich) and ammonium formate (252 mg, 4 mmol, Aldrich) to give the title compound. MS (ESI, pos. ion.) m/z: 284 (M+1).

(c) 4-(4-tert-Butyl-phenoxy)-7-(3-trifluoromethyl-pyridin-2-yl)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine. A solution of 4-(4-tert-butyl-phenoxy)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine, Example 16(b), (100 mg, 0.4 mmol), triethyl amine (0.1 mL) and 2-chloro-3-trifluoromethyl-pyridine (63 mg, 0.42 mmol) in 3-methyl-1-butanol (2 mL) was heated in a microwave synthesizer at 220 °C for 30 min. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by reversed phase HPLC (gradient, 10 to 95% of (0.1% TFA in CH₂CN) in (0.1% TFA in water). The pure fractions containing the product were combined and evaporated under reduced pressure. The residue was dissolved in EtOAc (20 mL), washed with saturated NaHCO₃ (3 mL), dried over MgSO₄, filtered, and evaporated in vacuo to give the title compound as a brown amorphous solid. MS (ESI, pos. ion.) m/z: 429 (M+1).
Example 17

4-(4-tert-Butyl-phenoxy)-7-(3-trifluoromethyl-pyridin-2-yl)-quinazoline: A mixture of 4-chloro-7-(3-trifluoromethyl-pyridin-2-yl)-quinazoline (214 mg, 0.69 mmol, prepared according to the procedure described in WO2003062209), 4-tert-butyl-phenol (135 mg, 0.9 mmol, Aldrich) and K₂CO₃ (139 mg, 1.0 mmol) in DMF (3 mL) was heated at 90 °C with stirring for 5 h. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient, 20 to 80% EtOAc/hexane) to provide the title compound as a white solid. Mp 162-163 °C. MS (ESI, pos. ion.) m/z: 424 (M+1).

Example 18

4-(4-tert-Butyl-cyclohexyloxy)-7-(3-trifluoromethyl-pyridin-2-yl)-quinazoline. To a solution of 4-tert-butyl-cyclohexanol (300 mg, 1.9 mmol, Aldrich) in THF (2 mL) and DMF (1 mL) was added NaH (51 mg, 2.0 mmol, 95%, Aldrich), and the mixture was stirred at 0 °C for 10 min. To the mixture was added 4-chloro-7-(3-trifluoromethyl-pyridin-2-yl)-quinazoline (350 mg, 1.13 mmol, prepared according to the procedure described in WO2003062209), and the stirring was continued for 2 h at room temperature. The reaction mixture was partitioned between EtOAc (50 mL) and saturated NH₄Cl (5 mL). The EtOAc layer was separated, dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (gradient, 20 to 80% EtOAc/hexane) provided the title compound as a white solid. MS (ESI, pos. ion.) m/z: 430 (M+1).
Example 19

\[
\text{N-}(4-(\text{Trifluoromethyl})\text{-phenyl})-7-(3-(\text{trifluoromethyl})\text{-2-pyridinyl})-4-\text{quinazolinamine}. \text{ A mixture of 4-chloro-7-} (\text{trifluoromethyl})\text{-2-pyridin-2-yl)}\text{-quinazoline (200 mg, 0.64 mmol, prepared according to the procedure described in WO2003062209) and 4-trifluoromethyl-aniline (104 mg, 0.64 mmol, Aldrich) in isopropanol (2 mL) was heated in a microwave synthesizer at 120 °C for 10 min. The reaction mixture was cooled to room temperature, diluted with DCM (10 mL), and filtered. The filter cake was washed consecutively with sat. aqueous solution of NaHCO₃, water and EtOAc, and dried in vacuo to afford the title compound as a yellow amorphous solid. MS (ESI, pos. ion.) } m/z: 435 (M+1).}
\]

Example 20

\[
\text{N-}(4-\text{tert-Butylcyclohexyl})-7-(3-(\text{trifluoromethyl})\text{-pyridin-2-yl)}\text{quinazolin-4-amine. This material was prepared analogously to the procedure described in Example 19. 4-Chloro-7-} (\text{trifluoromethyl})\text{-2-pyridin-2-yl)}\text{-quinazoline (120 mg, 0.39 mmol, prepared according to the procedure described in WO2003062209) reacted with 4-tert-butylcyclohexanamine (66 mg, 0.42 mmol} \text{ in isopropanol (2 mL) to afford the title compound as a yellow crystalline solid. MS (ESI, pos. ion.) } m/z: 429 (M+1).}
\]
Example 21

\[
\begin{align*}
\text{CF}_3 & \\
\text{N} & \\
\text{CF}_3 & \\
\text{N} & \\
\text{N} & \\
\text{H} & \\
\text{CF}_3 & \\
\end{align*}
\]

4-(4-(Trifluoromethyl)phenylamino)-7-(3-(trifluoromethyl)pyridin-2-yl)-6,7-dihydropyrido[3,4-d]pyrimidin-8(5H)-one. KMnO\(_4\) (36 mg, 0.22 mmol) was added to a mixture of (4-trifluoromethyl-phenyl)-[7-(3-trifluoromethyl-pyridin-2-yl)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl]-amine, Example 4(b), (100 mg, 0.23 mmol), and MgSO\(_4\) (47 mg, 0.39 mmol) in acetone (3.2 mL) and water (1.6 mL). The mixture was stirred at room temperature for 10 min, a second portion of KMnO\(_4\) (26 mg, 0.16 mmol) was added, and the stirring was continued for 2 h. The reaction mixture was filtered through a pad of Celite\textsuperscript{®}, and the filter cake was washed with acetone (50 mL). The filtrates were combined and evaporated in vacuo. The aqueous residue was extracted with EtOAc (2x30 mL). The combined EtOAc extracts were washed with sat. sodium thiosulfate, dried over MgSO\(_4\), filtered, and evaporated under reduced pressure. The brown residue was purified by silica gel column chromatography [gradient, 1 to 8% (2M NH\(_3\) in MeOH)/DCM] to provide the title compound as a brown amorphous solid. MS (ESI, pos. ion.) \(m/z\): 454 (M+1).

Example 22

\[
\begin{align*}
\text{CF}_3 & \\
\text{N} & \\
\text{HCl} & \\
\text{N} & \\
\text{CF}_3 & \\
\text{N} & \\
\text{Cl} & \\
\text{CF}_3 & \\
\end{align*}
\]

(a) 2-(Chloromethyl)-N-(4-(trifluoromethyl)phenyl)-7-(3-(trifluoromethyl)pyridin-2-yl)quinazolin-4-amine hydrochloride. A mixture of 4-chloro-2-(chloromethyl)-7-(3-(trifluoromethyl)pyridine-2-yl)quinazoline (300 mg, 0.837 mmol, prepared according to the procedure described in WO03/062209) and 4-(trifluoromethyl)benzeamine (161 mg, 1.00 mmol, Aldrich) in MeOH (2
mL) was heated in a microwave synthesizer at 140 °C for 10 min. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was washed with DCM, filtered and dried in vacuo to afford the title compound as a light-brown amorphous solid. MS (ESI, pos. ion.) m/z: 483 (M+1).

(b) 2-(Piperidin-1-ylmethyl)-N-(4-(trifluoromethyl)phenyl)-7-(3-(trifluoromethyl)pyridin-2-yl)quinazolin-4-amine. A mixture of 2-(chloromethyl)-N-(4-(trifluoromethyl)phenyl)-7-(3-trifluoromethyl)pyridine-2-yl)quinazolin-4-amine hydrochloride, Example 22(a), (50 mg, 0.103 mmol), piperidine (18 mg, 0.207 mmol) and sodium carbonate (10 mg, 0.103 mmol) in acetonitrile (2 mL) was heated in a microwave synthesizer at 80 °C for 10 min. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (gradient, 0 to 30% EtOAc/hexane) to afford the title compound as an amorphous off-white solid. MS (ESI, pos. ion.) m/z: 532 (M+1).

**Capsaicin-induced Ca2+ influx in primary dorsal root ganglion neurons**

Embryonic 19 day old (E19) dorsal root ganglia (DRG) were dissected from timed-pregnant, terminally anesthetized Sprague-Dawley rats (Charles River, Wilmington, MA) and collected in ice-cold L-15 media (Life Technologies, Grand Island, NY) containing 5% heat inactivated horse serum (Life Technologies). The DRG were then dissociated into single cell suspension using a papain dissociation system (Worthington Biochemical Corp., Freehold, NJ). The dissociated cells were pelleted at 200 x g for 5 min and re-suspended in EBSS containing 1 mg/ml ovomucoid inhibitor, 1 mg/ml ovalbumin and 0.005% DNase. Cell suspension was centrifuged through a gradient solution containing 10 mg/ml ovomucoid inhibitor, 10 mg/ml ovalbumin at 200 x g for 6 min to remove cell
debris; and filtered through a 88-μm nylon mesh (Fisher Scientific, Pittsburgh, PA) to remove any clumps. Cell number was determined with a hemocytometer and cells were seeded into poly-ornithine 100 μg/ml (Sigma) and mouse laminin 1 μg/ml (Life Technologies)-coated 96-well plates at 10 x 10⁶ cells/well in complete medium. The complete medium consists of minimal essential medium (MEM) and Ham’s F12, 1:1, penicillin (100 U/ml), and streptomycin (100 μg/ml), and nerve growth factor (10ng/ml), 10% heat inactivated horse serum (Life Technologies). The cultures were kept at 37 °C, 5% CO₂ and 100% humidity. For controlling the growth of non-neuronal cells, 5-fluoro-2'-deoxyuridine (75μM) and uridine (180μM) were included in the medium. Activation of VR1 is achieved in these cellular assays using either a capsaicin stimulus (ranging from 0.01-10μM) or by an acid stimulus (addition of 30mM Hepes/Mes buffered at pH 4.1). Compounds are also tested in an assay format to evaluate their agonist properties at VR1.

Capsaicin Antagonist Assay: E-19 DRG cells at 5 days in culture are incubated with serial concentrations of VR1 antagonists, in HBSS (Hanks buffered saline solution supplemented with BSA 0.1mg/ml and 1 mM Hepes at pH 7.4) for 15 min, 37 °C. Cells are then challenged with a VR1 agonist, capsaicin 200 nM, in activation buffer containing 0.1mg/ml BSA, 15 mM Hepes, pH 7.4, and 10 μCi/ml ⁴⁵Ca²⁺ (Amersham) in Ham’s F12 for 2 min at 37 °C.

Acid Antagonist Assay: Compounds are pre-incubated with E-19 DRG cells for 2 minutes prior to addition of Calcium-45 in 30mM Hepes/Mes buffer (Final Assay pH 5) and then left for an additional 2 minutes prior to compound washout. Final 45Ca (Amersham CES3-2mCi) at 10 μCi/mL.

Agonist Assay: Compounds are incubated with E-19 DRG cells for 2 minutes in the presence of Calcium-45 prior to compound washout. Final ⁴⁵Ca²⁺ (Amersham CES3-2mCi) at 10μCi/mL.

Compound Washout and Analysis: Assay plates are washed using an ELX405 plate washer (Bio-Tek Instruments Inc.) immediately after functional assay. Wash 3 X with PBS Mg²+Ca²+ free, 0.1 mg/mL BSA. Aspirate between washes. Read
plates using a MicroBeta Jet (Wallac Inc.). Compound activity is then calculated using appropriate computational algorithms.

45Calcium2+ Assay Protocol

Compounds may be assayed using Chinese Hamster Ovary cell lines stably expressing either human VR1 or rat VR1 under a CMV promoter. Cells can be cultured in Growth Medium, routinely passaged at 70% confluency using trypsin and plated in the assay plate 24 hours prior to compound evaluation.

Possible Growth Medium:

- DMEM, high glucose (Gibco 11965-084).
- 10% Dialyzed serum (HyClone SH30079.03).
- 1X Non-Essential Amino Acids (Gibco 11140-050).
- 1X Glutamine-Pen-Strep (Gibco 10378-016).
- Geneticin, 450μg/mL (Gibco 10131-035).

Compounds can be diluted in 100% DMSO and tested for activity over several log units of concentration [40μM-2pM]. Compounds may be further diluted in HBSS buffer (pH 7.4) 0.1 mg/mL BSA, prior to evaluation. Final DMSO concentration in assay would be 0.5%. Each assay plate can be controlled with a buffer only and a known antagonist compound (either capsazepine or one of the described VR1 antagonists).

Activation of VR1 can be achieved in these cellular assays using either a capsaicin stimulus (ranging from 0.1-1μM) or by an acid stimulus (addition of 30mM Hepes/Mes buffered at pH 4.1). Compounds may also tested in an assay format to evaluate their agonist properties at VR1.

Capsaicin Antagonist Assay: Compounds may be pre-incubated with cells (expressing either human or rat VR1) for 2 minutes prior to addition of Calcium-45 and Capsaicin and then left for an additional 2 minutes prior to compound washout. Capsaicin (0.5nM) can be added in HAM's F12, 0.1 mg/mL BSA, 15 mM Hepes at pH 7.4. Final 45Ca (Amersham CES3-2mCi) at 10μCi/mL.

Acid Antagonist Assay: Compounds can be pre-incubated with cells (expressing either human or rat VR1) for 2 minutes prior to addition of Calcium-45 in 30mM Hepes/Mes buffer (Final Assay pH 5) and then left for an additional 2 minutes prior to compound washout. Final 45Ca (Amersham CES3-2mCi) at 10μCi/mL.
Agonist Assay: Compounds can be incubated with cells (expressing either human or rat VR1) for 2 minutes in the presence of Calcium-45 prior to compound washout. Final $^{45}$Ca (Amersham CES3-2mCi) at 10$\mu$Ci/mL.

Compound Washout and Analysis: Assay plates can be washed using an ELX405 plate washer (Bio-Tek Instruments Inc.) immediately after functional assay. One can wash 3 X with PBS $\text{Mg}^{2+}/\text{Ca}^{2+}$ free, 0.1 mg/mL BSA, aspirating between washes. Plates may be read using a MicroBeta Jet (Wallac Inc.). Compound activity may then be calculated using appropriate computational algorithms.

Useful nucleic acid sequences and proteins may be found in U.S. Patent Nos. 6,335,180, 6,406,908 and 6,239,267, herein incorporated by reference in their entirety.

For the treatment of vanilloid-receptor-diseases, such as acute, inflammatory and neuropathic pain, dental pain, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, causalgia, sympathetically maintained pain, deafferentation syndromes, asthma, epithelial tissue damage or dysfunction, herpes simplex, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritus, vitiligo, general gastrointestinal disorders, gastric ulceration, duodenal ulcers, diarrhea, gastric lesions induced by necrotising agents, hair growth, vasomotor or allergic rhinitis, bronchial disorders or bladder disorders, the compounds of the present invention may be administered orally, parentally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes, subcutaneous, intravenous, intramuscular, intrasternal, infusion techniques or intraperitoneally.
Treatment of diseases and disorders herein is intended to also include the prophylactic administration of a compound of the invention, a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject (i.e., an animal, preferably a mammal, most preferably a human) believed to be in need of preventative treatment, such as, for example, pain, inflammation and the like.

The dosage regimen for treating vanilloid-receptor-mediated diseases, cancer, and/or hyperglycemia with the compounds of this invention and/or compositions of this invention is based on a variety of factors, including the type of disease, the age, weight, sex, medical condition of the patient, the severity of the condition, the route of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. Dosage levels of the order from about 0.01 mg to 30 mg per kilogram of body weight per day, preferably from about 0.1 mg to 10 mg/kg, more preferably from about 0.25 mg to 1 mg/kg are useful for all methods of use disclosed herein.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a capsule, a tablet, a suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a given amount of the active ingredient. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg, more preferably from about 5 to 150 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The daily parenteral dosage regimen will be from about 0.1 to about 30 mg/kg of total body
weight, preferably from about 0.1 to about 10 mg/kg, and more preferably from about 0.25 mg to 1 mg/kg.

Injectable preparations, such as sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known are using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butandiol. Among the acceptable vehicles and solvents that may be employed are water, Ringer’s solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (e.g., liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose.

For administration, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids,
acacia, gelatin, sodium alginate, polyvinyl-pyrrolidone, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glycercyl monostearate or glycercyl distearate alone or with a wax, or other materials well known in the art.

The pharmaceutical compositions may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (e.g., solutions, suspensions, or emulsions). The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an
optically active acid or base. Examples of appropriate acids are tartaric, diacetyl tartaric, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Likewise, the compounds of this invention may exist as isomers, that is compounds of the same molecular formula but in which the atoms, relative to one another, are arranged differently. In particular, the alkylene substituents of the compounds of this invention, are normally and preferably arranged and inserted into the molecules as indicated in the definitions for each of these groups, being read from left to right. However, in certain cases, one skilled in the art will appreciate that it is possible to prepare compounds of this invention in which these substituents are reversed in orientation relative to the other atoms in the molecule. That is, the substituent to be inserted may be the same as that noted above except that it is inserted into the molecule in the reverse orientation. One skilled in the art will appreciate that these isomeric forms of the compounds of this invention are to be construed as encompassed within the scope of the present invention.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. The salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentane propionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride,
hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate,
methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate,
persulfate, 2-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate,
thiocyanate, tosylate, mesylate, and undecanoate. Also, the basic nitrogen-
containing groups can be quaternized with such agents as lower alkyl halides, such
as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates
like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as
decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides
like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible
products are thereby obtained.

Examples of acids that may be employed to from pharmaceutically
acceptable acid addition salts include such inorganic acids as hydrochloric acid,
sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic
acid, succinic acid and citric acid. Other examples include salts with alkali metals
or alkaline earth metals, such as sodium, potassium, calcium or magnesium or
with organic bases.

Also encompassed in the scope of the present invention are
pharmaceutically acceptable esters of a carboxylic acid or hydroxyl containing
group, including a metabolically labile ester or a prodrug form of a compound of
this invention. A metabolically labile ester is one, which may produce, for
example, an increase in blood levels and prolong the efficacy of the corresponding
non-esterified form of the compound. A prodrug form is one, which is not in an
active form of the molecule as administered but which becomes therapeutically
active after some in vivo activity or biotransformation, such as metabolism, for
example, enzymatic or hydrolytic cleavage. For a general discussion of prodrugs
involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988)
carboxylate anion include a variety of esters, such as alkyl (for example, methyl,
ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-
methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl).
Amines have been masked as arylcarbonyloxymethyl substituted derivatives
which are cleaved by esterases in vivo releasing the free drug and formaldehyde
(Bungard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use. Esters of a compound of this invention, may include, for example, the methyl, ethyl, propyl, and butyl esters, as well as other suitable esters formed between an acidic moiety and a hydroxyl containing moiety. Metabolically labile esters, may include, for example, methoxymethyl, ethoxymethyl, iso-propoxymethyl, α-methoxyethyl, groups such as α-((C₁-C₄)alkyloxy)ethyl, for example, methoxyethyl, ethoxyethyl, propoxyethyl, iso-propoxyethyl, etc.; 2-oxo-1,3-dioxolen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, etc.; C₁-C₃ alkylthiomethyl groups, for example, methylthiomethyl, ethylthiomethyl, isopropylthiomethyl, etc.; acyloxymethyl groups, for example, pivaloyloxymethyl, α-acetoxymethyl, etc.; ethoxycarbonyl-1-methyl; or α-acyloxy-α-substituted methyl groups, for example α-aceetoxyethyl.

Further, the compounds of the invention may exist as crystalline solids which can be crystallized from common solvents such as ethanol, N,N-dimethylformamide, water, or the like. Thus, crystalline forms of the compounds of the invention may exist as polymorphs, solvates and/or hydrates of the parent compounds or their pharmaceutically acceptable salts. All of such forms likewise are to be construed as falling within the scope of the invention.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes, which are obvious to one skilled in the art, are intended to be within the scope and nature of the invention, which are defined, in the appended claims.
From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.
We Claim:

1. A compound having the structure:

![Chemical Structure Diagram]

or any pharmaceutically-acceptable salt or hydrate thereof, wherein:

- J is O, NH, S, S=O or S(=O)₂;
- X is independently in each instance N or C;
- Y¹, Y², Y³ and Y⁴ together are selected from -X=C-X=X-, -X-C-X-X-, -X-N-X- and -X-N-X=X-;

- m is independently at each instance, 0, 1, 2 or 3;

(a) \( R^1 \) is

![Chemical Structure Diagram]

and

(b) \( R^1 \) is a saturated, partially saturated or unsaturated 9- or 10-membered bicyclic ring containing 1, 2 or 3 N atoms and 0, 1 or 2 atoms selected from O and S, wherein the bicyclic ring is substituted by 0, 1 or 2 oxo groups and is also substituted by 0, 1, 2 or 3 substituents selected from \( R^6 \), \( C_{1-6} \) haloalkyl, halo, cyano, nitro, -C(=O)R, -C(=O)OR, -C(=O)NR²R, -C(NR³)NR²R, -OR, -OC(=O)R, -OC(=O)NR²R, -OC(=O)N(R)S(O)₂R, -OC₂₅alkylNR²R, -OC₂₅alkylOR, -SR, -S(=O)R, -S(=O)₂R, -S(=O)₂NR²R,
- 46 -

-S(=O)₂N(R₄)C(=O)R₅, -S(=O)₂N(R₄)C(=O)OR₅, -S(=O)₂N(R₄)C(=O)NR₄R₅,  
-NR₄R₅, -N(R₄)C(=O)R₅, -N(R₄)C(=O)OR₅, -N(R₄)C(=O)NR₄R₅,  
-N(R₄)₂C(=NR₄)NR₄R₅, -N(R₄)₂S(=O)₂R₅, -N(R₄)₂S(=O)₂NR₄R₅,  
-NR₄C₂₋₆alkylNR₄R₅ or -NR₄C₂₋₆alkylOR₅; and

R² is R⁷; and

R³ is, independently, in each instance, selected from C₁₋₄alkyl,  
C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R⁵, -C(=O)OR⁵, -C(=O)NR₄R₅,  
-C(=NR₄)NR₄R₅, -OR₅, -OC(=O)R⁵, -OC(=O)NR₄R₅, -OC(=O)NR₄R₅S(=O)₂R₅,  
-OC₂₋₆alkylNR₄R₅, -OC₂₋₆alkylOR₅, -SR₅, -S(=O)₂R₅, -S(=O)₂NR₄R₅,  
-S(=O)₂N(R₄)C(=O)R₅, -S(=O)₂N(R₄)C(=O)OR₅, -S(=O)₂N(R₄)C(=O)NR₄R₅,  
-NR₄R₅, -N(R₄)C(=O)R₅, -N(R₄)C(=O)OR₅, -N(R₄)C(=O)NR₄R₅,  
-N(R₄)₂C(=NR₄)NR₄R₅, -N(R₄)₂S(=O)₂R₅, -N(R₄)₂S(=O)₂NR₄R₅,  
-NR₄C₂₋₆alkylNR₄R₅ or -NR₄C₂₋₆alkylOR₅;

R⁴ is selected from C₁₋₄alkyl, C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R⁵,  
-C(=O)OR⁵, -C(=O)NR₄R₅, -C(=NR₄)NR₄R₅, -OR₅, -OC(=O)R⁵, -OC(=O)NR₄R₅,  
-OC(=O)NR₄R₅S(=O)₂R₅, -OC₂₋₆alkylNR₄R₅, -OC₂₋₆alkylOR₅, -SR₅, -S(=O)₂R₅,  
-S(=O)₂NR₄R₅, -S(=O)₂N(R₄)C(=O)R₅, -S(=O)₂N(R₄)C(=O)OR₅, -S(=O)₂N(R₄)C(=O)NR₄R₅,  
-NR₄R₅, -N(R₄)C(=O)R₅, -N(R₄)C(=O)OR₅, -N(R₄)C(=O)NR₄R₅,  
-N(R₄)₂C(=NR₄)NR₄R₅, -N(R₄)₂S(=O)₂R₅, -N(R₄)₂S(=O)₂NR₄R₅,  
-NR₄C₂₋₆alkylNR₄R₅ or -NR₄C₂₋₆alkylOR₅;

R⁵ is, independently, in each instance, selected from C₁₋₄alkyl,  
C₁₋₄haloalkyl, halo, cyano, nitro, oxo, -C(=O)R⁵, -C(=O)OR⁵, -C(=O)NR₄R₅,  
-C(=NR₄)NR₄R₅, -OR₅, -OC(=O)R⁵, -OC(=O)NR₄R₅, -OC(=O)NR₄R₅S(=O)₂R₅,  
-OC₂₋₆alkylNR₄R₅, -OC₂₋₆alkylOR₅, -SR₅, -S(=O)₂R₅, -S(=O)₂NR₄R₅,  
-S(=O)₂N(R₄)C(=O)R₅, -S(=O)₂N(R₄)C(=O)OR₅, -S(=O)₂N(R₄)C(=O)NR₄R₅,  
-NR₄R₅, -N(R₄)C(=O)R₅, -N(R₄)C(=O)OR₅, -N(R₄)C(=O)NR₄R₅,  
-N(R₄)₂C(=NR₄)NR₄R₅, -N(R₄)₂S(=O)₂R₅, -N(R₄)₂S(=O)₂NR₄R₅,  
-NR₄C₂₋₆alkylNR₄R₅ or -NR₄C₂₋₆alkylOR₅;

R⁶ is, independently, in each instance, selected from C₁₋₄alkyl,  
C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R⁵, -C(=O)OR⁵, -C(=O)NR₄R₅,  
-C(=NR₄)NR₄R₅, -OR₅, -OC(=O)R⁵, -OC(=O)NR₄R₅, -OC(=O)NR₄R₅S(=O)₂R₅,
-OC₂₅₆alkylNR²R⁴, -OC₂₅₆alkylOR⁴, -SR², -S(=O)R⁴, -S(O)₂R⁴, -S(=O)₂NR²R⁴, -S(O)₂N(R²)C(=O)R⁴, -S(O)₂N(R²)C(=O)OR⁴, -S(=O)₂N(R²)C(=O)NR²R⁴, -NR²R⁴, -N(R²)C(=O)R⁴, -N(R²)C(=O)OR⁴, -N(R²)C(=O)NR²R⁴, -N(R²)C(=O)NR²R⁴, -N(R²)S(=O)₂R⁴, -N(R²)S(=O)₂NR²R⁴

5  -NR⁴C₂₅₆alkylNR²R⁴ or -NR⁴C₂₅₆alkylOR⁴;

    R⁷ is selected from R⁸, R⁹, C₁₄haloalkyl, halo, cyano, -C(=O)R⁹,
    -C(=O)OR⁹, -C(=O)NR²R⁴, -C(=O)NR²R⁴, -OR⁹, -OC(=O)R⁹, -OC(=O)NR²R⁴,
    -OC(=O)N(R²)S(=O)₂R⁹, -OC₂₅₆alkylNR²R⁴, -OC₂₅₆alkylOR⁴, -SR⁹, -S(=O)R⁹,
    -S(O)₂R⁹, -S(O)₂NR²R⁴, -S(O)₂N(R²)C(=O)R⁹, -S(O)₂N(R²)C(=O)OR⁹,
    -S(O)₂N(R²)C(=O)NR²R⁴, -NR²R⁴, -N(R²)C(=O)R⁹, -N(R²)C(=O)OR⁹,
    -N(R²)C(=O)NR²R⁴, -N(R²)C(=O)NR²R⁴, -N(R²)S(=O)₂R⁹, -N(R²)S(=O)₂NR²R⁴,
    -N(R²)S(=O)₂NR²R⁴, -NR⁴C₂₅₆alkylNR²R⁴ or -NR⁴C₂₅₆alkylOR⁴;

10  R⁸ is independently, at each instance, H or R⁹;

    R⁹ is independently, at each instance, phenyl, benzyl or C₁₄alkyl, the

phenyl, benzyl and C₁₄alkyl being substituted by 0, 1, 2 or 3 substituents selected
from halo, C₁₄alkyl, C₁₅haloalkyl, -OC₁₄alkyl, -NH₂, -NHC₁₄alkyl,
-N(C₁₄alkyl)C₁₄alkyl;

    R¹₀ is independently at each instance C₁₄alkyl, C₁₄haloalkyl, halo, cyano,
    nitro, -C(=O)R¹₀, -C(=O)OR¹₀, -C(=O)NR²R⁴, -C(=O)NR²R⁴, -OR¹₀, -OC(=O)R¹₀,
    -OC(=O)NR²R⁴, -OC(=O)N(R²)S(=O)₂R¹₀, -OC₂₅₆alkylNR²R⁴, -OC₂₅₆alkylOR¹₀,
    -SR¹₀, -S(=O)₂R¹₀, -S(O)₂NR²R⁴, -S(O)₂N(R²)C(=O)R¹₀, -S(O)₂N(R²)C(=O)OR¹₀,
    -S(O)₂N(R²)C(=O)NR²R⁴, -NR²R⁴, -N(R²)C(=O)R¹₀, -N(R²)C(=O)OR¹₀,
    -N(R²)C(=O)NR²R⁴, -N(R²)C(=O)NR²R⁴, -N(R²)S(=O)₂R¹₀, -N(R²)S(=O)₂NR²R⁴,
    -N(R²)S(=O)₂NR²R⁴, -NR⁴C₂₅₆alkylNR²R⁴ or -NR⁴C₂₅₆alkylOR¹₀;

20  R¹¹ is independently at each instance C₁₄alkyl substituted by 0, 1, 2 or 3
    substituents independently selected from R² and additionally substituted by 0 or 1
    substituents selected from R²; and

    R² is independently at each instance a saturated, partially saturated or
    unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or

30  11-membered bicyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O
    and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo
    groups and the ring is substituted by 0, 1, 2 or 3 substituents selected from
C_{1,4}alkyl, C_{1,4}haloalkyl, halo, cyano, nitro, -C(=O)R, -C(=O)OR, -C(=O)NR\textsubscript{2}R, -C(=N)NR\textsubscript{2}R, -OR, -OC(=O)R, -OC(=O)NR\textsubscript{2}R, -OC(=O)N(R)S(=O)\textsubscript{2}R, -OC\textsubscript{2,6}alkylNR\textsubscript{2}R, -OC\textsubscript{2,6}alkylOR, -SR, -S(=O)R, -S(=O)\textsubscript{2}R, -S(=O)\textsubscript{2}NR\textsubscript{2}R, -S(=O)\textsubscript{2}N(R)C(=O)R, -S(=O)\textsubscript{2}N(R)C(=O)OR, -S(=O)\textsubscript{2}N(R)C(=O)NR\textsubscript{2}R, -NR\textsubscript{2}R, -N(R)C(=O)R, -N(R)C(=O)OR, -N(R)C(=O)NR\textsubscript{2}R, -N(R)C(=N)NR\textsubscript{2}R, -N(R)S(=O)\textsubscript{2}R, -N(R)S(=O)\textsubscript{2}NR\textsubscript{2}R, -NR\textsubscript{2}C\textsubscript{2,6}alkylNR\textsubscript{2}R and -NR\textsubscript{2}C\textsubscript{2,6}alkylOR.

2. A compound according to Claim 1, wherein J is O.

3. A compound according to Claim 1, wherein J is NH.

4. A compound according to Claim 1, wherein Y\textsubscript{1}, Y\textsubscript{2}, Y\textsubscript{3} and Y\textsubscript{4} together are -C=C-C=C-.

5. A compound according to Claim 1, wherein Y\textsubscript{1}, Y\textsubscript{2}, Y\textsubscript{3} and Y\textsubscript{4} together are -C-C-C-C-.

6. A compound according to Claim 1, wherein Y\textsubscript{1}, Y\textsubscript{2}, Y\textsubscript{3} and Y\textsubscript{4} together are -C-N-C-C-.

7. A compound according to Claim 1, wherein Y\textsubscript{1}, Y\textsubscript{2}, Y\textsubscript{3} and Y\textsubscript{4} together are -C-N-C-C-. 

8. A compound according to Claim 1, wherein R\textsubscript{1} is

\[ \begin{array}{c}
\text{R}^7 \\
\text{R}^2
\end{array} \]

R\textsubscript{2} is
9. A compound according to Claim 1, wherein R^7 is selected from C_1-alkyl, C_1-haloalkyl, halo and -OR^a.

10. A compound according to Claim 1, wherein R^7 is selected from C_1-alkyl and C_1-haloalkyl.

11. A compound according to Claim 1, wherein

10 R^1 is R^2; and

R^2 is a saturated, partially saturated or unsaturated 9- or 10-membered bicyclic ring containing 1, 2 or 3 N atoms and 0, 1 or 2 atoms selected from O and S, wherein the bicyclic ring is substituted by 0, 1 or 2 oxo groups and is also substituted by 0, 1, 2 or 3 substituents selected from R^9, C_1-haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=O)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)R^b, -OC_2-halylNR^aR^a, -OC_2-halylOR^a, -SR^a, -S(=O)R^b, -S(=O)R^b, -S(=O)NR^aR^a, -S(=O)NR^aR^a, -S(=O)CO(=O)OR^b, -S(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)CO(=O)NR^aR^a, -N(R^a)CO(=O)NR^aR^a, -N(R^a)CO(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=O)NR^aR^a.

12. A compound according to Claim 1, wherein R^7 is selected from R^9.

13. A compound according to Claim 1, wherein R^7 is selected from R^9.

14. A compound according to Claim 1, wherein J is S, S=O or S(=O)2.
15. A compound according to Claim 1 selected from the group of:

(5-chloro-6-(4-((4-(trifluoromethyl)phenyl)amino)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)-3-pyridinyl)methanol;

2-(piperidin-1-ylmethyl)-N-(4-(trifluoromethyl)phenyl)-7-(3-(trifluoromethyl)pyridin-2-yl)quinazolin-4-amine;

4-((4-(1,1-dimethylethyl)cyclohexyl)oxy)-7-(3-(trifluoromethyl)-2-pyridinyl)quinazoline;

4-((4-(1,1-dimethylethyl)phenyl)oxy)-7-(3-(trifluoromethyl)-2-pyridinyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine;

4-((4-(1,1-dimethylethyl)phenyl)oxy)-7-(3-(trifluoromethyl)-2-pyridinyl)quinazoline;

4-(4-(trifluoromethyl)phenyl)amino)-7-(3-(trifluoromethyl)pyridin-2-yl)-6,7-dihydropyrido[3,4-d]pyrimidin-8(5H)-one;

7-(3-(trifluoromethyl)-2-pyridinyl)-N-(6-(trifluoromethyl)-3-pyridinyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;

7-(3,5-dichloropyridin-2-yl)-N-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;

7-(3,5-difluoropyridin-2-yl)-N-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;

7-(3-chloro-2-pyridinyl)-N-(4-(1,1-dimethylethyl)cyclohexyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;

7-(3-chloro-2-pyridinyl)-N-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;

7-(phenylmethyl)-N-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;

7-(phenylmethyl)-N-(6-(trifluoromethyl)-3-pyridinyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;

7-chloro-N-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-quinazolinamine;

N-(4-((7-chloro-4-quinazolinyl)oxy)-1,3-benzothiazol-2-yl)acetamide;

N-(4-(1,1-dimethylethyl)cyclohexyl)-7-(3-(trifluoromethyl)-2-pyridinyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;
N-(4-(1,1-dimethylethyl)cyclohexyl)-7-(phenylmethyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;
N-(4-(1,1-dimethylethyl)phenyl)-7-(3-(trifluoromethyl)-2-pyridinyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;
N-(4-(1,1-dimethylethyl)phenyl)-7-(phenylmethyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;
N-(4-(trifluoromethyl)phenyl)-7-(3-(trifluoromethyl)-2-pyridinyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine;
N-(4-(trifluoromethyl)phenyl)-7-(3-(trifluoromethyl)-2-pyridinyl)-4-quinazolinamine;
N-(4-tert-butylocyclohexyl)-7-(3-(trifluoromethyl)pyridin-2-yl)quinazolin-4-amine;
or any pharmaceutically-acceptable salts or hydrates thereof.

16. The manufacture of a medicament for the treatment of acute, inflammatory and neuropathic pain, dental pain, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases, osteoarthritis, inflammatory bowel disorders, depression, anxiety, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, causalgia, sympathetically maintained pain, deafferentation syndromes, asthma, epithelial tissue damage or dysfunction, herpes simplex, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritus, vitiligo, general gastrointestinal disorders, gastric ulceration, duodenal ulcers, diarrhea, gastric lesions induced by necrotising agents, hair growth, vasomotor or allergic rhinitis, bronchial disorders or bladder disorders, comprising a compound according to any one of Claims 1-15.

17. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically-acceptable diluent or carrier.
A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 C07D401/04 C07D417/12 A61K31/517 A61K31/519
A61K31/428

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)

IPC 7 C07D A61K A61P

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

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>X,P</td>
<td>WO 2004/055004 A (NEUROGEN CORPORATION; BAKTHAVATCHALAM, RAJAGOPAL; BLUM, CHARLES, A; BR) 1 July 2004 (2004-07-01) compounds 2B3, 1D4</td>
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Further special categories of cited documents:

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

**A** earlier document but published on or after the international filing date

*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.

**X** document member of the same patent family

Date of the actual completion of the international search: 30 May 2005

Date of mailing of the international search report: 06/06/2005

Name and mailing address of the ISA:

European Patent Office, P.B. 5816 Patenteen 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040; Tx. 31 651 epo nl
Fax (+31-70) 340-3016

Authorized officer: Frelon, D
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<td>WO 2004/054582 A (NEUROGEN CORP 'US!; HERZBERG URI 'US!; CORTRIGHT DANIEL 'US!; HURT MA) 1 July 2004 (2004-07-01) compounds 214, 2M: p.78, 1.21,25,27; p.79, 1.14,15,24; p.81, 1.37; p.82, 1.1; p.84. 1.23,25,31,33; p,117, 1.7</td>
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<td>WO 03/062209 A (NEUROGEN CORPORATION; BAKTHAVATCHATAM, RAJAGOPAL; BLUM, CHARLES, A; BR) 31 July 2003 (2003-07-31) compounds1E4,115;tableII:38,63,87,102,133-142;tableIII:166-172,183-200,202-207,209,210,214,219-221,225;tableIV:260-263,267-277,283-289;tableV:293-295,299-301,305,306;2D,6;tableVI:611-613,3E9;569</td>
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<td>A</td>
<td>EP 1 306 372 A (NIPPON SHINYAKU CO., LTD) 2 May 2003 (2003-05-02) abstract; claims</td>
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Continuation of Box II.2

Claims Nos.: 1,2,3-10,11,12,13,14,15-17

The claims, especially claims 1-14, do not meet the requirements of Art. 6 PCT in that the matter for which a protection is sought is not concisely and clearly defined:

Present claims 1 to 14 relate to an extremely large number of possible compounds. In fact, these claims contain so many options, variables, possible permutations that a lack of clarity (and conciseness) within the meaning of Article 6 PCT and of disclosure within the meaning of Art. 5 PCT arises:

- A comprehensive search report is not feasible due to the amount of compounds particularly relevant for the issue of novelty revealed in the initial phase of the search. Numerous documents were retrieved and it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Art. 6 PCT).
- Certain definitions are so broad and unspecific that they overlap on each other leading to unacceptable redundancies: for instance, R7 can represent ...Re and haloalkyl...etc, and the definition of Re covers also alkyl substituted by Rd which includes "halo".
- The expression "(additionally) substituted by 0 (...) substituents" is meaningless: if there were no "substituent" at all, even H would be excluded.
- Claim 11 as drafted cannot depend on claim 1. Either, there is a typing error with the erroneous exchange between R1 and R2 (corresponding to the case (b) of claim 1), or claim 11 is directed to another subject-matter which is not unitary since either it does not share the same concept with claim 1 or the shared concept is known.
- Only example 22a actually illustrates the invention as claimed: all the other compounds are not part of the invention as claimed, particularly due to the fact that the rest R4, which should occur only once, must be different from H and, when R4 represents an alkyl group, it cannot be substituted.

The claimed subject-matter lacks therefore clarity and support and does not satisfy the requirements of Art. 5 and 6 PCT.

For these reasons, a meaningfull search over the whole breadth of the claim(s) is impossible.

The claimed subject-matter cannot be considered to be a reasonable generalisation of the actual and unique example. Consequently the search was carried out for those parts of the application which appear to be clear and concise on the basis of the example, i.e. essentially compounds wherein J = NH and R1 and R2 are as defined as in the case (a). Moreover, not searched subject-matter has no support in the description.

The applicant's attention is drawn to the fact that claims relating to
inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.
INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. [x] Claims Nos.:
   1, 2, 3–10, 11, 12, 13, 14, 15–17
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
   see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest.
[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
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