Title: 2-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS VANILLOID RECEPTOR LIGANDS AND THEIR USE IN TREATMENTS

Abstract: Substituted benzimidazoles 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, 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 hyperalgiesia and alldynia, neuropathic pain and associated hyperalgiesia and alldynia, 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.
2- SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS VANILLOID RECEPTOR LIGANDS AND THEIR USE IN TREATMENTS

This application claims the benefit of U.S. Provisional Application No. 60/646,187, filed January 20, 2005, 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, Helliwell 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 results 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 effect the function of the vanilloid receptor to increase or decrease the activity of sensory nerves.

VR1 gene knockout mice have been shown to have reduced 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).

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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 \( J, R^1, R^2, R^3, R^4, R^5 \) and \( R^6 \) 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 \( \text{NH}, \text{O}, \text{S(=O)} \) or \( \text{S(=O)}_2 \);
- \( n \) is independently, at each instance, 0, 1 or 2;
- \( R^1 \) is independently selected from \( H, R^e, R^i, \text{halo, nitro, cyano, -OR}^e, -OR^i, -OC_2-alkylNR^aR^f, -OC_2-alkylOR^f, -NR^aR^f, -NR^aR^i, -NR^fC_2-alkylNR^aR^f, -NR^fC_2-alkylOR^f, \text{naphthyl, -CO}_2R^e, -C(=O)R^e, -C(=O)NR^aR^f, -C(=O)NR^aR^i, -NR^fC(=O)NR^aR^f, -NR^fCO}_2R^e, -C_1-alkylOR^f, -C_1-alkylNR^aR^f, -S(=O)_2R^e, -S(=O)_2NR^aR^f, -NR^aS(=O)R^e \) and \( -OC(=O)NR^aR^f \), and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from \( \text{Br, Cl, F and I} \);
- \( R^2 \) is independently selected from \( H, R^e, R^i, \text{halo, nitro, cyano, -OR}^e, -OR^i, -OC_2-alkylNR^aR^f, -OC_2-alkylOR^f, -NR^aR^f, -NR^aR^i, -NR^fC_2-alkylNR^aR^f, -NR^fC_2-alkylOR^f, \text{naphthyl, -CO}_2R^e, -C(=O)R^e, -C(=O)NR^aR^e, -C(=O)NR^aR^i \),
-NR^1C(=O)R^e, -NR^1C(=O)R^1, -NR^2C(=O)NR^aR^f, -NR^fCO_2R^e, -C_1,4-alkylOR^f, -C_1,4-alkylNR^aR^f, -S(=O)_nR^e, -S(=O)_2NR^aR^f, -NR^aS(=O)_2R^e and -OC(=O)NR^aR^f, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I;

5  R^3 is independently selected from H, R^e, R^1, halo, nitro, cyano, -OR^e, -OR^1, -OC_2,6-alkylNR^aR^f, -OC_2,6-alkylOR^f, -NR^2R^1, -NR^aR^1, -NR^fC_2,6-alkylNR^aR^f, -NR^fC_2,6-alkylOR^f, naphthyl, -CO_2R^e, -C(=O)NR^aR^e, -C(=O)NR^aR^1, -NR^aC(=O)R^e, -NR^aC(=O)R^1, -NR^fC(=O)NR^aR^f, -NR^fC(=O)R^1, -NR^aS(=O)_2NR^aR^f, -NR^aS(=O)_2R^e and -OC(=O)NR^aR^f, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; wherein at least one of R^2 and R^3 is selected from -OCF_3, unsubstituted C_2,6-alkyl and C_1,4-alkyl substituted by 1, 2, 3 or 4 substituents selected from halo, C_1,4-haloalkyl, cyano, nitro, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, -C(=O)NR^aR^1, -OC(=O)NR^aR^a, -OC(=O)NR^aR^1, -S(=O)_2NR^aR^e, -S(=O)_2NR^aR^1, -S(=O)_2N(R^a)C(=O)R^a, -S(=O)_2N(R^a)C(=O)R^1, -S(=O)_2N(R^a)C(=O)NR^aR^a, -S(=O)_2N(R^a)C(=O)NR^aR^1, -S(=O)_2N(R^a)C(=O)NR^aR^f, -S(=O)_2N(R^a)C(=O)NR^aR^f, and wherein the C_1,4-alkyl is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I;

10 R^4 is independently selected from H, R^e, R^1, halo, nitro, cyano, -OR^e, -OR^1, -OC_2,6-alkylNR^aR^f, -OC_2,6-alkylOR^f, -NR^2R^f, -NR^aR^f, -NR^fC_2,6-alkylNR^aR^f, -NR^fC_2,6-alkylOR^f, naphthyl, -CO_2R^e, -C(=O)NR^aR^e, -C(=O)NR^aR^1, -NR^aC(=O)R^e, -NR^aC(=O)R^1, -NR^fC(=O)NR^aR^f, -NR^fC(=O)R^1, -NR^aS(=O)_2NR^aR^f, -NR^aS(=O)_2R^e and -OC(=O)NR^aR^f, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I;

15 R^5 is a saturated, partially saturated or unsaturated 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 available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2 or 3 substituents
independently selected from \( R^i \), \( R^i \), nitro, cyano, -OH, -OR, -OR,
-OC\(_2\)alkylnR\(_a\)R\(_f\), -OC\(_2\)alkyloR\(_f\), -NR\(_a\)R\(_i\), -NR\(_a\)R\(_i\), -NR\(_i\)C\(_2\)alkylnR\(_a\)R\(_f\),
-NR\(_i\)C\(_2\)alkyloR\(_f\), -naphthal, -CO\(_2\)R, -C(=O)R\(_e\), -C(=O)NR\(_a\)R\(_i\),
-C(=O)NR\(_i\)R\(_i\), -NR\(_i\)C(=O)R\(_f\), -NR\(_i\)C(=O)NR\(_a\)R\(_i\), -NR\(_i\)CO\(_2\)R, -C\(_1\)alkyloR,
-OC(=O)NR\(_a\)R\(_f\), -S(=O)\(_2\)NR\(_a\)R\(_i\), -NR\(_a\)S(=O)\(_2\)R\(_i\), -NR\(_a\)S(=O)\(_2\)R\(_a\) and
-OC(=O)NR\(_a\)R\(_f\), and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5
substituents independently selected from Br, Cl, F and I; or

\( R^a \) is phenyl substituted by 0, 1, 2 or 3 substituents selected from halo,
-OR, C\(_1\)alkyl, and C\(_1\)haloalkyl, and additionally substituted by C\(_1\)alkyl or
C\(_1\)alkyl(phenyl) wherein either is substituted by 0, 1, 2, 3 or 4 substituents
selected from halo, C\(_1\)haloalkyl, cyano, nitro, -C(=O)R\(_a\), -C(=O)OR,
-C(=O)NR\(_a\)R\(_a\), -C(=O)NR\(_a\)R\(_a\), -OR\(_a\), -OC(=O)R\(_a\), -OC(=O)NR\(_a\)R\(_a\),
-OC(=O)NR\(_a\)R\(_a\), -OC\(_2\)alkylnR\(_a\)R\(_a\), -OC\(_2\)alkyloR\(_a\), -OR\(_a\), -S(=O)\(_2\)R\(_a\),
-S(=O)\(_2\)NR\(_a\)R\(_a\), -S(=O)\(_2\)NR\(_a\)R\(_a\), -N(R\(_a\))C(=O)R\(_a\), -N(R\(_a\))C(=O)R\(_a\),
-N(R\(_a\))C(=O)NR\(_a\)R\(_a\), -NR\(_a\)C(=O)NR\(_a\)R\(_a\), -NR\(_a\)C(=O)NR\(_a\)R\(_a\),
-N(R\(_a\))S(=O)\(_2\)R\(_a\), -N(R\(_a\))S(=O)\(_2\)NR\(_a\)R\(_a\), -NR\(_a\)C\(_2\)alkylnR\(_a\)R\(_a\) and -NR\(_a\)C\(_2\)alkyloR\(_a\); and wherein the
C\(_1\)alkyl is additionally substituted by 0 or 1 groups independently selected from
R\(_b\) and additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently
selected from Br, Cl, F and I;

\( R^b \) is H or -(C\(_1\)alkyl)-R\(_i\), wherein the C\(_1\)alkyl is additionally substituted by
0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I;

\( R^a \) is independently, at each instance, H or R\(_b\);

\( R^b \) is independently, at each instance, phenyl, benzyl or C\(_1\)alkyl, the
phenyl, benzyl and C\(_1\)alkyl being substituted by 0, 1, 2 or 3 substituents selected
from halo, C\(_1\)alkyl, C\(_1\)haloalkyl, -OC\(_2\)alkyl, -NH\(_2\), -NHC\(_1\)alkyl,
-N(C\(_1\)alkyl)C\(_1\)alkyl;

\( R^a \) is independently, in each instance, phenyl substituted by 0, 1 or 2
groups selected from halo, C\(_1\)alkyl, C\(_1\)haloalkyl, cyano, nitro, -C(=O)R\(_a\),
-C(=O)OR\(_a\), -C(=O)NR\(_a\)R\(_a\), -C(=O)NR\(_a\)R\(_a\), -OR\(_a\), -OC(=O)R\(_a\), -OC(=O)NR\(_a\)R\(_a\),
-OC(=O)NR\(_a\)S(=O)\(_2\)R\(_a\), -OC\(_2\)alkylnR\(_a\)R\(_a\), -OC\(_2\)alkyloR\(_a\), -SR\(_a\), -S(=O)R\(_a\),
-S(=O)\(_2\)R\(_a\), -S(=O)\(_2\)NR\(_a\)R\(_a\), -S(=O)\(_2\)N(R\(_a\))C(=O)R\(_a\), -S(=O)\(_2\)N(R\(_a\))C(=O)R\(_a\).
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-S(=O)₂N(R^a)C(=O)NR^bR^a, -NR^aR^a, -N(R^b)C(=O)R^a, -N(R^b)C(=O)OR^a,
-N(R^b)C(=O)NR^bR^a, -N(R^b)C(NR^b)NR^aR^a, -N(R^b)S(=O)₂R^a,
-N(R^b)S(=O)₂NR^bR^a, -NR^aC₂₆₆alloylnR^bR^a and -NR^aC₂₆₆alloylOR^a; or R^a is a
saturated, partially saturated or unsaturated 5- or 6-membered ring heterocycle
containing 1, 2 or 3 heteroatoms independently selected from N, O and S, wherein
no more than 2 of the ring members are O or S, wherein the heterocycle is
optionally fused with a phenyl ring, and the carbon atoms of the heterocycle are
substituted by 0, 1 or 2 oxo or thioxoo groups, wherein the heterocycle or fused
phenyl ring is substituted by 0, 1 or 2 substituents selected from halo, C₁₋₆alkyl,
C₁₋₆haloalkyl, cyano, nitro, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^bR^a,
-C(=NR^b)NR^aR^a, -OR^a, -OC(=O)OR^a, -OC(=O)NR^bR^a, -OC(=O)N(R^b)S(=O)₂R^a,
-OC₂₆₆alloylnR^bR^a, -OC₂₆₆alloylOR^a, -SR^a, -S(=O)₂R^a, -S(=O)₂NR^bR^a,
-S(=O)₂N(R^b)C(=O)R^a, -S(=O)₂N(R^b)C(=O)OR^a, -S(=O)₂N(R^b)C(=O)NR^aR^a,
-NR^aR^a, -N(R^b)C(=O)OR^a, -N(R^b)C(=O)OR^a, -N(R^b)C(=O)NR^aR^a;
-N(R^b)C(=N)NR^bR^a, -N(R^b)S(=O)₂R^a, -N(R^b)S(=O)₂NR^bR^a,
-NR^aC₂₆₆alloylnR^bR^a and -NR^aC₂₆₆alloylOR^a;

R^a is, independently, in each instance, C₁₋₆alkyl or C₁₋₆alkyl(phenyl)
wherein either is substituted by 0, 1, 2, 3 or 4 substituents selected from halo,
C₁₋₆haloalkyl, cyano, nitro, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^bR^a,
-C(=NR^b)NR^aR^a, -OR^a, -OC(=O)R^a, -OC(=O)NR^bR^a, -OC(=O)N(R^b)S(=O)₂R^a,
-OC₂₆₆alloylnR^bR^a, -OC₂₆₆alloylOR^a, -SR^a, -S(=O)₂R^a, -S(=O)₂NR^bR^a,
-S(=O)₂N(R^b)C(=O)R^a, -S(=O)₂N(R^b)C(=O)OR^a, -S(=O)₂N(R^b)C(=O)NR^aR^a,
-NR^aR^a, -N(R^b)C(=O)OR^a, -N(R^b)C(=O)OR^a, -N(R^b)C(=O)NR^aR^a;
-N(R^b)C(=N)NR^bR^a, -N(R^b)S(=O)₂R^a, -N(R^b)S(=O)₂NR^bR^a,
-NR^aC₂₆₆alloylnR^bR^a and -NR^aC₂₆₆alloylOR^a; and wherein the C₁₋₆alkyl is
additionally substituted by 0 or 1 groups independently selected from R^b and
additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected
from Br, Cl, F and I;

R^b is, independently, in each instance, R^a or H;

R^a is, independently, in each instance, a saturated, partially saturated or
unsaturated 5- or 6-membered monocyclic ring containing 1, 2 or 3 atoms selected
from N, O and S, so long as the combination of O and S atoms is not greater than 2, wherein the ring is substituted by 0 or 1 oxo or thioxo groups;

R is, independently, in each instance, phenyl or a saturated, partially saturated or unsaturated 5- or 6-membered monocyclic ring containing 1, 2 or 3 atoms selected from N, O and S, so long as the combination of O and S atoms is not greater than 2, wherein the ring is substituted by 0 or 1 oxo or thioxo groups, wherein the phenyl or monocyte are substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, nitro, -C(=O)R, -C(=O)OR, -C(=O)NR, R, -C(=NR)NR, R, -OR, -OC(=O)R, -OC(=O)NR, R, -OC(=O)N(R)S(=O)2R, -OC,6alkylNR, R, -OC,6alkylOR, -SR, -S(=O)2R, -S(=O)2NR, R, -S(=O)2N(R)C(=O)OR, -S(=O)2N(R)C(=O)NR, R, -NR, R, -N(R)C(=O)R, -N(R)C(=O)OR, -N(R)C(=O)NR, R, -N(R)C(=O)NR, R, -N(R)S(=O)2R, -N(R)S(=O)2NR, R, -NR, C,6alkylNR, R and -NR, C,6alkylOR; and

R is 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 available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2 or 3 substituents independently selected from R, R, R, halo, nitro, cyano, -OH, -OR, -OR, -OC,6alkylNR, R, -OC,6alkylOR, -NR, R, -NR, R, -NR, C,6alkylNR, R, -NR, C,6alkylOR, -naphthyl, -CO, R, -C(=O)R, -C(=O)NR, R, -C(=O)NR, R, -NR, C(=O)R, -NR, C(=O)R, -NR, C(=O)R, -NR, R, -S(=O)3R, -S(=O)2NR, R, -NR, S(=O)2R, -NR, S(=O)2R and -OC(=O)NR, R, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

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

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

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

In another embodiment, in conjunction with the above and below embodiments, R¹ is H.

In another embodiment, in conjunction with the above and below embodiments, R¹ is independently selected from R⁶, R¹, halo, nitro, cyano, -OR⁶, -OR¹, -OC₂₂₆alkyINR⁸R₆², -OC₂₂₆alkyIOR¹, -NR⁸R¹, -NR⁶R¹, -NR²C₂₂₆alkyINR⁸R₆², -NR²C₂₂₆alkyIOR¹, naphthyl, -CO₂R⁶, -C(=O)R⁶, -C(=O)NR⁸R¹, -C(=O)NR²R¹, -NR²C(=O)R¹, -NR²C(=O)NR⁸R¹, -NR²C(=O)NR²R¹, -C₁₆alkyIOR¹, -C₁₆alkyINR⁸R¹, -S(=O)₆R⁶, -S(=O)₂NR⁸R¹, -NR⁸S(=O)₂R⁶ and -OC(=O)NR⁸R¹.

In another embodiment, in conjunction with the above and below embodiments, R¹ is independently selected from R⁶, R¹, nitro, cyano, -OR⁶, -OR¹, -OC₂₂₆alkyINR⁸R¹, -OC₂₂₆alkyIOR¹, -NR⁸R¹, -NR⁶R¹, -NR²C₂₂₆alkyINR⁸R¹, -NR²C₂₂₆alkyIOR¹, naphthyl, -CO₂R⁶, -C(=O)R⁶, -C(=O)NR⁸R¹, -C(=O)NR²R¹, -NR²C(=O)R¹, -NR²C(=O)NR⁸R¹, -NR²C(=O)NR²R¹, -C₁₆alkyIOR¹, -C₁₆alkyINR⁸R¹, -S(=O)₆R⁶, -S(=O)₂NR⁸R¹, -NR⁸S(=O)₂R⁶ and -OC(=O)NR⁸R¹.

In another embodiment, in conjunction with the above and below embodiments, R¹ is independently selected from nitro, cyano, -OR⁶, -OR¹, -OC₂₂₆alkyINR⁸R¹, -OC₂₂₆alkyIOR¹, -NR⁸R¹, -NR⁶R¹, -NR²C₂₂₆alkyINR⁸R¹, -NR²C₂₂₆alkyIOR¹, naphthyl, -CO₂R⁶, -C(=O)R⁶, -C(=O)NR⁸R¹, -C(=O)NR²R¹, -NR²C(=O)R¹, -NR²C(=O)NR⁸R¹, -NR²C(=O)NR²R¹, -C₁₆alkyIOR¹, -C₁₆alkyINR⁸R¹, -S(=O)₆R⁶, -S(=O)₂NR⁸R¹, -NR⁸S(=O)₂R⁶ and -OC(=O)NR⁸R¹.

In another embodiment, in conjunction with the above and below embodiments, R¹ is independently selected from R⁶ and R¹.

In another embodiment, in conjunction with the above and below embodiments, R² is H.

In another embodiment, in conjunction with the above and below embodiments, R² is independently selected from R⁶, R¹, halo, nitro, cyano, -OR⁶, -OR¹, -OC₂₂₆alkyINR⁸R¹, -OC₂₂₆alkyIOR¹, -NR⁸R¹, -NR⁶R¹, -NR²C₂₂₆alkyINR⁸R¹, -NR²C₂₂₆alkyIOR¹, naphthyl, -CO₂R⁶, -C(=O)R⁶, -C(=O)NR⁸R¹, -C(=O)NR²R¹, -NR²C(=O)R¹, -NR²C(=O)NR⁸R¹, -NR²C(=O)NR²R¹, -C₁₆alkyIOR¹, -C₁₆alkyINR⁸R¹, -S(=O)₆R⁶, -S(=O)₂NR⁸R¹, -NR⁸S(=O)₂R⁶ and -OC(=O)NR⁸R¹.
In another embodiment, in conjunction with the above and below embodiments, R\text{2} is independently selected from R\text{e}, R\text{1}, cyano, -OR\text{e}, -OR\text{1}, -OC\text{2}-alkylNR\text{e}R\text{f}, -OC\text{2}-alkylOR\text{f}, -NR\text{e}R\text{f}, -NR\text{e}R\text{1}, -NR\text{C}-alkylINR\text{a}R\text{f}, -NR\text{C}-alkylOR\text{f}, naphthyl, -CO\text{2}R\text{e}, -C(=O)R\text{e}, -C(=O)NR\text{e}R\text{c}, -C(=O)NR\text{e}R\text{1}, -NR\text{C}(=O)R\text{e}, -NR\text{C}(=O)R\text{1}, -NR\text{C}(=O)NR\text{a}R\text{f}, -NR\text{C}(=O)NR\text{a}R\text{1}, -NR\text{C}(=O)CO\text{2}R\text{e}, -C\text{1,6}alkylOR\text{f}, -C\text{1,6}alkylNR\text{a}R\text{f}, -S(=O)_{n}R\text{e}, -S(=O)_{2}NR\text{e}R\text{1}, -NR\text{e}S(=O)_{2}R\text{e}, and -OC(=O)NR\text{e}R\text{f}.

In another embodiment, in conjunction with the above and below embodiments, R\text{3} is H.

In another embodiment, in conjunction with the above and below embodiments, R\text{3} is independently selected from R\text{e}, R\text{1}, halo, nitro, cyano, -OR\text{e}, -OR\text{1}, -OC\text{2}-alkylNR\text{e}R\text{f}, -OC\text{2}-alkylOR\text{f}, -NR\text{a}R\text{f}, -NR\text{a}R\text{1}, -NR\text{C}-alkylINR\text{a}R\text{f}, -NR\text{C}(=O)R\text{e}, -NR\text{C}(=O)R\text{1}, -NR\text{C}(=O)NR\text{a}R\text{f}, -NR\text{C}(=O)NR\text{a}R\text{1}, -NR\text{C}(=O)CO\text{2}R\text{e}, -C\text{1,6}alkylOR\text{f}, -C\text{1,6}alkylNR\text{a}R\text{f}, -S(=O)_{n}R\text{e}, -S(=O)_{2}NR\text{a}R\text{1}, -NR\text{a}S(=O)_{2}R\text{e}, and -OC(=O)NR\text{a}R\text{f}.

In another embodiment, in conjunction with the above and below embodiments, R\text{3} is independently selected from R\text{e}, R\text{1}, cyano, -OR\text{e}, -OR\text{1}, -OC\text{2}-alkylNR\text{e}R\text{f}, -OC\text{2}-alkylOR\text{f}, -NR\text{a}R\text{f}, -NR\text{a}R\text{1}, -NR\text{C}-alkylINR\text{a}R\text{f}, -NR\text{C}(=O)R\text{e}, -NR\text{C}(=O)R\text{1}, -NR\text{C}(=O)NR\text{a}R\text{f}, -NR\text{C}(=O)NR\text{a}R\text{1}, -NR\text{C}(=O)CO\text{2}R\text{e}, -C\text{1,6}alkylOR\text{f}, -C\text{1,6}alkylNR\text{a}R\text{f}, -S(=O)_{n}R\text{e}, -S(=O)_{2}NR\text{a}R\text{1}, -NR\text{a}S(=O)_{2}R\text{e}, and -OC(=O)NR\text{a}R\text{f}.

In another embodiment, in conjunction with the above and below embodiments, R\text{2} is selected from unsubstituted C\text{2}-alkyl or C\text{1,6}alkyl substituted by 1, 2, 3 or 4 substituents selected from halo, C\text{1,6}haloalkyl, cyano, nitro, -C(=O)R\text{a}, -C(=O)OR\text{a}, -C(=O)NR\text{a}R\text{a}, -C(=O)NR\text{a}R\text{a}, -OR\text{a}, -OC(=O)R\text{a}, -OC(=O)NR\text{a}R\text{a}, -OC\text{2}-alkylINR\text{a}R\text{a}, -OC\text{2}-alkylOR\text{a}, -SR\text{a}, -S(=O)OR\text{a}, -S(=O)_{2}NR\text{a}R\text{a}, -S(=O)_{2}NR\text{a}R\text{a}, -S(=O)_{2}N(R\text{b})C(=O)R\text{a}, -S(=O)_{2}N(R\text{b})C(=O)R\text{a}, -S(=O)_{2}N(R\text{b})C(=O)R\text{a}, -S(=O)_{2}N(R\text{b})C(=O)R\text{a}, -N(R\text{b})C(=O)OR\text{a}, -N(R\text{b})C(=O)NR\text{a}R\text{a}, -N(R\text{b})C(=O)NR\text{a}R\text{a}, -N(R\text{b})C(=O)NR\text{a}R\text{a}, -N(R\text{b})C(=O)NR\text{a}R\text{a}, and -N\text{C}-alkylNR\text{a}R\text{a}, and wherein the C\text{1,6}alkyl is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.
In another embodiment, in conjunction with the above and below embodiments, R² is unsubstituted C₅₆alkyl.

In another embodiment, in conjunction with the above and below embodiments, R² is unsubstituted C₃₅alkyl.

In another embodiment, in conjunction with the above and below embodiments, R² is C₁₉alkyl substituted by 1, 2, 3 or 4 substituents selected from halo, C₁₄haloalkyl, cyano, nitro, -C(=O)R⁸, -C(=O)OR⁸, -C(=O)NR⁸R⁸,

-OC(=O)R⁸, -OC(=O)NR⁸R⁸, -OC(=O)N(R⁸)S(=O)₂R⁸,

-OC₂₅alkylNR⁸R⁸, -S(=O)₂OR⁸, -S(=O)₂NR⁸R⁸,

S(=O)₂N(R⁸)C(=O)R⁸, S(=O)₂N(R⁸)C(=O)OR⁸, S(=O)₂N(R⁸)C(=O)NR⁸R⁸,

-NR⁸R⁸, -N(R⁸)C(=O)R⁸, -N(R⁸)C(=O)OR⁸, -N(R⁸)C(=O)NR⁸R⁸,

-N(R⁸)S(=O)₂R⁸, -N(R⁸)S(=O)₂NR⁸R⁸,

-NR⁸C₂₅alkylNR⁸R⁸ and -NR⁸C₂₅alkylOR⁸; and wherein the C₁₉alkyl is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R² is C₁₉alkyl substituted by 1 substituent selected from -OR⁸,

-SR⁸, -S(=O)₂R⁸, and -NR⁸R⁸; and wherein the C₁₉alkyl is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R² is C₁₉alkyl substituted by 1, 2, 3 or 4 F atoms.

In another embodiment, in conjunction with the above and below embodiments, R³ is selected from unsubstituted C₅₆alkyl or C₃₅alkyl substituted by 1, 2, 3 or 4 substituents selected from halo, C₁₄haloalkyl, cyano, nitro,

-C(=O)R⁸, -C(=O)OR⁸, -C(=O)NR⁸R⁸, -C(=O)NR⁸R⁸, -OR⁸, -OC(=O)R⁸,

-OC(=O)NR⁸R⁸, -OC(=O)N(R⁸)S(=O)₂R⁸, -OC₂₅alkylNR⁸R⁸, -OC₂₅alkylOR³,

-SR³, -S(=O)₂R³, -S(=O)₂NR⁸R³, -S(=O)₂N(R⁸)C(=O)R³,

-S(=O)₂N(R⁸)C(=O)OR³, -S(=O)₂N(R⁸)C(=O)NR⁸R³,

-NR⁸R³, -N(R⁸)C(=O)R³, -N(R⁸)C(=O)OR³,

-N(R⁸)S(=O)₂R³, -N(R⁸)S(=O)₂NR⁸R³,

-N(R⁸)C₂₅alkylNR⁸R³ and -NR⁸C₂₅alkylOR³; and wherein the
$C_{1,9}$alkyl is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, $R^3$ is unsubstituted $C_{2,9}$alkyl.

In another embodiment, in conjunction with the above and below embodiments, $R^3$ is unsubstituted $C_{3,9}$alkyl.

In another embodiment, in conjunction with the above and below embodiments, $R^3$ is $C_{1,9}$alkyl substituted by 1, 2, 3 or 4 substituents selected from halo, $C_{1,4}$haloalkyl, cyano, nitro, -(=O)OR, -(=O)OR, -(=O)OR, -(=O)OR, -(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

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-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,

-$(=O)NR$^a$R$^a$,
In another embodiment, in conjunction with the above and below embodiments, R^4 is independently selected from R^e, R^f, nitro, cyano, -OR^e, -OR^f, -OC_2=C(=O)NR^aR^f, -OC_2=C(=O)OR^f, -NR^eR^f, -NR^fR^e, -NR^fC_2=C(=O)NR^aR^f, -NR^fC_2=C(=O)OR^f, -naphthyl, -CO_2R^e, -C(=O)R^e, -C(=O)NR^aR^e, -C(=O)NR^aR^f, -NR^fC(=O)NR^aR^f, -NR^fC(=O)OR^f, -C_1=alkylOR^f, -C_1=alkylNR^aR^f, -S(=O)_nR^e, -S(=O)_2NR^aR^f, -NR^aS(=O)_2R^e and -OC(=O)NR^aR^f.

In another embodiment, in conjunction with the above and below embodiments, R^4 is independently selected from nitro, cyano, -OR^e, -OR^f, -OC_2=C(=O)NR^aR^f, -OC_2=C(=O)OR^f, -NR^eR^f, -NR^fR^e, -NR^fC_2=C(=O)NR^aR^f, -NR^fC_2=C(=O)OR^f, naphthyl, -CO_2R^e, -C(=O)R^e, -C(=O)NR^aR^e, -C(=O)NR^aR^f, -NR^fC(=O)NR^aR^f, -NR^fC(=O)OR^f, -NR^fCO_2R^e, -C_1=alkylOR^f, -C_1=alkylNR^aR^f, -S(=O)_nR^e, -S(=O)_2NR^aR^f, -NR^aS(=O)_2R^e and -OC(=O)NR^aR^f.

In another embodiment, in conjunction with the above and below embodiments, R^4 is independently selected from R^e and R^f.

In another embodiment, in conjunction with the above and below embodiments, R^5 is a saturated, partially saturated or unsaturated 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 one of the rings of the bicyclic ring is a benzo ring and the bicyclic ring is attached at some point on the benzo ring, and wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2 or 3 substituents independently selected from R^f, R^i, nitro, cyano, -OH, -OR^e, -OR^f, -OC_2=C(=O)NR^aR^f, -OC_2=C(=O)OR^f, -NR^eR^f, -NR^fR^a, -NR^fC_2=C(=O)NR^aR^f, -NR^fC_2=C(=O)OR^f, naphthyl, -CO_2R^e, -C(=O)R^e, -C(=O)NR^aR^e, -C(=O)NR^aR^f, -NR^fC(=O)NR^aR^f, -NR^fC(=O)OR^f, -NR^fCO_2R^e, -C_1=alkylOR^f, -C_1=alkylNR^aR^f, -S(=O)_nR^e, -S(=O)_2NR^aR^f, -NR^aS(=O)_2R^e and -OC(=O)NR^aR^f, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R^5 is phenyl substituted by 0, 1, 2 or 3 substituents selected from halo, -OR^a, C_1=alkyl, and C_1=haloalkyl, and additionally substituted by C_1=alkyl or C_1=alkyl(phenyl) wherein either is substituted by 0, 1, 2, 3 or 4 substituents.
selected from halo, C₁₇ haloalkyl, cyano, nitro, -C(=O)R, -C(=O)OR,
-C(=O)NR₅R, -C(=NR₅)NR₅R, -OR, -OC(=O)R, -OC(=O)NR₅R, 
-OC(=O)N(R)S(=O)₂R, -OC₂₆alkylN₅R₅R, -OC₂₆alkylOR, -SR, -S(=O)R, 
-S(=O)₂R, -S(=O)₂NR₅R, -S(=O)₂N(R)C(=O)R, -S(=O)₂N(R)C(=O)OR, 
-S(=O)₂N(R)C(=O)OR, -N(R)₅OC(=O)NR₅R, -N(R)₅C(=NR₅)NR₅R, -N(R)₅S(=O)₂R, 
-N(R)₅S(=O)₂NR₅R, -NR₂₆alkylN₅R₅R, -NR₂₆alkylOR, and wherein the 
C₁₇ alkyl is additionally substituted by 0 or 1 groups independently selected from 
R⁵ and additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently 
selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below 
embodiments, R⁴ is a saturated, partially saturated or unsaturated 6-, 7-, 8-, 9-, 10-
or 11-membered bicyclic carbocyclic ring, wherein the available carbon atoms of 
the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is 
substituted by 0, 1, 2 or 3 substituents independently selected from R¹, R², 
cyano, -OH, -OR, -OR, -OC₂₆alkylNR₅R, -OC₂₆alkylOR, -NR₅R, -NR²R, 
-NR₂₆alkylNR₅R, -NR₂₆alkylOR, naphthyl, -CO₂R, -C(=O)R, 
-C(=O)NR₅R, -C(=O)NR₅R, -NR₂₆C(=O)R, -NR₂₆C(=O)NR₅R, 
-NR₅CO₂R, -C₁₇₆alkylOR, -C₁₇₆alkylNR₅R, -S(=O)₆R, -S(=O)₂NR₅R, 
-NR₅S(=O)₂R and -OC(=O)NR₅R, and the ring is additionally substituted by 0, 
1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below 
embodiments, R⁴ is a saturated, partially saturated or unsaturated 9-, 10- or 
11-membered bicyclic carbocyclic ring, wherein the ring is substituted by 1, 2 or 
3 substituents independently selected from R¹, R², cyano, -OH, -OR, -OR, 
-OC₂₆alkylNR₅R, -OC₂₆alkylOR, -NR₅R, -NR₂₆R, -NR₂₆C₂₆alkylNR₅R, 
-NR₂₆C₂₆alkylOR, naphthyl, -CO₂R, -C(=O)R, -C(=O)NR₅R, -C(=O)NR₂₆R, 
-NR₂₆C(=O)R, -NR₂₆C(=O)NR₅R, -NR₂₆CO₂R, -C₁₇₆alkylOR, 
-C₁₇₆alkylNR₅R, -S(=O)₆R, -S(=O)₂NR₅R, -NR₅S(=O)₂R and -OC(=O)NR₅R, 
and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents 
independently selected from Br, Cl, F and I.
In another embodiment, in conjunction with the above and below embodiments, R⁵ is a partially saturated or unsaturated 9-, 10- or 11-membered bicyclic carbocyclic ring, wherein the ring is substituted by 1, 2 or 3 substituents independently selected from R¹, R¹, nitro, cyano, -OH, -OR⁵, -OR¹,

-OC₂₆alkylnR⁵R⁵, -OC₂₆alkylnOR⁵, -NR⁵R⁵, -NR⁵R¹, -NR⁵C₂₆alkylnR⁵R⁵,
-NR³C₂₆alkylnOR¹, naphthyl, -CO₂R⁵, -C(=O)R⁵, -C(=O)NR⁵R¹, -C(=O)NR⁵R¹,
-NR⁵C(=O)R⁵, -NR⁵C(=O)R¹, -NR⁵C(=O)NR⁵R¹, -NR⁵CO₂R⁵, -C₁₈alkylnOR¹,
-C₁₈alkylnR⁵R¹, -S(=O)₉R⁵, -S(=O)₂NR⁵R⁵, -NR⁵S(=O)₂R⁵ and -OC(=O)NR⁵R⁵, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R⁵ is a saturated, partially saturated or unsaturated 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2 or 3 substituents independently selected from R¹, R¹, nitro, cyano, -OH, -OR⁵, -OR¹,

-OC₂₆alkylnR⁵R⁵, -OC₂₆alkylnOR⁵, -NR⁵R¹, -NR⁵R¹, -NR⁵C₂₆alkylnR⁵R⁵,
-NR³C₂₆alkylnOR¹, naphthyl, -CO₂R⁵, -C(=O)R⁵, -C(=O)NR⁵R¹, -C(=O)NR⁵R¹,
-NR³C(=O)R⁵, -NR³C(=O)R¹, -NR³C(=O)NR³R¹, -NR³CO₂R⁵, -C₁₈alkylnOR¹,
-C₁₈alkylnR⁵R¹, -S(=O)₉R⁵, -S(=O)₂NR⁵R⁵, -NR⁵S(=O)₂R⁵ and -OC(=O)NR⁵R⁵, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R⁵ is a saturated, partially saturated or unsaturated 9-, 10- or 11-membered bicyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2 or 3 substituents independently selected from R¹, R¹, nitro, cyano, -OH, -OR⁵, -OR¹,

-OC₂₆alkylnR⁵R⁵, -OC₂₆alkylnOR⁵, -NR⁵R¹, -NR⁵R¹, -NR⁵C₂₆alkylnR⁵R⁵,
-NR³C₂₆alkylnOR¹, naphthyl, -CO₂R⁵, -C(=O)R⁵, -C(=O)NR⁵R¹, -C(=O)NR⁵R¹,
-NR³C(=O)R⁵, -NR³C(=O)R¹, -NR³C(=O)NR³R¹, -NR³CO₂R⁵, -C₁₈alkylnOR¹,
-C₁₈alkylnR⁵R¹, -S(=O)₉R⁵, -S(=O)₂NR⁵R⁵, -NR⁵S(=O)₂R⁵ and -OC(=O)NR⁵R⁵,
and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R⁵ is a saturated, partially saturated or unsaturated 9-, 10- or 11-membered bicyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 1, 2 or 3 substituents independently selected from R⁶, R⁷, nitro, cyano, -OH, -OR⁸, -OR⁹, -OC₂,₆alkylNR⁸R⁹, -OC₂,₆alkylOR⁹, -NR⁸R⁹, -NR⁸R⁹, -NR⁸C₂,₆alkylNR⁸R⁹, -NR⁸C₂,₆alkylOR⁹, naphthyl, -CO₂R⁹, -C(=O)R⁹, -C(=O)NR⁸R⁹, -C(=O)NR⁸R⁹, -NR⁸C(=O)R⁹, -NR⁸C(=O)NR⁸R⁹, -NR⁸CO₂R⁹, -C₁₈alkylOR⁹, -C₁₆alkylNR⁸R⁹, -S(=O)₂R⁸, -S(=O)₂NR⁸R⁹, -NR⁸S(=O)₂R⁹ and -OC(=O)NR⁸R⁹, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R⁶ is H.

In another embodiment, in conjunction with the above and below embodiments, R⁶ is -(C₁₆alkyl)-R⁷, wherein the C₁₆alkyl is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

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, 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:
“Cα-β-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 C1-alkyl include, but are not limited to the following:

![Alkyl Examples](image)

"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 atom selected from F, Cl, Br and I.

“C₅-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:

![Heterocycle Examples](image)
"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, partially 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-hydroxy succinimide, 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 benzhydryl, 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 cycloalkylenylalkyl 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 benzyloxy carbonyl, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, trifluoro acetyl, 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 carboxy, hydroxy and mercapto 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, triethyldimethylsilyl, triisopropylsilyl, tertbutyldimethylsilyl, 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 aminooalcohol 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, phenyldimethylsilyl 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 aminooalcohol 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 benzzyloxy carbonyl 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 t-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:

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 alkylcarbonylalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bunsgaard 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 (Bunsgaard 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 (HPLC). 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
- mL - milliliters
- g - grams

- mg - milligrams
- M.P. - melting point
- M.S. - mass spectrometer
8-(5-(Trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-2-yloxy)quinolin-2-ol.

A mixture of 2-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazole (66 mg, 0.3 mol, prepared according to the procedure described in WO 2004/035549 A1), 2,8-dihydroquinoline (48 mg, 0.3 mmol, Fluka) and N,N-diisopropylethylamine (0.1 mL, 0.58 mmol, Aldrich) in EtOH (2 mL) was subjected to microwave irradiation at 180 °C with stirring for 60 min. The reaction mixture was allowed to cool to room temperature, the solvent was removed in vacuo and the residue was purified by silica gel chromatography, eluting with 80% EtOAc/hexane to give the title compound as an amorphous solid. MS (ESI, pos. ion) m/z: 346 (M+1).
Example 2

\[
\begin{align*}
\text{F} & \quad \text{F} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N}
\end{align*}
\]

\[\text{N-(5-(Trifluoromethyl)-1H-benzo[\text{d}]]imidazol-2-yl)quinolin-8-amine.}\]

A mixture of 2-chloro-5-(trifluoromethyl)-1H-benzo[\text{d}]]imidazole (66 mg, 0.3 mol, prepared according to the procedure described in WO 2004/035549 A1) and 8-aminoquinoline (29 mg, 0.6 mmol, Aldrich) in EtOH (2 mL) was subjected to microwave irradiation at 170 °C with stirring for 30 min. The reaction mixture was allowed to cool to room temperature, the solvent was removed in vacuo and the residue was purified by silica gel chromatography eluting with 3 % MeOH/DCM to give the title compound as an amorphous solid. MS (ESI, pos. ion) \(m/z\): 329 (M+1).

Table 1. The following examples were prepared from of 2-chloro-5-(trifluoromethyl)-1H-benzo[\text{d}]]imidazol (prepared according to the procedure described in WO 2004/035549 A1) and commercially available anilines according to the procedure described for the preparation of Example 2, or with slight modifications to that procedure.

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>M.P. (°C)</th>
<th>M.S. (ESI) (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><img src="image" alt="Structure" /></td>
<td>amorphous solid</td>
<td>344 (M+1)</td>
</tr>
</tbody>
</table>
Table 2. The following examples were prepared from various 2-chlorobenzimidazoles (prepared according to the procedures described in WO 2004/035549 A1) and 8-amino-naphthalen-2-ol according to the procedure described for the preparation of Example 2, or with slight modifications to that procedure.

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>M.P. (°C)</th>
<th>M.S. (ESI) m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image1" alt="Structure" /></td>
<td>amorphous solid</td>
<td>344 (M+1)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image2" alt="Structure" /></td>
<td>amorphous solid</td>
<td>344 (M+1)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image3" alt="Structure" /></td>
<td>amorphous solid</td>
<td>328 (M+1)</td>
</tr>
<tr>
<td>7</td>
<td><img src="image4" alt="Structure" /></td>
<td>amorphous solid</td>
<td>356 (M+1)</td>
</tr>
<tr>
<td>Example</td>
<td>Structure</td>
<td>M.P. (°C)</td>
<td>M.S. (ESI) m/z</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure 8" /></td>
<td>amorphous solid</td>
<td>378 (M+1)</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Structure 9" /></td>
<td>amorphous solid</td>
<td>424 (M+1)</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Structure 10" /></td>
<td>amorphous solid</td>
<td>412 (M+1)</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Structure 11" /></td>
<td>amorphous solid</td>
<td>344 (M+1)</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="Structure 12" /></td>
<td>amorphous solid</td>
<td>324 (M+1)</td>
</tr>
<tr>
<td>Example</td>
<td>Structure</td>
<td>M.P. (°C)</td>
<td>M.S. (ESI) m/z</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
<td>-----------</td>
<td>---------------</td>
</tr>
<tr>
<td>13</td>
<td><img src="image" alt="Structure 13" /></td>
<td>amorphous solid</td>
<td>378 (M+1)</td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="Structure 14" /></td>
<td>amorphous solid</td>
<td>354 (M+1)</td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Structure 15" /></td>
<td>amorphous solid</td>
<td>360 (M+1)</td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Structure 16" /></td>
<td>amorphous solid</td>
<td>355 (M+1)</td>
</tr>
<tr>
<td>17</td>
<td><img src="image" alt="Structure 17" /></td>
<td>amorphous solid</td>
<td>332 (M+1)</td>
</tr>
</tbody>
</table>
**Example 18**

![Chemical structure diagram](image)

N-(7-Bromo-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)quinolin-7-amine.

The reaction of 7-bromo-2-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazole (135 mg, 0.45 mmol, prepared according to the procedures described in WO 2004/035549 A1) with 7-aminoquinoline (43 mg, 0.3 mmol, Synchem) under the condition of **Example 2** afforded the title compound as an amorphous solid. MS (ESI, pos. ion) m/z: 407 (M+1).

**Example 19**

![Chemical structure diagram](image)

5-(7-Bromo-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-ylamino)naphthalen-2-ol.

The reaction of 7-bromo-2-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazole (240 mg, 0.8 mmol, prepared according to the procedure described in WO 2004/035549 A1) with 5-amino-2-naphthol (64 mg, 0.4 mmol, TCI-US) under the condition of **Example 2** afforded the title compound (57%) as an amorphous solid. MS (ESI, pos. ion) m/z: 423 (M+1).

**Example 20**

![Chemical structure diagram](image)
8-(5-(Trifluoromethyl)-1H-benzo[d]imidazol-2-yl)oxy)quinolin-2-amine.

The reaction of 2-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazole (66 mg, 0.3 mol, prepared according to the procedure described in WO 2004/035549 A1) with 2-amino-8-hydroxyquinoline (48 mg, 0.3 mmol, Fluka) under the condition of Example 1 afforded the title compound as an amorphous solid. MS (ESI, pos. ion) m/z: 345 (M+1).

**Example 21**

![Chemical Structure](image_url)

8-(5-(Trifluoromethyl)-1H-benzo[d]imidazol-2-yl)oxy)-1,2,3,4-tetrahydro-naphthalen-2-ol.

(a) 5,6,7,8-Tetrahydro-naphthalene-1,7-diol.

To a solution of 8-hydroxy-3,4-dihydro-naphthalene-2(1H)-one (0.5 g, 3.1 mmol, Maybridge) in methanol (20 mL) was added sodium borohydride (0.3 g, 7.9 mmol, Aldrich) with stirring at 0 °C. The mixture was stirred for 1 h at room temperature, diluted with water and extracted with EtOAc. The combined organic extracts were dried over Na2SO4, filtered, and evaporated under reduced pressure to afford the title compound.

(b) 8-(5-(Trifluoromethyl)-1H-benzo[d]imidazol-2-yl)oxy)-1,2,3,4-tetrahydro-naphthalen-2-ol.

A mixture of 2-chloro-5-(trifluoromethyl)-1H-benzo[d]imidazole (89 mg, 0.4 mol, prepared according to the procedure described in WO 2004/035549 A1), 5,6,7,8-tetrahydro-naphthalene-1,7-diol from step (a) above (49 mg, 0.3 mmol) and 2-methoxy-ethanol (1 mL, Aldrich) was subjected to microwave irradiation at 180 °C with stirring for 60 min twice. The solvent was removed in vacuo and the residue was purified by silica gel chromatography, eluting with 50% EtOAc/hexane to give the title compound as an amorphous solid. MS (ESI, pos. ion) m/z: 349 (M+1).
Example 22

8-(1-Phenethyl-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-ylamino)naphthalen-2-ol.

(a) 1-Phenethyl-5-(trifluoromethyl)-1H-benzo[d]imidazol-2(3H)-one.

A mixture of N1-phenethyl-4-trifluoromethyl-benzene-1,2-diamine (1 g, 3.57 mmol, Maybridge) and 1,1'-carbonyldiimidazole (0.65 g, 4 mmol, Aldrich) in DCM (25 mL) was stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue was diluted with EtOAc (50 mL). The EtOAc solution was washed successively with 1 N HCl (15 mL) and satd NaCl (20 mL), dried over MgSO₄ and filtered. The filtrate was evaporated under reduced pressure and the residue recrystallized in 70 % DCM/hexane to give the title compound. MS (ESI, pos. ion) m/z: 307 (M+1).

(b) 2-Chloro-1-phenethyl-5-(trifluoromethyl)-1H-benzo[d]imidazole.

A mixture of the benzoimidazol-2-one from step (b) above (0.85 g, 2.78 mmol) and POCl₃ (30 mL) was heated at 95 °C for 16 h. The reaction mixture was cooled to room temperature and evaporated in vacuo. The residue was dissolved in EtOAc (50 mL), washed successively with 1N NaOH (25 mL) and brine (30 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated in vacuo and the residue purified by silica gel chromatography, eluting with 30 % EtOAc/hexane to give the title compound. MS (ESI, pos. ion) m/z: 325 (M+1).

(c) 8-(1-Phenethyl-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-ylamino)naphthalen-2-ol.

The reaction of 2-chloro-1-phenethyl-5-(trifluoromethyl)-1H-benzo[d]imidazole from step (b) above (98 mg, 0.3 mol) with 8-amino-
naphthalen-2-ol (64 mg, 0.2 mmol, Aldrich) under the condition of Example 21(b) afforded the title compound. MS (ESI, pos. ion) m/z: 448(M+1).

**Example 23**

![Chemical Structure Image]

8-(5-Phenyl-1H-benzo[d]imidazol-2-ylamino)naphthalen-2-ol.

A mixture of 8-(5-bromo-1H-benzo[d]imidazol-2-ylamino)naphthalen-2-ol (18 mg, 0.05 mmol, Example 14), phenylboronic acid (12 mg, 0.1 mmol, Aldrich), PdCl$_2$(PPh$_3$)$_2$ (3.5 mg, 0.005 mmol, Aldrich), Na$_2$CO$_3$.H$_2$O (12 mg, 0.1 mmol), dimethoxyethane (0.35 mL), H$_2$O (0.15 mL) and EtOH (0.1 mL) was subjected to microwave irradiation at 120 °C with stirring for 10 min. The reaction mixture was cooled to room temperature, diluted with water (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na$_2$SO$_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give the title compound. MS (ESI, pos. ion) m/z: 352 (M+1).

**Example 24**

![Chemical Structure Image]

8-(5-(3,4,5-Trifluorophenyl)-1H-benzo[d]imidazol-2-ylamino)-1,2,3,4-tetrahydronaphthalen-2-ol
The reaction of 8-(5-bromo-1H-benzo[d]imidazo[2-ylamino]-1,2,3,4-tetrahydronaphthalen-2-ol (36 mg, 0.1 mol, **Example 26**) with 3,4,5-trifluorophenylboronic acid (26 mg, 0.15 mmol, Asymchem) under the condition of **Example 23** afforded the title compound. MS (ESI, pos. ion) m/z: 410 (M+1).

**Example 25**

![Chemical Structure Image]

8-(5-(Trifluoromethyl)-1H-benzo[d]imidazo[2-ylamino]-1,2,3,4-tetrahydronaphthalen-2-ol.

The reaction of 2-chloro-6-(trifluoromethyl)-1H-benzo[d]imidazole (154 mg, 0.7 mol, prepared according to the procedure described in WO 2004/035549 A1) with 8-amino-1,2,3,4-tetrahydronaphthalen-2-ol (83 mg, 0.5 mmol, prepared according to the procedure described in WO 2003/095420 A1) under the condition of **Example 21(b)** afforded the title compound. MS (ESI, pos. ion) m/z: 348 (M+1).

**Example 26**

![Chemical Structure Image]

8-(5-Bromo-1H-benzo[d]imidazo[2-ylamino]-1,2,3,4-tetrahydronaphthalen-2-ol.

The reaction of 5-bromo-2-chloro-1H-benzo[d]imidazole (345 mg, 1.5 mol, prepared according to the procedure described in WO 2004/035549 A1) with 8-amino-1,2,3,4-tetrahydronaphthalen-2-ol (163 mg, 1.0 mmol, prepared according to the procedure described in WO 2003/095420 A1) under the condition of **Example 21(b)** afforded the title compound. MS (ESI, pos. ion) m/z: 358 (M+1).
Biological Assays

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

Embryonic 19 day old (E19) dorsal root ganglia (DRG) were dissected from
5 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,
15 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 103
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
20 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
30 mM 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
25 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. at 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 \(^{45}\text{Ca}^{2+}\) (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 \(^{45}\text{Ca}^{2+}\) (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 \(^{45}\text{Ca}^{2+}\) (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.

\(^{45}\text{Calcium}^{2+}\) 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 be 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 $^{45}$Ca (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 $^{45}$Ca (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 10μCi/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 Mg$^{2+}$/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-butane diol. 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 dosage 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-pyrrolidine, 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 glyceryl monostearate or glyceryl 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, diacetyltartaric, dibenzoyltartaric, ditoluoyltartraric, 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, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methansulfonate, 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 form 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) 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 arylicarbonyloxyalkyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bundgaard 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-propoxyethyl, α-methoxyethyl, groups such as α-((C1-C4)alkoxy)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, pivaloyloxyethyl, α-acetoxymethyl, etc.; ethoxycarbonyl-1-methyl; or α-acetoxy-α-substituted methyl groups, for example α-acetoxyethyl.

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:

\[
\begin{array}{c}
\text{R}^3 \\
\text{R}^4 \\
\text{R}^5 \\
\text{R}^6 \\
\end{array}
\]

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

- J is NH, O, S, S(=O) or S(=O)_2;
- n is independently, at each instance, 0, 1 or 2;
- R^1 is independently selected from H, R^2, R^3, halo, nitro, cyano, -OR^4, -OR^5,
- OC_2alkyNR^6R^7, -OC_2alkyOR^6, -NR^6R^7, -NR^6R^3, -NR^6C_2alkyNR^6R^3,
- NR^6C_2alkyOR^9, naphthyl, -CO_2R^8, -C(=O)R^9, -C(=O)NR^8R^9, -C(=O)NR^8R^3,
- NR^6C(=O)R^3, -NR^6C(=O)R^3, -NR^6C(=O)NR^8R^9, -NR^6CO_2R^9, -C_1alkyloR^6,
- C_1alkyINR^6R^9, -S(=O)_nR^6, -S(=O)_2NR^8R^9, -NR^8S(=O)_2R^9 and -OC(=O)NR^8R^9,
- and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I;

- R^2 is independently selected from H, R^3, R^4, halo, nitro, cyano, -OR^4, -OR^5,
- OC_2alkyINR^6R^7, -OC_2alkyINR^6R^3, -NR^6R^7, -NR^6R^3, -NR^6C_2alkyNR^6R^3,
- NR^6C_2alkyINR^6R^9, naphthyl, -CO_2R^8, -C(=O)R^9, -C(=O)NR^8R^9, -C(=O)NR^8R^3,
- NR^6C(=O)R^3, -NR^6C(=O)R^3, -NR^6C(=O)NR^8R^9, -NR^6CO_2R^9, -C_1alkyloR^6,
- C_1alkyINR^6R^9, -S(=O)_nR^6, -S(=O)_2NR^8R^9, -NR^8S(=O)_2R^9 and -OC(=O)NR^8R^9,
- and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I;

- R^3 is independently selected from H, R^8, R^4, halo, nitro, cyano, -OR^4, -OR^5,
- OC_2alkyINR^6R^7, -OC_2alkyINR^6R^3, -NR^6R^7, -NR^6R^3, -NR^6C_2alkyINR^6R^3,
- NR^6C_2alkyINR^6R^9, naphthyl, -CO_2R^8, -C(=O)R^9, -C(=O)NR^8R^9, -C(=O)NR^8R^3,
- NR^6C(=O)R^3, -NR^6C(=O)R^3, -NR^6C(=O)NR^8R^9, -NR^6CO_2R^9, -C_1alkyloR^6,
- C_1alkyINR^6R^9, -S(=O)_nR^6, -S(=O)_2NR^8R^9, -NR^8S(=O)_2R^9 and -OC(=O)NR^8R^9,
- and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; wherein at least one of R^2 and R^3 is
selected from -OCF₃, unsubstituted C₂galkyl and C₁₉alkyl substituted by 1, 2, 3 or 4 substituents selected from halo, C₁₄haloalkyl, cyano, nitro, -C(=O)R₈,
-C(=O)OR₈, -C(=O)NR₈R₈, -C(=O)NR₈R₈, -OR₈, -OC(=O)R₈, -OC(=O)NR₈R₈,
-OC(=O)N(R₈)S(=O)₂R₈, -OC₂₆alkylNR₈R₈, -OC₂₆alkylOR₈, -SR₈, -S(=O)₂R₈,
-S(=O)₂R₈, -S(=O)₂N(R₈)C(=O)R₈, -S(=O)₂N(R₈)C(=O)OR₈, -S(=O)₂N(R₈)C(=O)OR₈,
-S(=O)₂N(R₈)C(=O)OR₈, -NR₈R₈, -NR₈R₈, -NR₈R₈, -NR₈C(=O)R₈, -NR₈C(=O)R₈,
-NR₈C(=O)NR₈R₈, -NR₈C(=O)NR₈R₈, -N(R₈)S(=O)₂R₈, -N(R₈)S(=O)₂R₈,
-N(R₈)S(=O)₂NR₈R₈, -NR₈C₂₆alkylNR₈R₈ and -NR₈C₂₆alkylOR₈; and wherein the C₁₉alkyl is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I;

R₄ is independently selected from H, R₅, R₆, halo, nitro, cyano, -OR₆, -OR₆,
-OC₂₆alkylNR₈R₈, -OC₂₆alkylOR₈, -NR₈R₈, -NR₈R₈, -NR₈C₂₆alkylNR₈R₈,
-NR₈C₂₆alkylOR₈, naphthyl, -CO₂R₆, -C(=O)NR₈R₈, -C(=O)NR₈R₈, -C(=O)NR₈R₈,
-NR₈C(=O)R₆, -NR₈C(=O)R₆, -NR₈C(=O)R₆, -NR₈CO₂R₆, -C₁₄alkylOR₈,
-C₁₄alkylNR₈R₈, -S(=O)₆R₈, -S(=O)₂N(R₈)₂R₈ and -OC(=O)NR₈R₈,
and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I;

R₅ is a saturated, partially saturated or unsaturated 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 available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2 or 3 substituents independently selected from R₆, R₇, nitro, cyano, -OH, -OR₇, -OR₇,
-OC₂₆alkylNR₈R₇, -OC₂₆alkylOR₇, -NR₈R₇, -NR₈R₇, -NR₈C₂₆alkylNR₈R₇,
-NR₈C₂₆alkylOR₇, naphthyl, -CO₂R₇, -C(=O)NR₈R₇, -C(=O)NR₈R₇, -C(=O)NR₈R₇,
-NR₈C(=O)R₇, -NR₈C(=O)R₇, -NR₈C(=O)R₇, -NR₈CO₂R₇, -C₁₄alkylOR₇,
-C₁₄alkylNR₈R₇, -S(=O)₇R₇, -S(=O)₂N(R₈)₂R₇ and -OC(=O)NR₈R₇, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; or

R₆ is phenyl substituted by 0, 1, 2 or 3 substituents selected from halo,
-OR₆, C₁₄alkyl, and C₁₄haloalkyl, and additionally substituted by C₁₉alkyl or C₁₄alkyl(phenyl) wherein either is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C₁₄haloalkyl, cyano, nitro, -C(=O)R₈, -C(=O)OR₈, -C(=O)NR₈R₈,
-C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^a, -OC(=O)NR^aR^a, -OC(=O)N(R^b)S(=O)R^a, 
-OC_2=alky1NR^aR^a, -OC_2=alky1OR^a, -SR^a, -S(=O)R^a, -S(=O)_2R^a, -S(=O)NR^aR^a, 
-S(=O)_2N(R^b)C(=O)R^a, -S(=O)_2N(R^b)C(=O)OR^a, -S(=O)_2N(R^b)C(=O)NR^aR^a, 
-NR^aR^a, -N(R^b)C(=O)R^a, -N(R^b)C(=O)OR^a, -N(R^b)C(=O)NR^aR^a, 
5  -N(R^b)C(=NR^a)NR^aR^a, -N(R^b)S(=O)_2R^a, -N(R^b)S(=O)_2NR^aR^a, 
-NR^aC_2=alky1NR^aR^a and -NR^aC_2=alky1OR^a; and wherein the C_1,2-alkyl is 
additionally substituted by 0 or 1 groups independently selected from R^b and 
additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected 
from Br, Cl, F and I; 
10  R^6 is H or -(C_1-alkyl)-R^1, wherein the C_1,2-alkyl is additionally substituted 
by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; 
R^a is independently, at each instance, H or R^b; 
R^b is independently, at each instance, phenyl, benzyl or C_1,4-alkyl, the 
phenyl, benzyl and C_1,6-alkyl being substituted by 0, 1, 2 or 3 substituents selected 
from halo, C_1-alkyl, C_1,3-haloalkyl, -OC_1,4-alkyl, -NH_2, -NHC_1,4-alkyl, 
-N(C_1-alkyl)C_1-alkyl; 
15  R^2 is independently, in each instance, phenyl substituted by 0, 1 or 2 
groups selected from halo, C_1,6-alkyl, C_1,4-haloalkyl, cyano, nitro, -C(=O)R^a, 
-C(=O)OR^a, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^a, -OC(=O)NR^aR^a, 
20  -OC(=O)N(R^b)S(=O)_2R^a, -OC_2=alky1NR^aR^a, -OC_2=alky1OR^a, -SR^a, -S(=O)R^a, 
-S(=O)_2R^a, -S(=O)_2NR^aR^a, -S(=O)_2N(R^b)C(=O)R^a, -S(=O)_2N(R^b)C(=O)OR^a, 
-S(=O)_2N(R^b)C(=O)NR^aR^a, -NR^aR^a, -N(R^b)C(=O)R^a, -N(R^b)C(=O)OR^a, 
-N(R^b)C(=O)NR^aR^a, -N(R^b)S(=O)_2R^a, -N(R^b)S(=O)_2NR^aR^a and -NR^aC_2=alky1OR^a; or R^c is a 
25  saturated, partially saturated or unsaturated 5- or 6-membered ring heterocycle 
containing 1, 2 or 3 heteroatoms independently selected from N, O and S, wherein 
no more than 2 of the ring members are O or S, wherein the heterocycle is 
optionally fused with a phenyl ring, and the carbon atoms of the heterocycle are 
substituted by 0, 1 or 2 oxo or thioxo groups, wherein the heterocycle or fused 
phenyl ring is substituted by 0, 1, 2 or 3 substituents selected from halo, C_1,4-alkyl, 
C_1,3-haloalkyl, cyano, nitro, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, 
-C(=NR^b)NR^aR^a, -OR^a, -OC(=O)R^a, -OC(=O)NR^aR^a, -OC(=O)N(R^b)S(=O)_2R^a,
-OC₃₋₆alkylNR₉R₈, -OC₃₋₆alkylOR₉, -SR₉, -S(=O)R₉, -S(=O)₂R₈, -S(=O)₂NR₉R₈, -S(=O)₂N(R₉)C(=O)OR₉, -S(=O)₂N(R₉)C(=O)NR₉R₈, -NR₉R₈, -N(R₉)C(=O)OR₉, -N(R₉)C(=O)NR₉R₈, -N(R₉)C(N=N₉)NR₈R₈, -N(R₉)C(S)=O, -N(R₉)S(=O)₂R₈, -N(R₉)S(=O)₂NR₉R₈,
5  -NR₉C₅₋₆alkylNR₉R₈ and -NR₉C₅₋₆alkylOR₉;

R₉ is, independently, in each instance, C₁₋₉alkyl or C₁₋₄alkyl(phenyl) wherein either is substituted by 0, 1, 2, 3 or 4 substituents selected from halo,
C₁₋₄haloalkyl, cyano, nitro, -C(=O)R₈, -C(=O)OR₈, -C(=O)NR₉R₈,
-C(=N₉)NR₉R₈, -OR₈, -OC(=O)R₈, -OC(=O)NR₉R₈, -OC(=O)N(R₉)S(=O)₂R₈,
10  -OC₃₋₆alkylNR₉R₈, -OC₃₋₆alkylOR₈, -SR₈, -S(=O)R₈, -S(=O)₂R₈, -S(=O)₂NR₉R₈,
    -S(=O)₂N(R₉)C(=O)OR₈, -S(=O)₂N(R₉)C(=O)NR₉R₈, -NR₉R₈, -N(R₉)C(=O)OR₈, -N(R₉)C(=O)NR₉R₈,
    -N(R₉)C(N=N₉)NR₈R₈, -N(R₉)S(=O)₂R₈, -N(R₉)S(=O)₂NR₉R₈,
15  -NR₉C₅₋₆alkylNR₉R₈ and -NR₉C₅₋₆alkylOR₉; and wherein the C₁₋₉alkyl is additionally substituted by 0 or 1 groups independently selected from R₉ and additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I;

R₉ is, independently, in each instance, R₉ or H;

R₈ is, independently, in each instance, a saturated, partially saturated or unsaturated 5- or 6-membered monocyclic ring containing 1, 2 or 3 atoms selected from N, O and S, so long as the combination of O and S atoms is not greater than 2, wherein the ring is substituted by 0 or 1 oxo or thioxo groups;

R₉ is, independently, in each instance, phenyl or a saturated, partially saturated or unsaturated 5- or 6-membered monocyclic ring containing 1, 2 or 3 atoms selected from N, O and S, so long as the combination of O and S atoms is not greater than 2, wherein the ring is substituted by 0 or 1 oxo or thioxo groups, wherein the phenyl or monocycle are substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, nitro, -C(=O)R₈, -C(=O)OR₈, -C(=O)NR₉R₈,
-C(=N₉)NR₉R₈, -OR₈, -OC(=O)R₈, -OC(=O)NR₉R₈, -OC(=O)N(R₉)S(=O)₂R₈,
20  -OC₃₋₆alkylNR₉R₈, -OC₃₋₆alkylOR₈, -SR₈, -S(=O)R₈, -S(=O)₂R₈, -S(=O)₂NR₉R₈,
    -S(=O)₂N(R₉)C(=O)OR₈, -S(=O)₂N(R₉)C(=O)NR₉R₈, -NR₉R₈, -N(R₉)C(=O)OR₈, -N(R₉)C(=O)NR₉R₈,
    -NR₉R₈, -N(R₉)C(=O)R₈, -N(R₉)C(=O)OR₈, -N(R₉)C(=O)NR₉R₈,
25  -NR₉R₈, -N(R₉)C(=O)R₈, -N(R₉)C(=O)OR₈, -N(R₉)C(=O)NR₉R₈,
-N(R²)C(=NR⁴)NR⁵R⁷, -N(R⁴)S(=O)⁴R⁸, -N(R⁴)S(=O)₂NR³R⁷,
-NR²C₂₋₆alkylNR³R⁷ and -NR²C₂₋₆alkylOR³; and
R¹ is 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 available carbon atoms of the
ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is
substituted by 0, 1, 2 or 3 substituents independently selected from R⁵, R⁶, R⁷,
halo, nitro, cyano, -OH, -OR⁸, -OR⁹, -OC₂₋₆alkylNR³R⁷, -OC₂₋₆alkylOR³, -NR²R⁷,
-NR²R⁷, -NR²C₂₋₆alkylNR³R⁷, -NR²C₂₋₆alkylOR³, naphthyl, -CO₂R⁷, -C(=O)R⁷,
-C(=O)NR³R⁸, -C(=O)NR³R⁹, -NR²C(=O)R⁸, -NR²C(=O)NR³R⁹,
-NR²CO₂R⁹, -C₁₋₄alkylOR³, -C₁₋₄alkylINR³R⁷, -S(=O)₂R⁷, -S(=O)₂NR³R⁷,
-NR³S(=O)₂R⁷, -NR³S(=O)₂R⁸ and -OC(=O)NR³R⁷, and the ring is additionally
substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F
and I.

2. A compound according to Claim 1, wherein R¹ is independently
selected from nitro, cyano, -OR⁸, -OR⁹, -OC₂₋₆alkylINR³R⁷, -OC₂₋₆alkylOR³,
-NR²R⁷, -NR²R⁷, -NR²C₂₋₆alkylINR³R⁷, -NR²C₂₋₆alkylOR³, naphthyl, -CO₂R⁷,
-C(=O)R⁷, -C(=O)NR³R⁸, -C(=O)NR³R⁹, -NR²C(=O)R⁸, -NR²C(=O)NR³R⁹,
-NR²C(=O)NR³R⁹, -NR²CO₂R⁹, -C₁₋₄alkylOR³, -C₁₋₄alkylINR³R⁷, -S(=O)₂R⁷,
-S(=O)₂NR³R⁷, -NR³S(=O)₂R⁷ and -OC(=O)NR³R⁷.

3. A compound according to Claim 1, wherein R¹ is independently
selected from R⁷ and R⁹.

4. A compound according to Claim 1, wherein R² is unsubstituted
C₂₋₆alkyl.

5. A compound according to Claim 1, wherein R² is C₁₋₄alkyl
substituted by 1, 2, 3 or 4 substituents selected from halo, C₁₋₄haloalkyl, cyano,
nitro, -C(=O)R⁸, -C(=O)OR⁸, -C(=O)NR³R⁷, -C(=NR³)NR³R⁷, -OR⁸, -OC(=O)R⁸,
-OC(=O)NR³R⁷, -OC(=O)N(R³)S(=O)₂R⁷, -OC₂₋₆alkylINR³R⁷, -OC₂₋₆alkylOR³,
-SR, -S(=O)R, -S(=O)₂R, -S(=O)₂NR²R³, -S(=O)₂N(R³)C(=O)R⁴,
-S(=O)₂N(R³)C(=O)OR⁴, -S(=O)₂N(R³)C(=O)NR²R³, -NR²R³, -N(R³)C(=O)R⁴,
-N(R³)C(=O)OR⁴, -N(R³)C(=O)NR²R³, -N(R³)C(=O)NR²R³, -N(R³)S(=O)₂R⁴,
-N(R³)S(=O)₂NR²R³, -NR³C₂₆alkylNR²R³ and -NR³C₂₆alkylOR³; and wherein the
5 C₁₆alkyl is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

6. A compound according to Claim 1, wherein
   R¹ is H;
   R² is independently selected from R⁵, R¹, halo, nitro, cyano, -OR⁵,
   -OR¹, -OC₂₆alkylNR⁵R⁶, -OC₂₆alkylOR¹, -NR²R³, -NR²R¹, -NR³C₂₆alkylNR⁵R³,
   -NR³C₂₆alkylOR¹, naphthyl, -CO₂R³, -C(=O)R³, -C(=O)NR⁵R³, -C(=O)NR⁵R¹,
   -NR³C(=O)R³, -NR³C(=O)R¹, -NR³C(=O)NR²R³, -NR³CO₂R³, -C₁₆alkylOR¹,
   -C₁₆alkylNR⁵R³, -S(=O)₃R⁵, -S(=O)₂NR³R⁶, -NR³S(=O)₂R⁵ and -OC(=O)NR⁵R³;
   R³ is H; and
   R⁴ is H.

7. A compound according to Claim 6, wherein R² is C₁₆alkyl
   substituted by 1, 2, 3 or 4 F atoms.

8. A compound according to Claim 1, wherein
   R¹ is H;
   R² is H;
   R³ is independently selected from R⁵, R¹, halo, nitro, cyano, -OR⁵,
   -OR¹, -OC₂₆alkylNR⁵R³, -OC₂₆alkylOR¹, -NR²R³, -NR²R¹, -NR³C₂₆alkylNR⁵R³,
   -NR³C₂₆alkylOR¹, naphthyl, -CO₂R³, -C(=O)R³, -C(=O)NR⁵R³, -C(=O)NR⁵R¹,
   -NR³C(=O)R³, -NR³C(=O)R¹, -NR³C(=O)NR²R³, -NR³CO₂R³, -C₁₆alkylOR¹,
   -C₁₆alkylNR⁵R³, -S(=O)₃R⁵, -S(=O)₂NR³R⁶, -NR³S(=O)₂R⁵ and -OC(=O)NR⁵R³;
   R⁴ is H.
9. A compound according to Claim 8, wherein R^3 is C_{1-9}alkyl substituted by 1, 2, 3 or 4 F atoms.

10. A compound according to Claim 1, wherein R^5 is a saturated, partially saturated or unsaturated 9-, 10- or 11-membered bicyclic carbocyclic ring, wherein the ring is substituted by 1, 2 or 3 substituents independently selected from R^f, R^i, nitro, cyano, -OH, -OR^e, -OR^i, -OC_{2-6}alkyl NR^gR^h, -OC_{2-6}alkylOR^g, -NR^gR^h, -NR^gR^i, -NR^fC_{2-6}alkylNR^gR^h, -NR^fC_{2-6}alkylOR^g, naphthyl, -CO_{2-6}R^e, -C(=O)R^e, -C(=O)NR^gR^h, -C(=O)NR^gR^i, -NR^fC(=O)R^e, -NR^fC(=O)R^i, -NR^fC(=O)NR^gR^h, -NR^fC(=O)NR^gR^i, -NR^fC(=O)NR^fR^h, -NR^fC(=O)NR^fR^i, -NR^fNR^gR^h, -NR^fNR^gR^i, -NR^fNR^fR^h, -NR^fNR^fR^i, -S(=O)NR^gR^h, -S(=O)NR^fR^h, -S(=O)NR^gR^i, -S(=O)NR^fR^i, and -OC(=O)NR^gR^h and -OC(=O)NR^gR^i, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

11. A compound according to Claim 1, wherein R^5 is a saturated, partially saturated or unsaturated 9-, 10- or 11-membered bicyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2 or 3 substituents independently selected from R^f, R^i, nitro, cyano, -OH, -OR^e, -OR^i, -OC_{2-6}alkyl NR^gR^h, -OC_{2-6}alkylOR^g, -NR^gR^h, -NR^gR^i, -NR^fC_{2-6}alkylNR^gR^h, -NR^fC_{2-6}alkylOR^g, naphthyl, -CO_{2-6}R^e, -C(=O)R^e, -C(=O)NR^gR^h, -C(=O)NR^gR^i, -NR^fC(=O)R^e, -NR^fC(=O)R^i, -NR^fC(=O)NR^gR^h, -NR^fC(=O)NR^gR^i, -NR^fCO_{2-6}R^e, -NR^fC_{1-6}alkylOR^g, -C_{1-6}alkylNR^gR^h, -S(=O)NR^gR^h, -S(=O)NR^fR^h, -S(=O)NR^gR^i, -S(=O)NR^fR^i, and -OC(=O)NR^gR^h, -OC(=O)NR^fR^h, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

12. A compound according to Claim 1 selected from the group of:
5-(5-(trifluoromethyl)-1H-benzo[d]imidazol-2-ylamino)naphthalen-2-ol;
5-(7-bromo-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-ylamino)naphthalen-2-ol;
6-(5-(trifluoromethyl)-1H-benzo[d]imidazol-2-ylamino)naphthalen-1-ol;
8-(1-isopropyl-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(1-phenethyl-5-(trifluoromethyl)-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(5-(3,4,5-trifluorophenyl)-1H-benz[d]imidazol-2-ylamino)-1,2,3,4-tetrahydronaphthalen-2-ol;
8-(5-(trifluoromethoxy)-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(5-(trifluoromethyl)-1H-benz[d]imidazol-2-ylamino)-1,2,3,4-tetrahydronaphthalen-2-ol;
8-(5-(trifluoromethyl)-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(5-(trifluoromethyl)-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(5-(trifluoromethyl)-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(5-(trifluoromethyl)-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(5-(trifluoromethyl)-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(5-(trifluoromethyl)-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(5-bromo-1H-benz[d]imidazol-2-ylamino)-1,2,3,4-tetrahydronaphthalen-2-ol;
8-(5-bromo-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(5-chloro-6-methyl-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(5-phenyl-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(5-tert-butyl-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(6-chloro-5-(trifluoromethyl)-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(6-chloro-5-nitro-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(7-bromo-5-(trifluoromethyl)-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
8-(7-chloro-5-(trifluoromethyl)-1H-benz[d]imidazol-2-ylamino)naphthalen-2-ol;
N-(5-(trifluoromethyl)-1H-benz[d]imidazol-2-yl)quinolin-8-amine;
N-(7-bromo-5-(trifluoromethyl)-1H-benz[d]imidazol-2-yl)quinolin-7-amine; and
N-(naphthalen-1-yl)-5-(trifluoromethyl)-1H-benz[d]imidazol-2-amine;
or any pharmaceutically-acceptable salts or hydrates thereof.

13. The use of a compound according to any one of Claims 1-12 in the
manufature of a medicinal.
14. The use of a compound according to any one of Claims 1-12 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, 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.

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

INV. C07D401/12 C07D235/30 C07D235/26 A61K31/4184 A61K31/4709
A61P29/00

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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<tbody>
<tr>
<td>X</td>
<td>WO 2004/075823 A2 (FR.) 10 September 2004 (2004-09-10) see claim 1 and manyl examples, especially examples 433, 442, 509 and e.g. 429, 430 and 432;</td>
<td>1, 5, 6, 10, 11, 13, 15</td>
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<td>X</td>
<td>US 2004/122237 A1 (AMIRI, PAYMAN ET AL) 24 June 2004 (2004-06-24) see claim 1 and RN number compounds: 611212-63-6, 611212-78-3, 611212-24-2, 611213-26-4, 611213-36-6, 611214-41-6, 611215-03-3, 611215-18-0, 611215-47-5, 611215-53-3, 611215-98-6, 611216-00-3</td>
<td>1, 2, 4, 6, 8, 11, 13, 15</td>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

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

*E* earlier document published on or after the international filing date

*L* document which may throw doubts on priority claims 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

*Y* 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

**X** 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.

*Y* document member of the same patent family

Date of the actual completion of the international search

12 May 2006

Date of mailing of the international search report

23/05/2006

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

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Traegler-Goeldel, M
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<th>Category</th>
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<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>WO 02/46169 A1 (AVENTIS PHARMA DEUTSCHLAND G.M.B.H., GERMANY) 13 June 2002 (2002-06-13) see claim 1 and all examples 1-18</td>
<td>1-9,13, 15</td>
</tr>
<tr>
<td>X</td>
<td>BENDALE, PRAVIN M. ET AL: &quot;Rapid Microwave-Assisted Liquid-Phase Combinatorial Synthesis of 2-(Arylamino)benzimidazoles&quot; JOURNAL OF COMBINATORIAL CHEMISTRY , 4(4), 359-361 CODEN: JCCFF; ISSN: 1520-4766, 2002, XP009066121 see entries 1 to 10 and 15 to 23 in table 1</td>
<td>1,8,10, 13,15</td>
</tr>
<tr>
<td>X</td>
<td>HUANG, KUO-TING ET AL: &quot;Liquid-phase combinatorial synthesis of aminobenzimidazoles&quot; BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS , 12(7), 1001-1003 CODEN: BMCLEB; ISSN: 0960-894X, 2002, XP009066122 see entries 1 to 4 and 9 to 16 of table 1</td>
<td>1,8,10, 13,15</td>
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