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(54) Title: SUBSTITUTED SULFONAMIDOPROPIONAMIDES AND METHODS OF USE

(57) Abstract: This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating inflammation-related disorders, including pain.

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SUBSTITUTED SULFONAMIDOPROPIONAMIDES AND METHODS OF USE**BACKGROUND OF THE INVENTION**5 Field of the Invention

This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating inflammation-related disorders, including pain.

10 State of the Art

More than two million people in the United States alone are incapacitated by chronic pain on any given day (T. Jessell & D. Kelly, Pain and Analgesia in PRINCIPLES OF NEURAL SCIENCE, third edition (E. Kandel, J. Schwartz, T. Jessell, eds., (1991))).

Unfortunately, current treatments for pain are only partially effective, and many cause lifestyle
15 altering, debilitating, and/or dangerous side effects. For example, non-steroidal anti-inflammatory drugs ("NSAIDs") such as aspirin, ibuprofen, and indomethacin are moderately effective against inflammatory pain but they are also renally toxic, and high doses tend to cause gastrointestinal irritation, ulceration, bleeding, increased cardiovascular risk, and confusion. Patients treated with opioids frequently experience confusion and constipation, and
20 long-term opioid use is associated with tolerance and dependence. Local anesthetics such as lidocaine and mixelitine simultaneously inhibit pain and cause loss of normal sensation. In addition, when used systemically, local anesthetics are associated with adverse cardiovascular effects. Thus, there is currently an unmet need in the treatment of chronic pain.

Pain is a perception based on signals received from the environment and transmitted
25 and interpreted by the nervous system (for review, see M. Millan, Prog. Neurobiol. 57:1-164 (1999)). Noxious stimuli such as heat and touch cause specialized sensory receptors in the skin to send signals to the central nervous system ("CNS"). This process is called nociception, and the peripheral sensory neurons that mediate it are nociceptors. Depending on the strength of the signal from the nociceptor(s) and the abstraction and elaboration of that signal by the CNS,
30 a person may or may not experience a noxious stimulus as painful. When one's perception of pain is properly calibrated to the intensity of the stimulus, pain serves its intended protective function. However, certain types of tissue damage cause a phenomenon, known as hyperalgesia or pronociception, in which relatively innocuous stimuli are perceived as intensely painful because the person's pain thresholds have been lowered. Both inflammation

and nerve damage can induce hyperalgesia. Thus, persons afflicted with inflammatory conditions, such as sunburn, osteoarthritis, colitis, carditis, dermatitis, myositis, neuritis, inflammatory bowel disease, collagen vascular diseases (which include rheumatoid arthritis and lupus) and the like, often experience enhanced sensations of pain. Similarly, trauma, surgery, amputation, abscess, causalgia, collagen vascular diseases, demyelinating diseases, trigeminal neuralgia, cancer, chronic alcoholism, stroke, thalamic pain syndrome, diabetes, herpes infections, acquired immune deficiency syndrome ("AIDS"), toxins and chemotherapy cause nerve injuries that result in pain.

As the mechanisms by which nociceptors transduce external signals under normal and hyperalgesic conditions become better understood, processes implicated in hyperalgesia can be targeted to inhibit the lowering of the pain threshold and thereby lessen the amount of pain experienced.

Bradykinin (BK) and the related peptide, kallidin (Lys-BK) mediate the physiological actions of kinins on the cardiovascular and renal systems. However, the active peptides, BK and kallidin, are quickly degraded by peptidases in the plasma and other biological fluids and by those released from a variety of cells, so that the half-life of BK in plasma is reported to be approximately 17 seconds (1). BK and kallidin are rapidly metabolized in the body by carboxypeptidase N, which removes the carboxyterminal arginine residue to generate des-Arg BK or des-Arg kallidin. Des-Arg-kallidin is among the predominant kinins in man and mediate the pathophysiological actions of kinins in man. In addition to being a very potent proinflammatory peptide, des-Arg-BK or des-Arg-kallidin is known to induce vasodilation, vascular permeability, and bronchoconstriction (for review, see Regoli and Barabe, Pharmacological Rev, 32(1), 1-46 (1980)). In addition, des-Arg-BK and des-Arg-kallidin appear to be particularly important mediators of inflammation and inflammatory pain as well as being involved in the maintenance thereof. There is also a considerable body of evidence implicating the overproduction of des-Arg-kallidin in conditions in which pain is a prominent feature such as septic shock, arthritis, angina, and migraine.

The membrane receptors that mediate the pleiotropic actions of kinins are of two distinct classes, designated B1 and B2. Both classes of receptors have been cloned and sequenced from a variety of species, including man (Menke, et al, J. Biol. Chem. 269, 21583-21586 (1994); Hess et al, Biochem. Biophys. Res. Commun. 184, 260-268 (1992)). They are typical G protein coupled receptors having seven putative membrane spanning regions. In various tissues, BK receptors are coupled to every known second messenger. B2 receptors, which have a higher affinity for BK, appear to be the most prevalent form of bradykinin

receptor. Essentially all normal physiological responses and many pathophysiological responses to bradykinin are mediated by B2 receptors.

B1 receptors, on the other hand, have a higher affinity for des-Arg-BK compared with BK, whereas des-Arg-BK is inactive at B2 receptors. In addition, B1 receptors are not normally expressed in most tissues. Their expression is induced upon injury or tissue damage as well as in certain kinds of chronic inflammation or systemic insult (F. Marceau, et al., Immunopharmacology, 30, 1-26 (1995)). Furthermore, responses mediated by B1 receptors are up-regulated from a null level following administration of bacterial lipopolysaccharide (LPS) or inflammatory cytokines in rabbits, rats, and pigs.

The pain-inducing properties of kinins coupled with the inducible expression of B1 receptors make the B1 receptor an interesting target in the development of anti-inflammatory, antinociceptive, antihyperalgesic and analgesic agents that may be directed specifically at injured tissues with minimal actions in normal tissues.

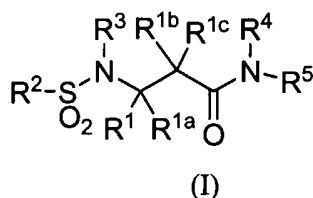
Certain compounds have been described as bradykinin antagonists. WO 03/07958, published 30 Jan. 2003, describes tetrahydroquinoxalines. Dihydroquinoxalinones are described in a JACS communication.

Piperazine-2,3,5-triones are described in Tet. Lett., 40, 7557-7560 (1999). European application 641779, published 8 Mar. 1995, describes 3,6-dioxopiperazines as platelet aggregation inhibitors.

Clearly, there is a need for new, safe and effective treatments for inflammation and pain. Such agents are provided in the present invention.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, this invention is directed to a class of compounds useful in treating inflammation and pain and having the structure of Formula (I):



wherein:

R^1 is selected from H, cyano, $-C(O)OC_{1-8}alkyl$, $-C(O)OH$, $-C(=O)NR^aR^a$, or $-C_{1-8}alkyl$ substituted by 0, 1, 2, or 3 groups independently selected from R^b , cyano, oxo, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$,

-OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^a, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 5 additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms independently selected from Br, Cl, F and I;

R^{1a} and R^{1b} are each independently, H, F, Cl, -OCH₃, -C₁₋₂alkyl or -CF₃;

R^{1c} is H, -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b,
 -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b,
 10 -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a,
 -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a,
 -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a, -NR^aC₂₋₆alkylOR^a, or -C₁₋₆alkyl
 substituted by 0, 1, 2 or 3 substituents selected from -C₁₋₄haloalkyl, halo, cyano, nitro,
 15 -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a or -NR^aC₂₋₆alkylOR^a;

20 R² is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or
 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic hydrocarbon ring containing 0, 1, 2, 3 or 4 atoms
 selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo
 groups and the ring is substituted by 0, 1, 2 or 3 substituents independently selected from R^c,
 R^g, C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,
 25 -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a,
 -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b,
 -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
 -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b,
 -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and the ring is additionally
 30 substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I;

R³ is H, phenyl, benzyl or -C₁₋₆alkyl, the phenyl, benzyl and -C₁₋₆alkyl being
 substituted by 0, 1, 2 or 3 substituents independently selected from R^c, R^g, -C₁₋₄haloalkyl, halo,
 cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b,
 -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b,

-S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b,
 -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a,
 -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and
 -NR^aC₂₋₆alkylOR^a, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atom selected from Br,
 5 Cl, F and I;

R⁴ is H, phenyl, benzyl or -C₁₋₆alkyl, the phenyl, benzyl and C₁₋₆alkyl being substituted
 by 0, 1, 2 or 3 substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, -OC₁₋₄alkyl,
 -NH₂, -NHC₁₋₄alkyl, and -N(C₁₋₄alkyl)C₁₋₄alkyl, and additionally substituted by 0, 1, 2, 3, 4, 5
 or 6 atom selected from Br, Cl, F and I;

10 R⁵ is a saturated, partially saturated or unsaturated 8-, 9-, 10- or 11-membered bicyclic
 or 12-, 13-, 14- or 15- membered tricyclic hydrocarbon ring containing 0, 1, 2, 3 or 4 atoms
 selected from N, O and S, wherein the carbon and sulfur atoms of the ring are substituted by 0,
 1 or 2 oxo groups and the ring is substituted by R⁶, R⁷ or R⁸ independently selected from basic
 moieties, and additionally substituted by 0, 1, 2 or 3 substituents independently selected from
 15 R⁶, R⁷ and R⁸ which are selected from R^g, -C₁₋₈alkyl, -C₁₋₄haloalkyl, cyano, nitro, -C(=O)R^b,
 -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 20 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and the
 ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents selected from R⁶, R⁷, R⁸, R⁹ and
 R¹⁰ which are independently selected from Br, Cl, F and I;

wherein, R³ and R⁴ together may additionally be C₂₋₃alkylene substituted by 0, 1 or 2
 substituents independently selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, oxo, cyano, nitro,
 25 -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 30 additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and
 I; or

R^{1c} and R⁴ together may additionally be C₂₋₄alkylene substituted by 0, 1 or 2
 substituents selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b,
 -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,

-OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 5 additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and I; or

a substituent on R² that is vicinal to the -SO₂-R² bond together with R³ may additionally be C₁₋₃alkylene substituted by 0, 1 or 2 substituents selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,
 10 -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and additionally substituted
 15 by 0, 1, 2, 3 or 4 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 -C₁₋₆alkyl, the phenyl, benzyl and -C₁₋₆alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, -C₁₋₄alkyl, -C₁₋₃haloalkyl, -OC₁₋₄alkyl, -NH₂, -NHC₁₋₄alkyl, -N(C₁₋₄alkyl)C₁₋₄alkyl;

20 R^d is independently at each instance -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 25 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a or -NR^aC₂₋₆alkylOR^a;

R^c is independently at each instance -C₁₋₆alkyl substituted by 0, 1, 2 or 3 substituents independently selected from R^d and additionally substituted by 0 or 1 substituents selected from R^e; and

30 R^e is independently at each instance a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic hydrocarbon ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents independently selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,

-OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and the
 5 ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; or

any pharmaceutically-acceptable salt or hydrate thereof.

In one embodiment, in conjunction with any one of the below embodiments, R¹ is selected from H or -C₁₋₈alkyl substituted by 0, 1, 2, or 3 groups independently selected from
 10 R^g, cyano, oxo, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a,
 -OC(=O)R^a, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a,
 -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^a,
 -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a,
 -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and
 15 -NR^aC₂₋₆alkylOR^a, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms independently selected from Br, Cl, F and I;

R^{1a} and R^{1b} are each independently, H, F, Cl, -OCH₃, -C₁₋₂alkyl or -CF₃;

R^{1c} is H, -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b,
 -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b,
 20 -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a,
 -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a,
 -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a, -NR^aC₂₋₆alkylOR^a, or -C₁₋₆alkyl
 substituted by 0, 1, 2 or 3 substituents selected from -C₁₋₄haloalkyl, halo, cyano, nitro,
 25 -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a or -NR^aC₂₋₆alkylOR^a;

30 R² is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic hydrocarbon ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents independently selected from R^c, R^g, C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,

- $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$,
 $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$,
 $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$,
 $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$,
5 $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, 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 H, phenyl, benzyl or $-\text{C}_{1-6}\text{alkyl}$, the phenyl, benzyl and $-\text{C}_{1-6}\text{alkyl}$ being substituted by 0, 1, 2 or 3 substituents independently selected from R^c , R^g , $-\text{C}_{1-4}\text{haloalkyl}$, halo, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$,
10 $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$,
 $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$,
 $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and
 $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atom selected from Br,
15 Cl, F and I;
 R^4 is H, phenyl, benzyl or $-\text{C}_{1-6}\text{alkyl}$, the phenyl, benzyl and $\text{C}_{1-6}\text{alkyl}$ being substituted by 0, 1, 2 or 3 substituents independently selected from $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-3}\text{haloalkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{NH}_2$, $-\text{NHC}_{1-4}\text{alkyl}$, and $-\text{N}(\text{C}_{1-4}\text{alkyl})\text{C}_{1-4}\text{alkyl}$, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atom selected from Br, Cl, F and I;
20 R^5 is a saturated, partially saturated or unsaturated 8-, 9-, 10- or 11-membered bicyclic or 12-, 13-, 14- or 15- membered tricyclic hydrocarbon ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon and sulfur atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by R^6 , R^7 or R^8 independently selected from basic moieties, and additionally substituted by 0, 1, 2 or 3 substituents independently selected from
25 R^6 , R^7 and R^8 which are selected from R^g , $-\text{C}_{1-8}\text{alkyl}$, $-\text{C}_{1-4}\text{haloalkyl}$, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$,
 $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$,
 $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$,
 $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$,
30 $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents selected from R^6 , R^7 , R^8 , R^9 and R^{10} which are independently selected from Br, Cl, F and I;
wherein, R^3 and R^4 together may additionally be $\text{C}_{2-3}\text{alkylene}$ substituted by 0, 1 or 2 substituents independently selected from $-\text{C}_{1-8}\text{alkyl}$, $-\text{C}_{1-4}\text{haloalkyl}$, halo, oxo, cyano, nitro,

-C(=O)R^v, -C(=O)OR^v, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 5 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and
 I; or

R^{1c} and R⁴ together may additionally be C₂₋₄alkylene substituted by 0, 1 or 2
 substituents selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b,
 10 -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 15 additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and
 I; or

a substituent on R² that is vicinal to the -SO₂-R² bond together with R³ may
 additionally be C₁₋₃alkylene substituted by 0, 1 or 2 substituents selected from -C₁₋₈alkyl, -
 C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,
 20 -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a,
 -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b,
 -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
 -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b,
 -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and additionally substituted
 25 by 0, 1, 2, 3 or 4 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 -C₁₋₆alkyl, the phenyl, benzyl
 and -C₁₋₆alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, -C₁₋₄alkyl, -
 C₁₋₃haloalkyl, -OC₁₋₄alkyl, -NH₂, -NHC₁₋₄alkyl, -N(C₁₋₄alkyl)C₁₋₄alkyl;

30 R^d is independently at each instance -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, cyano, nitro,
 -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,

$-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$,
 $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ or $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$;

R^c is independently at each instance $-\text{C}_{1-6}\text{alkyl}$ substituted by 0, 1, 2 or 3 substituents independently selected from R^d and additionally substituted by 0 or 1 substituents selected from R^g ; and

R^g is independently at each instance a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic hydrocarbon ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents independently selected from $-\text{C}_{1-8}\text{alkyl}$, $-\text{C}_{1-4}\text{haloalkyl}$, halo, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, 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 any one of the below embodiments, R^1 is selected from H or $-\text{C}_{1-8}\text{alkyl}$ substituted by 0, 1, 2, or 3 groups independently selected from R^g , cyano, oxo, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I;

R^{1a} and R^{1b} are each independently, H, F, Cl, $-\text{OCH}_3$, $-\text{C}_{1-2}\text{alkyl}$ or $-\text{CF}_3$;

R^{1c} is H, $-\text{C}_{1-8}\text{alkyl}$, $-\text{C}_{1-4}\text{haloalkyl}$, halo, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, or $-\text{C}_{1-6}\text{alkyl}$ substituted by 0, 1, 2 or 3 substituents selected from $\text{C}_{1-4}\text{haloalkyl}$, halo, cyano, nitro,

- C(=O)R^a, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 5 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a or -NR^aC₂₋₆alkylOR^a;

- R² 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 carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and
 the ring is substituted by 0, 1, 2 or 3 substituents selected from R^c, R^g, -C₁₋₄haloalkyl, halo,
 10 cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b,
 -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b,
 -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b,
 -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a,
 -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and
 15 -NR^aC₂₋₆alkylOR^a, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents
 independently selected from Br, Cl, F and I;

- R³ is H, phenyl, benzyl or -C₁₋₆alkyl, the phenyl, benzyl and -C₁₋₆alkyl being
 substituted by 0, 1, 2 or 3 substituents selected from R^c, R^g, C₁₋₄haloalkyl, halo, cyano, nitro,
 -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 20 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atom selected from Br, Cl, F and I;

- 25 R⁴ is H, phenyl, benzyl or -C₁₋₆alkyl, the phenyl, benzyl and -C₁₋₆alkyl being
 substituted by 0, 1, 2 or 3 substituents selected from C₁₋₄alkyl, C₁₋₃haloalkyl, -OC₁₋₄alkyl,
 -NH₂, -NHC₁₋₄alkyl, and -N(C₁₋₄alkyl)C₁₋₄alkyl, and additionally substituted by 0, 1, 2, 3, 4, 5
 or 6 atom selected from Br, Cl, F and I;

- R⁵ is a saturated, partially saturated or unsaturated 8-, 9-, 10- or 11-membered bicyclic
 30 or 12-, 13-, 14- or 15- membered tricyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N,
 O and S, wherein the carbon and sulfur atoms of the ring are substituted by 0, 1 or 2 oxo
 groups and the ring is substituted by 1, 2 or 3 basic moieties, and additionally substituted by 0,
 1, 2 or 3 substituents selected from R^g, -C₁₋₈alkyl, -C₁₋₄haloalkyl, cyano, nitro, -C(=O)R^b,
 -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,

-OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and the
 5 ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br,
 Cl, F and I;

wherein, R³ and R⁴ together may additionally be C₂₋₃alkylene substituted by 0, 1 or 2
 substituents selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b,
 -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 10 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and
 15 I; or

R^{1c} and R⁴ together may additionally be C₂₋₄alkylene substituted by 0, 1 or 2
 substituents selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b,
 -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 20 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and
 I; or

a substituent on R² that is vicinal to the -SO₂-R² bond together with R³ may
 additionally be C₁₋₃alkylene substituted by 0, 1 or 2 substituents selected from C₁₋₈alkyl,
 C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,
 -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a,
 -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b,
 30 -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
 -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b,
 -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and additionally substituted
 by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and I;

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

R^c is independently, at each instance, phenyl, benzyl or $-C_{1-6}$ alkyl, the phenyl, benzyl and $-C_{1-6}$ alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4} alkyl, C_{1-3} haloalkyl, $-OC_{1-4}$ alkyl, $-NH_2$, $-NHC_{1-4}$ alkyl, $-N(C_{1-4}alkyl)C_{1-4}alkyl$;

R^d is independently at each instance $-C_{1-8}$ alkyl, C_{1-4} haloalkyl, halo, cyano, nitro,
 5 $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$,
 $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$,
 $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$,
 $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$,
 $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

10 R^e is independently at each instance $-C_{1-6}$ alkyl substituted by 0, 1, 2 or 3 substituents independently selected from R^d and additionally substituted by 0 or 1 substituents selected from R^g ; and

R^g is independently at each instance a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 0, 1,
 15 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents selected from -
 C_{1-8} alkyl, $-C_{1-4}$ haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$,
 $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$,
 $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$,
 20 $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$,
 $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$,
 $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

25 In another embodiment, in conjunction with any one of the above and below embodiments, the basic moieties are independently selected from amino, cycloalkylamino-
 (C_1-C_6) alkyl, cycloalkyl(C_1-C_6)alkylamino(C_1-C_6)alkyl, heterocyclylamino(C_1-C_6)alkyl,
heterocyclyl(C_1-C_6)alkyl-amino(C_1-C_6)alkyl, arylamino(C_1-C_6)alkyl, aryl(C_1-C_6)alkylamino-
 (C_1-C_6) alkyl, (C_1-C_6) alkylamino(C_1-C_6)alkoxy, (C_1-C_6) alkylamino(C_1-C_6)alkoxy(C_1-C_6)-
 30 alkoxy, amino(C_1-C_6)alkoxy, amino(C_1-C_6)alkyl, (C_1-C_6) alkylamino(C_1-C_6)alkyl,
 (C_1-C_4) alkylamino- (C_2-C_6) alkenyl, 4-8-membered nitrogen-containing
heterocyclyl(C_2-C_6)alkenyl, 5-6 membered heterocyclyloxy, 5-6 membered nitrogen-
containing heterocyclyl and 5-7 membered nitrogen-containing heterocyclylalkyl; more
specifically amino, cycloalkylamino(C_1-C_6)alkyl, cycloalkyl(C_1-C_6)alkylamino- (C_1-C_6) alkyl,

heterocyclylamino(C₁-C₆)alkyl, heterocyclyl(C₁-C₆)alkylamino-(C₁-C₆)alkyl, arylamino(C₁-C₆)alkyl, aryl(C₁-C₆)alkylamino(C₁-C₆)alkyl, (C₁-C₆)alkyl amino(C₁-C₆)alkoxy, (C₁-C₆)alkylamino(C₁-C₆)alkoxy(C₁-C₆)alkoxy, amino(C₁-C₆)alkoxy, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, (C₁-C₄)alkylamino-(C₂-C₆)alkenyl, 5-8-membered nitrogen-containing heterocyclyl(C₂-C₆)alkenyl, heterocyclyl(C₁-C₆)amino(C₂-C₆)alkyl, 5-6 membered heterocycloxy, 5-6 membered nitrogen-containing heterocyclyl and 5-7 membered nitrogen-containing heterocyclyl(C₁-C₆)alkyl wherein each basic moiety can be substituted by 0, 1, 2 or 3 groups independently selected from halo, -NH₂, -OH, -CN, -CF₃, (C₁-C₆)alkylamino, haloalkyl, oxo, (C₁-C₆)alkoxy, (C₁-C₆)alkoxyalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, di(C₁-C₆)alkylamino, =NCN and (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl, each of which is substituted by 0, 1, 2 or 3 groups independently selected from halo, -NH₂, -OH, -CN, -CF₃, (C₁-C₆)alkylamino, haloalkyl, oxo, (C₁-C₆)alkoxy, (C₁-C₆)alkoxyalkyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, or di(C₁-C₆)alkylamino.

In another embodiment, in conjunction with any one of the above and below embodiments, the basic moieties are independently selected from amino, mono-C₁₋₄-alkylamino-C₁₋₄-alkyl, di-C₁₋₄-alkylamino-C₁₋₄-alkyl, mono-C₁₋₄-alkylamino-C₂₋₄-alkenyl, di-C₁₋₄-alkylamino-C₂₋₄-alkenyl, 5-8 membered nitrogen-containing heterocyclyl-C₂₋₄-alkenyl, optionally substituted 5-6 membered nitrogen-containing heterocyclyl or 5-8 membered nitrogen-containing heterocyclyl-C₁₋₄-alkyl.

In another embodiment, in conjunction with any one of the above and below embodiments, the basic moieties are independently selected from amino, aminomethyl, isopropylaminomethyl, *t*-butylaminomethyl, 2-*t*-butylaminoethyl, 2-*tert*-butylamino-1-methylethyl, 1-*tert*-butylaminoethyl, 1-(*tert*-butylamino-methyl)-vinyl, 1-(piperidin-1-ylmethyl)-vinyl, *N*-isobutyl-aminomethyl, *N*-isobutyl-aminoethyl, (2,2-dimethyl)propylaminomethyl, *N*-isopropyl-*N*-ethylaminomethyl, *N*-isopropyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-methylaminomethyl, *N*-*iso*-butyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-ethylaminomethyl, *N*-isobutyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-isopropylaminomethyl, *N,N*-di(isopropyl)aminomethyl, *N,N*-dimethylaminomethyl, *N,N*-diethylaminomethyl, *N,N*-di(*t*-butyl)-aminomethyl, cyclopropylaminomethyl, cyclopropylaminoethyl, cyclopropylmethylaminomethyl, cyclopropylmethylaminoethyl, cyclobutylaminomethyl, cyclobutylaminoethyl, cyclobutylmethylaminomethyl, cyclobutylmethylaminoethyl, 4,5-dihydro-imidazolyl, 1-piperidinylmethyl, 4-fluoropiperidin-1-ylmethyl, 4,4-difluoropiperidin-1-ylmethyl, 3-hydroxypiperidin-1-ylmethyl, 4-hydroxypiperidin-1-ylmethyl, 4-(piperidin-1-yl)piperidinylmethyl, 4-(dimethylamino)piperidin-1-ylmethyl, 2,6-dimethylpiperidin-1-

ylmethyl, 4-morpholinylmethyl, 1-pyrrolidinylmethyl, 2-methylpyrrolidin-1-ylmethyl, 2,5-dimethylpyrrolidin-1-ylmethyl, piperazin-1-ylmethyl, azocan-1-ylmethyl, azepan-1-ylmethyl, (7-azabicyclo[2.2.1]hept-7-yl)methyl, (1,3,3-trimethyl-6-azaicyclo[3.2.1]oct-6-yl)methyl, 2-piperidinyl and 4-methylpiperazin-1-ylmethyl, in conjunction with any of the above or below
 5 embodiments.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is H.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is C_{1-8} alkyl substituted by 0, 1, 2, or 3 groups independently selected from
 10 R^g , cyano, oxo, nitro, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and
 15 $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is C_{1-8} alkyl substituted by 0, 1, 2, or 3 groups independently selected from
 20 R^g , cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br,
 25 Cl, F and I.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is $-C_{1-8}alkyl$.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is $-C_{3-8}alkyl$.

30 In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is $-CH_3$.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is $-C_{1-8}alkyl$ substituted by 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is $-CF_3$.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is $-C_{1-8}alkyl$ substituted by 1, 2, or 3 groups independently selected from R^g , cyano, oxo, nitro, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is $-C_{1-8}alkyl$ substituted by 1 oxo group and 0, 1 or 2 groups independently selected from R^g , cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is $-C_{1-8}alkyl$ substituted by 1, 2 or 3 groups independently selected from oxo, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is $-C(=O)OR^a$ or $-C(=O)NR^aR^a$.

In another embodiment, in conjunction with any one of the above and below embodiments, R^{1a} and R^{1b} are each independently, H, F, Cl, $-OCH_3$, $-C_{1-2}alkyl$ or $-CF_3$.

In another embodiment, in conjunction with any one of the above and below embodiments, R^{1a} is H and R^{1b} F, Cl, $-OCH_3$, $-C_{1-2}alkyl$ or $-CF_3$.

In another embodiment, in conjunction with any one of the above and below embodiments, R^{1a} is F, Cl, $-OCH_3$, $-C_{1-2}alkyl$ or $-CF_3$ and R^{1b} is H.

In another embodiment, in conjunction with any one of the above and below embodiments, R^{1a} and R^{1b} are each independently, H or F.

- 5 In another embodiment, in conjunction with any one of the above and below embodiments, R^{1c} is $-C_{1-8}alkyl$, $-C_{1-4}haloalkyl$, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, or $-C_{1-6}alkyl$ substituted by 0, 1, 2 or 3 substituents selected from $-C_{1-4}haloalkyl$, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$.
- 10
- 15

- In another embodiment, in conjunction with any one of the above and below embodiments, R^{1c} is $-C_{1-6}alkyl$ substituted by 0, 1, 2 or 3 substituents selected from
- 20 $C_{1-4}haloalkyl$, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;
- 25

In another embodiment, in conjunction with any one of the above and below embodiments, R^{1c} is H or F.

In another embodiment, in conjunction with any one of the above and below embodiments, R^{1a} , R^{1b} , and R^{1c} are H.

- 30 In another embodiment, in conjunction with any one of the above and below embodiments, R^2 is phenyl or naphthyl, both of which are substituted by 0, 1, 2 or 3 substituents selected from R^c , R^g , $-C_{1-4}haloalkyl$, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$,

-S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a,
 -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F
 5 and I.

In another embodiment, in conjunction with any one of the above and below
 embodiments, R² is phenyl or naphthyl, both of which are substituted by 1, 2 or 3 substituents
 selected from R^c, R^g, -C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a,
 -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b,
 10 -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a,
 -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a,
 -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F
 15 and I.

In another embodiment, in conjunction with any one of the above and below
 embodiments, R² 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 1, 2, 3 or 4 atoms
 selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo
 20 groups and the ring is substituted by 0, 1, 2 or 3 substituents selected from R^c, R^g, -
 C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,
 -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a,
 -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b,
 -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
 25 -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b,
 -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, 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 any one of the above and below
 embodiments, R² is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered
 30 monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic hydrocarbon ring containing 1, 2, 3
 or 4 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0,
 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents selected from R^c, R^g, -
 C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,
 -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a,

-OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b,
 -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
 -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b,
 -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and the ring is additionally
 5 substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below
 embodiments, R² is an unsaturated 5-, 6- or 7-membered monocyclic ring containing 1, 2 or 3
 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or
 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents selected from R^c, R^g, -
 10 C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,
 -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a,
 -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b,
 -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
 -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b,
 15 -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, 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 any one of the above and below
 embodiments, R² is an unsaturated 5-, 6- or 7-membered monocyclic hydrocarbon ring
 containing 1, 2 or 3 atoms selected from N, O and S, wherein the carbon atoms of the ring are
 20 substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents
 selected from R^c, R^g, -C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a,
 -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b,
 -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a,
 -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a,
 25 -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, 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 any one of the above and below
 30 embodiments, R² is selected from 2-naphthyl, 1-naphthyl, phenyl, 3-chlorophenyl, 4-
 chlorophenyl, 3,5-dichlorophenyl, 3,4-dichlorophenyl, 2,4,6-trichlorophenyl, 3-fluorophenyl,
 3-methoxyphenyl, 4-methoxyphenyl, 3-biphenyl, 3-chloro-4-methylphenyl, 4-chloro-3-
 methylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 3-
 methylphenyl, [2.1.3]-benzoxadiazol-4-yl, thien-2-yl, 3-pyridyl, 8-quinolyl and 5-isoquinolyl.

in another embodiment, in conjunction with any one of the above and below
embodiments, R³ is H.

In another embodiment, in conjunction with any one of the above and below
embodiments, R³ is phenyl, benzyl or C₁₋₆alkyl, the phenyl, benzyl and -C₁₋₆alkyl being
5 substituted by 0, 1, 2 or 3 substituents selected from R^c, R^g, -C₁₋₄haloalkyl, halo, cyano, nitro,
-C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
-OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
-S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
-NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
10 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atom selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below
embodiments, R³ is phenyl substituted by 0, 1, 2 or 3 substituents selected from R^c, R^g, -
C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,
15 -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a,
-OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b,
-S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
-N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b,
-N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and additionally substituted
20 by 0, 1, 2, 3, 4, 5 or 6 atom selected from Br, Cl, F and I.

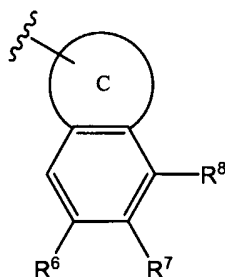
In another embodiment, in conjunction with any one of the above and below
embodiments, R³ is -C₁₋₆alkyl substituted by 0, 1, 2 or 3 substituents selected from R^c, R^g,
C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,
-OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a,
25 -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b,
-S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
-N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b,
-N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and additionally substituted
by 0, 1, 2, 3, 4, 5 or 6 atom selected from Br, Cl, F and I.

30 In another embodiment, in conjunction with any one of the above and below
embodiments, R⁴ is H.

In another embodiment, in conjunction with any one of the above and below
embodiments, R⁴ is phenyl, benzyl or -C₁₋₆alkyl, the phenyl, benzyl and C₁₋₆alkyl being
substituted by 0, 1, 2 or 3 substituents selected from C₁₋₄alkyl, C₁₋₃haloalkyl, -OC₁₋₄alkyl,

-NH₂, -NHC₁₋₄alkyl, and -N(C₁₋₄alkyl)C₁₋₄alkyl, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atom selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below embodiments, R⁵ is:



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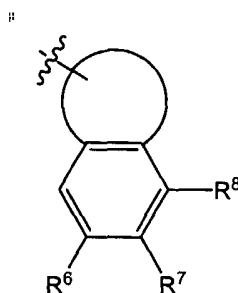
wherein

the C ring is a saturated or partially saturated 6- or 7-membered ring containing 0, 1 or 2 atoms selected from N, O and S, wherein the carbon and sulfur atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0 or 1 substituents selected from R^g, C₁₋₈alkyl, C₁₋₄haloalkyl, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from Br, Cl, F and I; and

R⁶, R⁷ and R⁸ are independently selected from H, a basic moiety, R^g, C₁₋₈alkyl, C₁₋₄haloalkyl, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a, -NR^aC₂₋₆alkylOR^a, Br, Cl, F and I; provided that 1 or 2 of R⁶, R⁷ and R⁸ are a basic moiety.

25

In another embodiment, in conjunction with any one of the above and below embodiments, R⁵ is:



wherein:

the part of the ring that is attached to the nitrogen atom in Formula (I) is a saturated or partially saturated 6- or 7-membered hydrocarbon ring containing 0, 1 or 2 atoms selected from N, O and S, wherein the carbon and sulfur atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0 or 1 substituents selected from R^g , C_{1-8} alkyl, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from Br, Cl, F and I; and

R^6 , R^7 and R^8 are independently selected from H, a basic moiety, R^g , C_{1-8} alkyl, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, Br, Cl, F and I; provided that 1 or 2 of R^6 , R^7 and R^8 are a basic moiety.

In another embodiment, in conjunction with any one of the above and below embodiments, R^6 and R^8 are H; and wherein R^7 is selected from amino, aminomethyl, isopropylaminomethyl, *t*-butylaminomethyl, 2-*t*-butylaminoethyl, 2-*tert*-butylamino-1-methyl-ethyl, 1-*tert*-butylaminoethyl, 1-(*tert*-butylamino-methyl)-vinyl, 1-(piperidin-1-ylmethyl)-vinyl, *N*-isobutyl-aminomethyl, *N*-isobutyl-aminoethyl, (2,2-dimethyl)propylaminomethyl, *N*-isopropyl-*N*-ethylaminomethyl, *N*-isopropyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-methylaminomethyl, *N*-*iso*-butyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-ethylaminomethyl, *N*-isobutyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-isopropylaminomethyl, *N*,*N*-di(isopropyl)aminomethyl, *N*,*N*-dimethylaminomethyl, *N*,*N*-diethylaminomethyl, *N*,*N*-di(*t*-butyl)-aminomethyl, cyclopropylaminomethyl, cyclopropylaminoethyl,

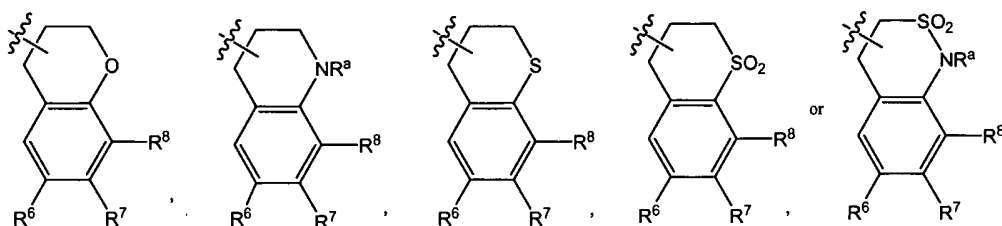
cyclopropylmethylaminomethyl, cyclopropylmethylaminoethyl, cyclobutylaminomethyl, cyclobutylaminoethyl, cyclobutylmethylaminomethyl, cyclobutylmethylaminoethyl, 4,5-dihydro-imidazolyl, 1-piperidinylmethyl, 4-fluoropiperidin-1-ylmethyl, 4,4-difluoropiperidin-1-ylmethyl, 3-hydroxypiperidin-1-ylmethyl, 4-hydroxypiperidin-1-ylmethyl, 4-(piperidin-1-yl)piperidinylmethyl, 4-(dimethylamino)piperidin-1-ylmethyl, 2,6-dimethylpiperidin-1-ylmethyl, 4-morpholinylmethyl, 1-pyrrolidinylmethyl, 2-methylpyrrolidin-1-ylmethyl, 2,5-dimethylpyrrolidin-1-ylmethyl, piperazin-1-ylmethyl, azocan-1-ylmethyl, azepan-1-ylmethyl, (7-azabicyclo[2.2.1]hept-7-yl)methyl, (1,3,3-trimethyl-6-azaicyclo[3.2.1]oct-6-yl)methyl, 2-piperidinyl and 4-methylpiperazin-1-ylmethyl.

- 10 In another embodiment, in conjunction with any one of the above and below embodiments, R^7 and R^8 are H; and R^6 is selected from amino, aminomethyl, isopropylaminomethyl, *t*-butylaminomethyl, 2-*t*-butylaminoethyl, 2-tert-butylamino-1-methyl-ethyl, 1-tert-butylaminoethyl, 1-(tert-butylamino-methyl)-vinyl, 1-(piperidin-1-ylmethyl)-vinyl, *N*-isobutyl-aminomethyl, *N*-isobutyl-aminoethyl, (2,2-dimethyl)propylaminomethyl, *N*-isopropyl-*N*-ethylaminomethyl, *N*-isopropyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-methylaminomethyl, *N*-*iso*-butyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-ethylaminomethyl, *N*-isobutyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-isopropylaminomethyl, *N,N*-di(isopropyl)aminomethyl, *N,N*-dimethylaminomethyl, *N,N*-diethylaminomethyl, *N,N*-di(*t*-butyl)-aminomethyl, cyclopropylaminomethyl, cyclopropylaminoethyl,
- 20 cyclopropylmethylaminomethyl, cyclopropylmethylaminoethyl, cyclobutylaminomethyl, cyclobutylaminoethyl, cyclobutylmethylaminomethyl, cyclobutylmethylaminoethyl, 4,5-dihydro-imidazolyl, 1-piperidinylmethyl, 4-fluoropiperidin-1-ylmethyl, 4,4-difluoropiperidin-1-ylmethyl, 3-hydroxypiperidin-1-ylmethyl, 4-hydroxypiperidin-1-ylmethyl, 4-(piperidin-1-yl)piperidinylmethyl, 4-(dimethylamino)piperidin-1-ylmethyl, 2,6-dimethylpiperidin-1-ylmethyl, 4-morpholinylmethyl, 1-pyrrolidinylmethyl, 2-methylpyrrolidin-1-ylmethyl, 2,5-dimethylpyrrolidin-1-ylmethyl, piperazin-1-ylmethyl, azocan-1-ylmethyl, azepan-1-ylmethyl, (7-azabicyclo[2.2.1]hept-7-yl)methyl, (1,3,3-trimethyl-6-azaicyclo[3.2.1]oct-6-yl)methyl, 2-piperidinyl and 4-methylpiperazin-1-ylmethyl.

- 30 In another embodiment, in conjunction with any one of the above and below embodiments, R^6 and R^7 are H; and R^8 is selected from amino, aminomethyl, isopropylaminomethyl, *t*-butylaminomethyl, 2-*t*-butylaminoethyl, 2-tert-butylamino-1-methyl-ethyl, 1-tert-butylaminoethyl, 1-(tert-butylamino-methyl)-vinyl, 1-(piperidin-1-ylmethyl)-vinyl, *N*-isobutyl-aminomethyl, *N*-isobutyl-aminoethyl, (2,2-dimethyl)propylaminomethyl, *N*-isopropyl-*N*-ethylaminomethyl, *N*-isopropyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-

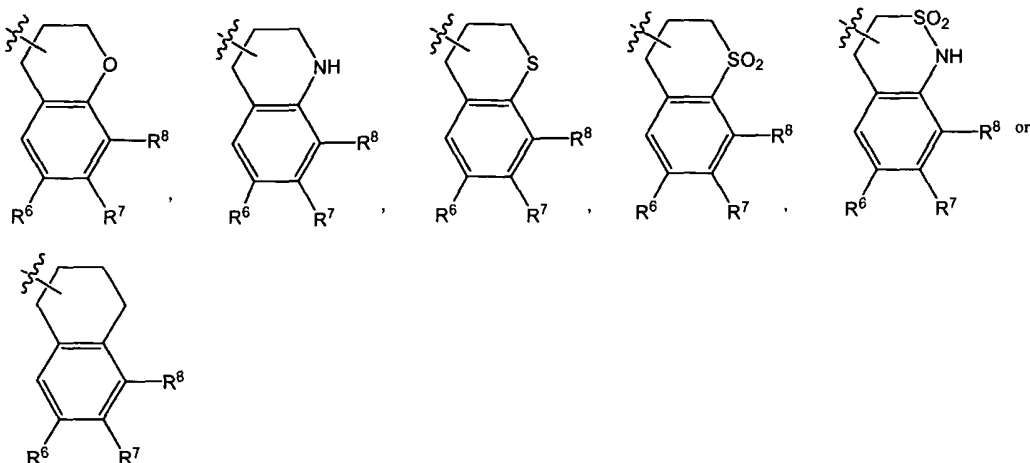
- methylaminomethyl, *N*-*iso*-butyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-ethylaminomethyl, *N*-isobutyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-isopropylaminomethyl, *N,N*-di(isopropyl)aminomethyl, *N,N*-dimethylaminomethyl, *N,N*-diethylaminomethyl, *N,N*-di(*t*-butyl)-aminomethyl, cyclopropylaminomethyl, cyclopropylaminoethyl,
- 5 cyclopropylmethylaminomethyl, cyclopropylmethylaminoethyl, cyclobutylaminomethyl, cyclobutylaminoethyl, cyclobutylmethylaminomethyl, cyclobutylmethylaminoethyl, 4,5-dihydro-imidazolyl, 1-piperidinylmethyl, 4-fluoropiperidin-1-ylmethyl, 4,4-difluoropiperidin-1-ylmethyl, 3-hydroxypiperidin-1-ylmethyl, 4-hydroxypiperidin-1-ylmethyl, 4-(piperidin-1-yl)piperidinylmethyl, 4-(dimethylamino)piperidin-1-ylmethyl, 2,6-dimethylpiperidin-1-
- 10 ylmethyl, 4-morpholinylmethyl, 1-pyrrolidinylmethyl, 2-methylpyrrolidin-1-ylmethyl, 2,5-dimethylpyrrolidin-1-ylmethyl, piperazin-1-ylmethyl, azocan-1-ylmethyl, azepan-1-ylmethyl, (7-azabicyclo[2.2.1]hept-7-yl)methyl, (1,3,3-trimethyl-6-azaicyclo[3.2.1]oct-6-yl)methyl, 2-piperidinyl and 4-methylpiperazin-1-ylmethyl.

- In another embodiment, in conjunction with any one of the above and below
- 15 embodiments, R^5 is:



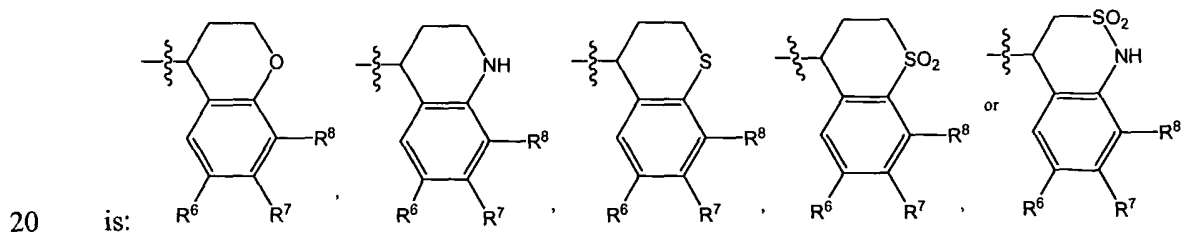
- each of which are substituted by 0 or 1 substituents selected from R^b , C_{1-8} alkyl, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$,
- 20 $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1, 2 or 3 substituents independently
- 25 selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below embodiments, R^5 is:



- where the part of the above rings that is attached to the nitrogen atom in Formula (I) [i.e., dihydropyranyl, tetrahydropyridinyl, dihydrothiopyranyl, 1,1-dioxodihydrothiopyranyl portion of the ring including the nitrogen ring atom] is substituted by 0 or 1 substituents
- 5 selected from R^6 , C_{1-8} alkyl, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1, 2 or 3 substituents independently selected from Br, Cl, F and I and R^6 , R^7 and R^8 are independently selected from H, a basic moiety, R^6 , C_{1-8} alkyl, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, Br, Cl, F and I; provided that 1 or 2 of R^6 , R^7 and R^8 are a basic moiety.

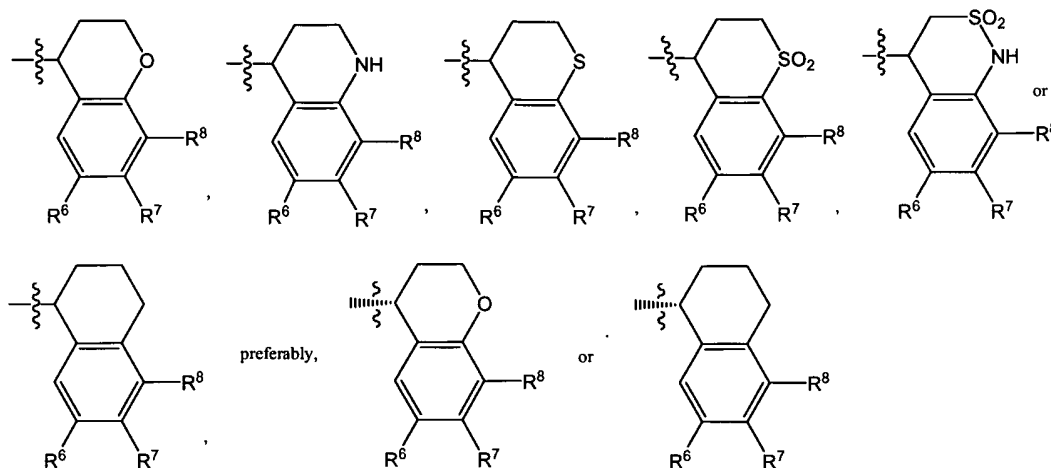
In another embodiment, in conjunction with any one of the above and below embodiments, R^5



each of which are substituted by 0 or 1 substituents selected from R^6 , C_{1-8} alkyl, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$,

- OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a,
 -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b,
 -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a,
 -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and
 5 -NR^aC₂₋₆alkylOR^a, and additionally substituted by 0, 1, 2 or 3 substituents independently
 selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below
 embodiments, R⁵ is:



- 10 where the part of the above rings that is attached to the nitrogen atom in Formula (I)
 [i.e., dihydropyranyl, tetrahydropyridinyl, dihydrothiopyranyl, 1,1-dioxodihydrothiopyranyl
 portion of the ring including the nitrogen ring atom] is substituted by 0 or 1 substituents
 selected from R⁶, C₁₋₈alkyl, C₁₋₄haloalkyl, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a,
 -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b,
 15 -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a,
 -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a,
 -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 additionally substituted by 0, 1, 2 or 3 substituents independently selected from Br, Cl, F and I
 20 and R⁶, R⁷ and R⁸ are independently selected from H, a basic moiety, R⁶, C₁₋₈alkyl,
 C₁₋₄haloalkyl, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a,
 -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a,
 -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b,
 -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a,

$-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, Br, Cl, F and I; provided that 1 or 2 of R^6 , R^7 and R^8 are a basic moiety.

In another embodiment, in conjunction with any one of the above and below embodiments, R^3 and R^4 together may additionally be C_{2-3} alkylene substituted by 1 or 2 substituents selected from C_{1-8} alkyl, C_{1-4} haloalkyl, halo, oxo, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below embodiments, R^3 and R^4 together may additionally be C_{2-3} alkylene.

In another embodiment, in conjunction with any one of the above and below embodiments, R^{1c} and R^4 together may additionally be C_{2-4} alkylene substituted by 1 or 2 substituents selected from C_{1-8} alkyl, C_{1-4} haloalkyl, halo, oxo, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with any one of the above and below embodiments, R^{1c} and R^4 together may additionally be C_{2-4} alkylene.

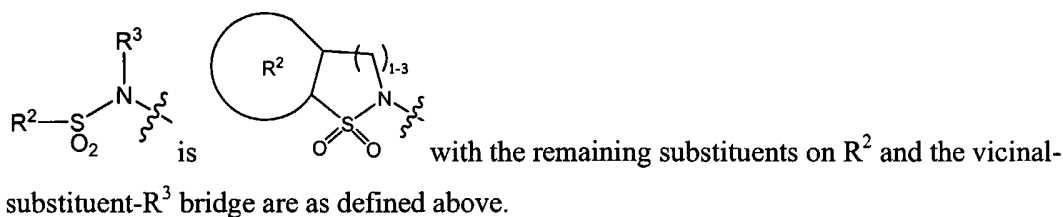
In another embodiment, in conjunction with any one of the above and below embodiments, a substituent on R^2 that is vicinal to the $-\text{SO}_2-\text{R}^2$ bond together with R^3 may additionally be C_{1-3} alkylene substituted by 1 or 2 substituents selected from C_{1-8} alkyl, C_{1-4} haloalkyl, halo, oxo, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$,

$-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and I.

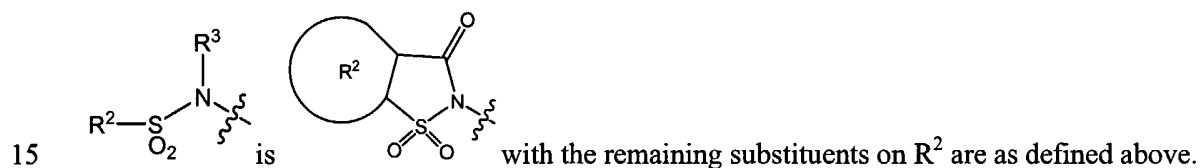
In another embodiment, in conjunction with any one of the above and below embodiments, a substituent on R^2 that is vicinal to the $-SO_2-R^2$ bond together with R^3 may additionally be $C_{1-3}alkylene$.

In another embodiment, in conjunction with any one of the above and below embodiments, a substituent on R^2 that is vicinal to the $-SO_2-R^2$ bond together with R^3 may additionally be $-C(=O)$.

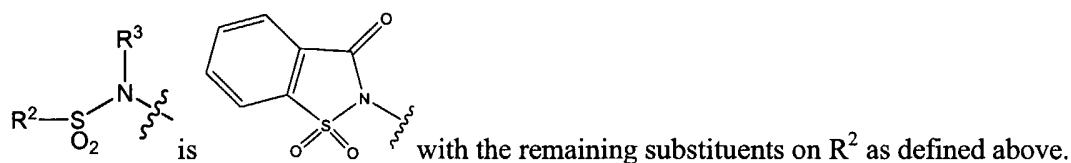
In another embodiment, in conjunction with any one of the above and below embodiments:



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



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



In another embodiment:

20 R^1 is hydrogen, cyano, $-C(O)OC_{1-8}alkyl$, $-C(O)OH$, $-C(=O)NR^aR^a$, $-C_{1-8}alkyl$ substituted by 0, 1, 2, 3 atoms independently selected from halo; preferably R^1 is hydrogen or trifluoromethyl, $-C(O)O-tert-butyl$, $-C(O)OH$, cyano, or $-C(O)NH_2$; more preferably hydrogen or trifluoromethyl;

R^{1a} , R^{1b} , R^3 , and R^4 are hydrogen; and

25 R^{1c} is hydrogen, halo, or $-OH$, preferably hydrogen, fluoro or $-OH$, more preferably hydrogen.

Within this embodiment, and more preferred groups of compounds contained therein, a more preferred group of compounds is that wherein:

R^2 is phenyl, naphthenyl, 5- or 6-membered monocyclic saturated or unsaturated hydrocarbon ring containing 1, 2, 3 or 4 atoms selected from N, O and S, or 9- or 10-membered unsaturated hydrocarbon ring containing 1, 2, 3 or 4 atoms selected from N, O and S, preferably phenyl, benzodioxinyl, quinolinyl, isoquinolinyl, naphthalenyl, 2,3-dihydrobenzofuranyl, tetrahydrofuranyl, 2,3-dihydroindolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazine substituted with 0, 1, 2, or three substituents independently selected from halo, C_{1-4} haloalkyl, $-C_{1-6}$ alkyl, nitro, -OH, -NH₂, R^g , $-OC_{1-6}$ alkyl, or $-OC_{1-6}$ alkyl substituted with one, two, or three halo; preferably, 0, 1, 2, or three substituents independently selected from fluoro, chloro, trifluoromethyl, methyl, *tert*-butyl, trifluoromethoxy, methoxy, nitro, -OH, -NH₂, phenyl, or oxazolyl; more preferably R^2 is 2-trifluoromethylphenyl, 3-bromophenyl, 4-bromo-3-trifluoromethylphenyl, 3-chloro-4-fluorophenyl, 3-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 3-methylphenyl, 4-chloro-2-fluorophenyl, 2-chloro-4-fluorophenyl, naphthalene-2-yl, 3-*tert*-butylphenyl, 4-*tert*-butylphenyl, [1.3]-oxazol-4-ylphenyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl, 1,2,3,4-tetrahydroquinolin-8-yl, 4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl, 3-chloro-2-fluorophenyl, 3-methoxyphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 3,5-dimethylphenyl, 3,4-dimethylphenyl, 2-fluoro-5-methylphenyl, 4-trifluoromethylphenyl, 4-chlorophenyl, 2,5-dichlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 2-chloro-6-methylphenyl, 3-fluoro-6-methylphenyl, 5-chloro-2-methoxyphenyl, 4-chloro-3-trifluoromethylphenyl, 2-chloro-5-trifluoromethylphenyl, 5-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 2,6-dichloro-4-trifluoromethylphenyl, 4-ethylphenyl, 4-chloro-3-methylphenyl, 4-chloro-2,5-dimethylphenyl, 3-chloro-4-methylphenyl, 3,4-dimethoxyphenyl, 3,5-dichloro-2-hydroxyphenyl, isoquinolin-6-yl, quinolin-8-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzo[b][1,4]dioxin-6-yl, 2-nitrophenyl, 2-aminophenyl, 2-fluoro-5-trifluoromethylphenyl, 6-chloronaphthalen-2-yl, 5-chloronaphthalen-1-yl, 2-nitro-4-trifluoromethylphenyl, or 4-biphenyl, 3-biphenyl.

Within the above embodiment and preferred and more preferred groups contained within this embodiment, an even more preferred group of compounds is that wherein R^5 is unsaturated 10-membered bicyclic hydrocarbon ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, preferably 1(*R*)-1,2,3,4-tetrahydronaphthalen-1-yl or 4(*R*)-chroman-4-yl, substituted with cycloalkylamino- (C_1-C_6) alkyl, cycloalkyl (C_1-C_6) alkylamino (C_1-C_6) alkyl, C_{1-6} alkylamino- C_{1-6} alkyl, 5-8 membered nitrogen-containing saturated heterocyclyl- C_{2-4} -alkenyl,

5-6 membered nitrogen-containing partially unsaturated or unsaturated heterocyclyl, 6 or 7 membered saturated heterocyclyl-(C₁₋₆)-alkylamino(C₁₋₆)alkyl, (C₁₋₆)alkylamino(C₁₋₆)alkyl substituted with -OH, (C₁₋₆)alkoxy (C₁₋₆)alkylamino or -NHCO(C₁₋₆)alkyl, or 5-7 membered nitrogen-containing saturated heterocyclyl-C₁₋₄-alkyl wherein the heterocyclyl ring optionally contains an oxygen or nitrogen ring atom and is substituted with 0, 1, or 2 substituents independently selected from halo, -OH, or -C₁₋₆alkyl and additionally with 0 or 1 substituent selected from halo or nitro. Preferably, R⁵ is 1,2,3,4-tetrahydronaphthalen-1-yl substituted at the 6-position or chroman-4-yl substituted at the 7 position with cyclopropylaminomethyl, cyclopropylmethylaminomethyl, cyclobutylaminomethyl, cyclohexylaminomethyl, cyclopentylaminomethyl, 1-cyclopropylaminoethyl, 1-cyclobutylaminoethyl, 1-cyclopentylaminoethyl, 2-methylpropylaminomethyl, 2,2-dimethylpropylaminomethyl, 1-methylethylaminomethyl, tert-butylaminomethyl, 1,1-dimethylpropylaminomethyl, pyridine-4-ylaminomethyl, (piperidin-1-ylCH₂)C=CH₂, tetrahydrofuran-2-ylmethylaminomethyl, morpholin-4-ylmethyl, piperidin-1-ylmethyl, pyrrolidin-1-ylmethyl, 4-hydroxypiperidin-1-ylmethyl, 4-fluoropiperidin-1-ylmethyl, 4-methylpiperidin-1-ylmethyl, 3-hydroxypiperidin-1-ylmethyl, 2,6-dimethylpiperidin-1-ylmethyl, homopiperidin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 2-(pyrrolidin-1-yl)ethylaminomethyl, 2-(piperidin-1-yl)ethylaminomethyl, 2-(morpholin-1-yl)ethylaminomethyl, -CH₂NH(CH₃)₂CH₂OH, -CH₂NH(CH₃)₂CH₂OCH₃, 2-(dimethylamino)ethylaminomethyl, 2-(diethylamino)ethylaminomethyl or 2,5-dihydro-1H-imidazol-2-yl.

A family of specific compounds of particular interest within Formula (I) consists of compounds and pharmaceutically-acceptable salts thereof as follows:

- (2R)-3-(((2,3-dichlorophenyl)sulfonyl)(methyl)amino)-2-hydroxy-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide;
- 25 (2R)-3-(((2,3-dichlorophenyl)sulfonyl)(methyl)amino)-2-methyl-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide;
- (2R)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-2-methyl-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide;
- (2R,3R)-4,4,4-trifluoro-2-hydroxy-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3R)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3R)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-N-((1R)-6-(((1,1-dimethylethyl)amino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;

- (3R)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- 5 (3*R*)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- (3*R*)-3-(((2,6-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-4-fluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 10 (3*R*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- (3*R*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- 15 (3*R*)-3-(((4-chlorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- (3*R*)-3-(((5-chloro-2-(methyloxy)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((5-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 20 (3*R*)-3-((2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-3-(((8-(methyloxy)-5-quinoliny)l)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3*R*)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-((8-quinoliny)l)sulfonyl)amino)butanamide;
- 30 (3*R*)-4-hydroxy-3-(((4-methylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4-fluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3R)-N-((1R)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3R)-N-((1R)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)butanamide;
- 5 (3R)-N-((1R)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((2,4,6-trimethylphenyl)sulfonyl)amino)butanamide;
- (3R)-N-((1R)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((4-methylphenyl)sulfonyl)amino)butanamide;
- (3R)-N-((1R)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4-fluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 10 (3R)-N-((4R)-7-((cyclopentylamino)methyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3R,4R)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-4-hydroxy-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)pentanamide;
- 15 (3S)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3S)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3S)-3-(((2,6-dichloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 20 (3S)-3-(((2,6-dichloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)-N-((1R)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3S)-3-(((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3S)-3-(((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-N-((1R)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3S)-3-(((2-fluoro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3S)-3-(((2-nitro-4-(trifluoromethyl)phenyl)sulfonyl)amino)-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 30 (3S)-3-(((3,4-bis(methyloxy)phenyl)sulfonyl)amino)-4,4,4-trifluoro-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3S)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-N-((1R)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

- (3*S*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-(1-piperidinylmethyl)ethenyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((3,5-dichloro-2-hydroxyphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*S*)-3-(((3-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((3-chloro-4-methylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-(1,1-dimethylethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-
- 10 methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-(1,3-oxazol-5-yl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-bromo-3-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 15 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-((3-hydroxy-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-
- 20 (1-pyrrolidinyl)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-((3-hydroxy-1-piperidinyl)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- 25 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-
- 30 methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((2-methylpropyl)-amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1-methylethyl)-amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((cyclopropylmethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclobutylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((3*S*)-3-hydroxy-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((1,1-dimethylethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- 10 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(cyclopentylamino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- 15 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((2-methylpropyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((1-methylethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((cyclopropylmethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- 20 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-((cyclobutylamino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((3*S*)-3-hydroxy-1-piperidinyl)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- 25 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(1-pyrrolidinylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-3-(trifluoromethyl)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((5-chloro-1-naphthalenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 30 (3*S*)-3-(((6-chloro-2-naphthalenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((6-chloro-2-naphthalenyl)sulfonyl)(cyclopentyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

- (3*S*)-3-(((6-chloro-2-naphthalenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclopentylamino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((6-chloro-2-naphthalenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*S*)-3-(((1,1'-biphenyl-3-ylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((1,1'-biphenyl-4-ylsulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)-amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((1,1'-biphenyl-4-ylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-
- 10 tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-((2,3-dihydro-1-benzofuran-5-ylsulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(methyl((3-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 15 (3*S*)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)-*N*-((1*R*)-6-(1-(1-piperidinyl-
- 20 methyl)ethenyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-4,4,4-trifluoro-3-((6-isoquinolylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-4,4,4-trifluoro-3-(methyl((3-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2*R*)-tetrahydro-2-furanylmethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2*S*)-tetrahydro-2-furanylmethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((1-methylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-
- 30 naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-(1-piperidinyl)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-(1-pyrrolidinyl)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-(4-morpholinyl)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-hydroxy-1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-methylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((3*S*)-3-hydroxy-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-fluoro-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-
- 10 naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-hydroxy-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-methyl-1-piperazinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-methyl-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-(1-piperidinylmethyl)ethenyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2,4,6-trimethylphenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-
- 20 naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2,4,6-trimethylphenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 25 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(4-morpholinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-
- 30 (((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((4*R*)-7-(((2-methylpropyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((4*R*)-7-(((3*R*)-3-hydroxy-1-piperidinyl)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*S*)-4,4,4-trifluoro-*N*-((4*R*)-7-((4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*S*)-4,4,4-trifluoro-*N*-((4*R*)-7-(4-morpholinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4-fluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)-5-hexynamide;
- 10 (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2-nitro-4-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((2-(acetyl amino)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 20 (3*S*)-*N*-((1*R*)-6-(((2-(diethyl amino)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((2-(dimethyl amino)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 25 (3*S*)-*N*-((1*R*)-6-(((2-(methoxy)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((2,2-dimethylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((2-methylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3*S*)-*N*-((1*R*)-6-(((2*R*,6*S*)-2,6-dimethyl-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((cyclopropyl)methyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*S*)-*N*-((1*R*)-6-((1*R*)-1-((2-(methyloxy)ethyl)amino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((1*R*)-1-(cyclobutylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*S*)-*N*-((1*R*)-6-((1*R*)-1-(cyclopropylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((1*S*)-1-((2-methylpropyl)amino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((1*S*)-1-((cyclopropylmethyl)amino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 10 (3*S*)-*N*-((1*R*)-6-((1*S*)-1-(cyclopentylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((1*S*)-1-(cyclopentylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((3-pyridinylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*S*)-*N*-((1*R*)-6-((cyclobutylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((cyclohexylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((cyclopentyl((2-fluoro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2-fluoro-5-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 20 (3*S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 25 (3*S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2-fluoro-5-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(methyl((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3*S*)-*N*-((1*R*)-6-(1-(1-piperidinylmethyl)ethenyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- (3*S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-chloro-4-methylphenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- 5 (3*S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3,4-bis(methyloxy)phenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- (3*S*)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 10 (3*S*)-*N*-((1*R*)-6-acetyl-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-formyl-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*S*)-*N*-((4*R*)-6-chloro-7-(((1,1-dimethylethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((1,1-dimethylethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((1,1-dimethylethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 20 (3*S*)-*N*-((4*R*)-7-(((1-methylethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((2-(methyloxy)ethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 25 (3*S*)-*N*-((4*R*)-7-(((2,2-dimethylpropyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((2-methylpropyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((3*R*)-3-hydroxy-1-piperidinyl)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3*S*)-*N*-((4*R*)-7-(((cyclopropylmethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-((4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*S*)-*N*-((4*R*)-7-((cyclohexylamino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-((cyclopentylamino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*S*)-*N*-((4*R*)-7-((cyclopropylamino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(1-azepanylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- (3*S*)-*N*-((4*R*)-7-(1-azepanylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)-4,4,4-trifluoro-3-10 (((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(1-pyrrolidinylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 1,1-dimethylethyl *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-alpha-asparaginate;
- 1,1-dimethylethyl *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-alpha-asparaginate;
- 1,1-dimethylethyl *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-alpha-asparaginate;
- 20 1,1-dimethylethyl *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-alpha-asparaginate;
- 2-((2*R*)-2-methyl-1-((4-methylphenyl)sulfonyl)-3-oxo-2-piperazinyl)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)acetamide;
- 25 2-(3,4-dichloro-benzenesulfonylamino)-*N*-(6-pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-succinamic acid;
- 3-(2-chloro-5-trifluoromethyl-benzenesulfonylamino)-*N*-(6-([(2-chloro-5-trifluoromethyl-benzenesulfonyl)-cyclopentyl-amino]-methyl)-1,2,3,4-tetrahydro-naphthalen-1-yl)-butyramide;
- 30 3-(6-bromo-1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide;
- 3-(6-bromo-1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide;

- 3*R*-(3,4-dichloro-benzenesulfonylamino)-4,4,4-trifluoro-*N*-(6-piperidin-1-ylmethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-butyramide;
- 3*S*-(3,4-dichloro-benzenesulfonylamino)-4,4,4-trifluoro-*N*-(6-piperidin-1-ylmethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-butyramide;
- 5 *N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-phenyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(3-(trifluoromethyl)phenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-fluorophenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 10 *N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-methyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-(((2,2-dimethylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-fluorophenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 15 *N*-1-((1*R*)-6-((1*S*)-1-(cyclopentylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-phenyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-((1*S*)-1-(cyclopentylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-methyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-((4-fluoro-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-phenyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 20 *N*-1-((1*R*)-6-((4-fluoro-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-methyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-fluorophenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 25 *N*-1-((1*R*)-6-((diethylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-fluorophenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-(trifluoromethyl)phenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 30 *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-aspartamide;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-aspartamide;

- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-asparagine;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(((2-methylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-aspartamide;
- 5 *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-((4-fluoro-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-aspartamide;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-aspartamide;
- 10 *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-asparagine;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-aspartamide;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-aspartamide;
- 15 *N*-2-((4-methylphenyl)sulfonyl)-*N*-4-((1*R*)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-aspartamide;
- N*-2-((4-methylphenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-aspartamide;
- N*-2-((4-methylphenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-asparagine;
- 20 *N*-3-((2-aminophenyl)sulfonyl)-*N*-1-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-beta-alaninamide;
- N*-3-((2-nitrophenyl)sulfonyl)-*N*-1-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-beta-alaninamide;
- 25 *N*-3-((3,4-dichlorophenyl)sulfonyl)-*N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-fluorophenyl)-beta-alaninamide;
- N*-3-(1-methylethyl)-*N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-3-(2-amino-2-oxoethyl)-*N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 30 *N*-3-(2-fluoroethyl)-*N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-3-(2-naphthalenylsulfonyl)-*N*-3-(phenylmethyl)-*N*-1-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-beta-alaninamide;

- N*-3-(2-naphthalenylsulfonyl)-*N*-3-phenyl-*N*-1-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)-beta-alaninamide;
- N*-3-(3-amino-3-oxopropyl)-*N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 5 *N*-3-(4-fluorophenyl)-*N*-1-((1*R*)-6-(((2-methylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-3-(4-fluorophenyl)-*N*-1-((1*R*)-6-((4-fluoro-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-3-cyclohexyl-*N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 10 *N*-3-cyclopropyl-*N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-3-cyclopropyl-*N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 15 *N*-3-methyl-*N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-4-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-2-((4-methylphenyl)sulfonyl)-*D*-aspartamide;
- N*-4-((4*R*)-6-chloro-7-methyl-3,4-dihydro-2*H*-chromen-4-yl)-*N*-2-((3,4-dichlorophenyl)sulfonyl)-*D*-aspartamide;
- 20 *N*-4-((4*R*)-6-chloro-7-methyl-3,4-dihydro-2*H*-chromen-4-yl)-*N*-2-((4-methylphenyl)sulfonyl)-*D*-aspartamide;
- phenylmethyl *N*-2-((4-methylphenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-alpha-asparaginate;
- 25 (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(2-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-3-(3-bromophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-3-(3-chloro-4-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 30 (*R*)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-7-(piperidin-1-ylmethyl)chroman-4-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-(trifluoromethoxy)phenylsulfonamido)butanamide;

- (*R*)-4,4,4-trifluoro-3-(3-methylphenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-3-(4-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 5 (*R*)-3-(2-chloro-4-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-tert-butyl 2-(naphthalene-3-sulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoate;
- (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-((4-methylpiperidin-1-yl)methyl)-1,2,3,4-tetrahydro-
- 10 naphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-methyl 4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)-2-(3-(trifluoromethyl)phenylsulfonamido)butanoate;
- (*R*)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)-2-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid;
- 15 (*R*)-*N*1-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)succinamide;
- (*R*)-3-cyano-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)propanamide;
- (*R*)-2-(naphthalene-3-sulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-
- 20 tetrahydronaphthalen-1-ylamino)butanoic acid;
- (*R*)-methyl 2-(naphthalene-3-sulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoate;
- (*R*)-3-(3-tert-butylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 25 (*R*)-methyl 2-(3,4-dichlorophenylsulfonamido)-4-oxo-4-((*R*)-6-(pyrrolidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoate;
- (*R*)-4,4,4-trifluoro-3-(3-(oxazol-5-yl)phenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-3-(3,4-dihydro-2H-benzo[b][1,4]dioxepine-8-sulfonamido)-4,4,4-trifluoro-*N*-((*R*)-
- 30 6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-*N*-((*S*)-6-(4,5-dihydro-1H-imidazol-2-yl)-1,2,3,4-tetrahydronaphthalen-2-yl)-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(1,2,3,4-tetrahydroquinoline-8-sulfonamido)butanamide;

- (*R*)-4,4,4-trifluoro-3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-sulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(4-methylpiperidin-1-yl)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 5 (*R*)-4,4,4-trifluoro-*N*-((*R*)-5-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(((*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide; (*R*)-3-(3-chloro-2-fluoro-*N*-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-7-
- 10 (piperidin-1-ylmethyl)chroman-4-yl)butanamide;
- (*R*)-4,4,4-trifluoro-*N*-((*R*)-7-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-4,4,4-trifluoro-3-(3-methoxyphenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-yl-methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 15 (*R*)-3-(3,5-dimethylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-3-(3,4-dimethylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-yl-methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide
- (2*R*,3*R*)-3-(3-chloro-2-fluorophenylsulfonamido)-*N*-((*R*)-6-chloro-7-(piperidin-1-
- 20 ylmethyl)chroman-4-yl)-4,4,4-trifluoro-2-hydroxybutanamide;
- (*R*)-4,4,4-trifluoro-3-(2-fluoro-5-methylphenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-(trifluoromethyl)phenylsulfonamido)butanamide;
- 25 (2*R*,3*R*)-3-(2,5-dichlorophenylsulfonamido)-4,4,4-trifluoro-2-hydroxy-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (2*R*,3*R*)-3-(2,3-dichlorophenylsulfonamido)-4,4,4-trifluoro-2-hydroxy-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (2*R*,3*R*)-3-(3,4-dichlorophenylsulfonamido)-4,4,4-trifluoro-2-hydroxy-*N*-((*R*)-6-
- 30 (piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-3-(2-chloro-6-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-4,4,4-trifluoro-3-(5-fluoro-2-methylphenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;

(*R*)-4,4,4-trifluoro-*N*-((*R*)-7-(piperidin-1-ylmethyl)chroman-4-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide; and

(*R*)-3-(4-ethylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide.

5 In a second aspect, this invention is directed to a pharmaceutical composition comprising a compound of Formula (I) or any pharmaceutically-acceptable salt or hydrate thereof and a pharmaceutically acceptable excipient.

In a third aspect, this invention is directed to a method of treating a disease in a patient mediated by the B1 receptor comprising administering to the patient a pharmaceutical
10 composition comprising a therapeutically effective amount of a compound of Formula (I) or any pharmaceutically-acceptable salt or hydrate thereof and a pharmaceutically acceptable excipient. Specifically, the compounds of the present invention are useful in the treatment of a disorder such as acute pain, dental pain, back pain, lower back pain, pain from trauma, surgical pain, pain resulting from amputation or abscess, causalgia, fibromyalgia,
15 demyelinating diseases, trigeminal neuralgia, cancer, chronic alcoholism, stroke, thalamic pain syndrome, diabetes, acquired immune deficiency syndrome ("AIDS"), toxins and chemotherapy, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases, lupus, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or
20 unstable bladder disorders, psoriasis, skin complaints with inflammatory components, sunburn, carditis, dermatitis, myositis, neuritis, collagen vascular diseases, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, sympathetically maintained pain, deafferentation syndromes, asthma, vasomotor or allergic rhinitis, epithelial tissue
25 damage or dysfunction, herpes simplex, post-herpetic neuralgia, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritis, vitiligo, general gastrointestinal disorders, colitis, inflammatory bowel disease, gastric ulceration, duodenal ulcers, thalamic pain syndrome, diabetes, toxins and chemotherapy, septic shock, and bronchial disorders preferably
30 osteoarthritis.

The invention also provides for the use of the compounds of the present invention for the prevention or for the treatment of a disorder such as acute pain, dental pain, back pain, lower back pain, pain from trauma, surgical pain, pain resulting from amputation or abscess, causalgia, fibromyalgia, demyelinating diseases, trigeminal neuralgia, cancer, chronic

alcoholism, stroke, thalamic pain syndrome, diabetes, acquired immune deficiency syndrome ("AIDS"), toxins and chemotherapy, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases, lupus, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, sunburn, carditis, dermatitis, myositis, neuritis, collagen vascular diseases, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, sympathetically maintained pain, deafferentation syndromes, asthma, vasomotor or allergic rhinitis, epithelial tissue damage or dysfunction, herpes simplex, post-herpetic neuralgia, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritis, vitiligo, general gastrointestinal disorders, colitis, inflammatory bowel disease, gastric ulceration, duodenal ulcers, thalamic pain syndrome, diabetes, toxins and chemotherapy, septic shock, and bronchial disorders.

In a fourth aspect, this invention is directed to the use of one or more of the compounds of the present invention in the manufacture of a medicament. Preferably, the medicament is useful in the treatment of a disorder such as acute pain, dental pain, back pain, lower back pain, pain from trauma, surgical pain, pain resulting from amputation or abscess, causalgia, fibromyalgia, demyelinating diseases, trigeminal neuralgia, cancer, chronic alcoholism, stroke, thalamic pain syndrome, diabetes, acquired immune deficiency syndrome ("AIDS"), toxins and chemotherapy, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases, lupus, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, sunburn, carditis, dermatitis, myositis, neuritis, collagen vascular diseases, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, sympathetically maintained pain, deafferentation syndromes, asthma, vasomotor or allergic rhinitis, epithelial tissue damage or dysfunction, herpes simplex, post-herpetic neuralgia, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritis, vitiligo, general gastrointestinal disorders, colitis, inflammatory bowel disease, gastric ulceration, duodenal ulcers, thalamic pain syndrome, diabetes, toxins and chemotherapy, septic shock, and bronchial disorders.

even more preferably, the medicament is useful in the treatment of a disorder such as pain or inflammation.

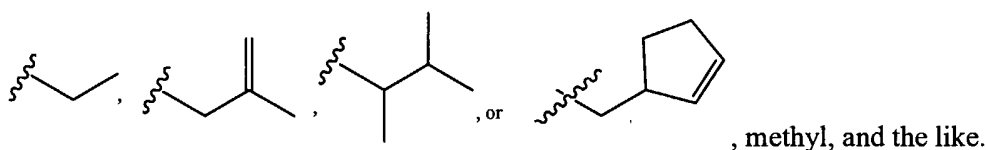
The compounds of this invention may also act as inhibitors of other receptors or kinases, and thus be effective in the treatment of diseases associated with other protein kinases.

- 5 Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

Definitions:

- 10 Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

- The term "C_{α-β}alkyl" means an alkyl group having 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 as indicated in the claims unless otherwise indicated. The
- 15 alkyl groups described in this section may also contain one or two double or triple bonds. When the alkyl group has a double bond it is also referred to herein as alkenyl. When the alkyl group has a triple bond it is also referred to herein as alkynyl. Examples of C₁₋₆alkyl include, but are not limited to, the following:



- 20 The term "alkylamino" denotes amino groups which have been substituted with one alkyl radical and with two alkyl radicals, including terms "*N*-alkylamino" and "*N,N*-dialkylamino". More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable
- 25 "alkylamino" may be mono or dialkylamino such as *N*-methylamino, *N*-ethylamino, *N,N*-dimethylamino, *N,N*-diethylamino and the like.

The terms "*N*-aralkyl-*N*-alkylamino" and "*N*-alkyl-*N*-arylamino" denote amino groups which have been substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

- 30 The term "aminoalkyl" embraces linear or branched alkyl radicals having one to ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" radicals having one to six carbon atoms

and one or more amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.

5 The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom independently substituted with an alkyl radical. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkyl radicals may be mono or dialkyl substituted, such as *N*-methylaminomethyl, *N,N*-dimethyl-aminoethyl, *N,N*-diethylaminomethyl and the like.

10 The term "aminoalkenyl" embraces linear or branched alkyl radicals having two to ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkenyl radicals are "lower aminoalkenyl" radicals having two to six carbon atoms and one or more amino radicals. Examples of such radicals include aminoethenyl, aminopropenyl, aminobutenyl and aminohexenyl. Even more preferred are lower
15 aminoalkenyl radicals having two or three carbon atoms.

The term "alkylaminoalkenyl" embraces aminoalkenyl radicals having the nitrogen atom independently substituted with an alkyl radical. More preferred alkylaminoalkenyl radicals are "lower alkylaminoalkenyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkenyl radicals having alkyl radicals of one
20 to three carbon atoms. Suitable alkylaminoalkenyl radicals may be mono or dialkyl substituted, such as *N*-methylaminovinyl, *N,N*-dimethyl-aminovinyl, *N,N*-diethylaminovinyl, and the like.

The term "alkoxy" embrace linear or branched oxy-containing radicals (-OR) having alkyl portions of one to ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy"
25 radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals
30 include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy, and fluoropropoxy.

The term "alkoxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more alkoxy radicals. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals respectively having one

to six carbon atoms. Examples of such radicals include methoxymethyl, methoxyethyl, and the like. Even more preferred are lower alkoxyalkyl radicals respectively having one to three carbon atoms alkyl radicals.

The term "aminoalkoxy" embraces alkoxy radicals substituted with an amino radical.
5 More preferred aminoalkoxy radicals are "lower aminoalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Suitable aminoalkoxy radicals may be aminoethoxy, aminopropoxy and the like.

The term "alkylaminoalkoxy" embraces alkoxy radicals substituted with alkylamino radicals. More preferred alkylaminoalkoxy radicals are "lower alkylaminoalkoxy" radicals
10 having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxy radicals may be mono or dialkyl substituted, such as *N*-methylaminoethoxy, *N,N*-dimethylaminoethoxy, *N,N*-diethylaminoethoxy and the like.

The term "alkylaminoalkoxyalkoxy" embraces alkoxy radicals substituted with
15 alkylaminoalkoxy radicals as defined above. More preferred alkylaminoalkoxyalkoxy radicals are "lower alkylaminoalkoxyalkoxy" radicals independently having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxyalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxyalkoxy radicals may be mono or dialkyl substituted, such as *N*-methylaminoethoxymethoxy, *N,N*-
20 dimethylaminoethoxymethoxy, *N,N*-diethylaminomethoxymethoxy, and the like.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. More preferred aryl is phenyl. The "aryl" group
25 may have 1 to 3 substituents such as lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy, and lower alkylamino unless otherwise indicated.

The term "aralkyl" embraces aryl substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are lower aralkyl radicals phenyl attached to alkyl portions
30 having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "arylalkenyl" embraces aryl substituted alkenyl radicals. Preferable arylalkenyl radicals are "lower arylalkenyl" radicals having aryl radicals attached to alkenyl

radicals having two to six carbon atoms. Examples of such radicals include phenylethenyl. The aryl in said arylalkenyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy unless otherwise indicated.

The term "*N*-arylaminomethyl" denotes aminomethyl radicals substituted with an aryl radical. More preferred arylaminomethyl radicals are "lower *N*-arylaminomethyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are phenylaminomethyl radicals having one to three carbon atoms. Examples of such radicals include *N*-phenylaminomethyl and *N*-phenylaminoethyl.

The term "aralkylaminomethyl" embraces aralkyl radicals as described above, attached to an aminomethyl radical as defined herein. More preferred are lower aralkylaminomethyl radicals independently having alkyl radicals of one to three carbon atoms.

The term "basic moiety" or "basic moieties" means a chemical moiety that has a measured or calculated pK_a of from about 7 to about 13. The term also can include a chemical moiety that is protonable, to some extent, between a pH range of from about 7 to about 10. Examples of basic moieties include, but are not limited to, amino, cycloalkylamino-(C_1 - C_6)alkyl, cycloalkyl(C_1 - C_6)alkylamino(C_1 - C_6)alkyl, heterocyclylamino(C_1 - C_6)alkyl, heterocyclyl(C_1 - C_6)alkylamino(C_1 - C_6)alkyl, arylamino(C_1 - C_6)alkyl, aryl(C_1 - C_6)alkylamino-(C_1 - C_6)alkyl, (C_1 - C_6)alkylamino(C_1 - C_6)alkoxy, (C_1 - C_6)alkylamino(C_1 - C_6)alkoxy(C_1 - C_6)-alkoxy, amino(C_1 - C_6)alkoxy, amino(C_1 - C_6)alkyl, (C_1 - C_6)alkylamino(C_1 - C_6)alkyl, (C_1 - C_4)alkylamino-(C_2 - C_6)alkenyl, 4-8-membered nitrogen-containing heterocyclyl(C_2 - C_6)alkenyl, 5-6 membered heterocyclolkoxy, 5-6 membered nitrogen-containing heterocyclyl and 5-7 membered nitrogen-containing heterocyclylalkyl; more specifically amino, cycloalkylamino(C_1 - C_6)alkyl, cycloalkyl(C_1 - C_6)alkylamino-(C_1 - C_6)alkyl, heterocyclylamino(C_1 - C_6)alkyl, heterocyclyl(C_1 - C_6)alkylamino-(C_1 - C_6)alkyl, arylamino(C_1 - C_6)alkyl, aryl(C_1 - C_6)alkylamino(C_1 - C_6)alkyl, (C_1 - C_6)alkyl amino(C_1 - C_6)alkoxy, (C_1 - C_6)alkylamino(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy, amino(C_1 - C_6)alkoxy, amino(C_1 - C_6)alkyl, (C_1 - C_6)alkylamino(C_1 - C_6)alkyl, (C_1 - C_4)alkylamino-(C_2 - C_6)alkenyl, 5-8-membered nitrogen-containing heterocyclyl(C_2 - C_6)alkenyl, heterocyclyl(C_1 - C_6)amino(C_2 - C_6)alkyl, 5-6 membered heterocyclolkoxy, 5-6 membered nitrogen-containing heterocyclyl and 5-7 membered nitrogen-containing heterocyclyl(C_1 - C_6)alkyl. Each basic moiety can be substituted by 0, 1, 2 or 3 groups independently selected from halo, $-NH_2$, $-OH$, $-CN$, $-CF_3$, (C_1 - C_6)alkylamino, haloalkyl, oxo, (C_1 - C_6)alkoxy, (C_1 - C_6)alkoxyalkyl, (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, di(C_1 - C_6)alkylamino, $=NCN$; and (C_1 - C_6)alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl, each of which is substituted by 0, 1, 2 or 3 groups independently selected from halo, $-NH_2$,

-OH, -CN, -CF₃, (C₁-C₆)alkylamino, haloalkyl, oxo, (C₁-C₆)alkoxy, (C₁-C₆)alkoxyalkyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, or di(C₁-C₆)alkylamino. In one embodiment, the basic moiety is selected from cycloalkylamino(C₁-C₆)alkyl, cycloalkyl(C₁-C₆)alkyl-amino(C₁-C₆)alkyl, heterocyclylamino(C₁-C₆)alkyl, heterocyclyl(C₁-C₆)alkylamino-
 5 (C₁-C₆)alkyl, arylamino(C₁-C₆)alkyl, aryl(C₁-C₆)alkylamino(C₁-C₆)alkyl, (C₁-C₆)alkyl amino(C₁-C₆)alkoxy, (C₁-C₆)alkylamino(C₁-C₆)alkoxy(C₁-C₆)alkoxy, amino(C₁-C₆)alkoxy, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, (C₁-C₄)alkylamino-(C₂-C₆)alkenyl, 4-8-membered nitrogen-containing heterocyclyl(C₂-C₆)alkenyl, heterocyclyl(C₁-C₆)amino-(C₂-C₆)alkyl, 5-6 membered heterocycloxy, 5-6 membered nitrogen-containing heterocyclyl
 10 and 5-7 membered nitrogen-containing heterocyclylalkyl. In another embodiment, the basic moiety is selected from cycloalkylamino(C₁-C₆)alkyl, cycloalkyl(C₁-C₆)alkylamino-(C₁-C₆)alkyl, heterocyclylamino(C₁-C₆)alkyl, heterocyclyl(C₁-C₆)alkylamino(C₁-C₆)alkyl, arylamino(C₁-C₆)alkyl, aryl(C₁-C₆)alkylamino(C₁-C₆)alkyl, (C₁-C₆)alkyl amino(C₁-C₆)alkoxy, (C₁-C₆)alkylamino(C₁-C₆)alkoxy(C₁-C₆)alkoxy, amino(C₁-C₆)alkoxy, amino(C₁-C₆)alkyl,
 15 (C₁-C₆)alkylamino(C₁-C₆)alkyl, (C₁-C₄)alkylamino-(C₂-C₆)alkenyl, 4-8-membered nitrogen-containing heterocyclyl(C₂-C₆)alkenyl, heterocyclyl(C₁-C₆)amino(C₂-C₆)alkyl, 5-6 membered heterocycloxy, 5-6 membered nitrogen-containing heterocyclyl and 5-7 membered nitrogen-containing heterocyclyl-alkyl any of which are substituted by halo, C₁₋₆alkyl or cycloalkyl. More specifically, the basic moiety is amino,
 20 aminomethyl, isopropylaminomethyl, *t*-butylaminomethyl, 2-*t*-butylaminoethyl, 2-*tert*-butylamino-1-methyl-ethyl, 1-*tert*-butylaminoethyl, 1-(*tert*-butylamino-methyl)-vinyl, 1-(piperidin-1-ylmethyl)-vinyl, *N*-isobutyl-aminomethyl, *N*-isobutyl-aminoethyl, (2,2-dimethyl)propylaminomethyl, *N*-isopropyl-*N*-ethylaminomethyl, *N*-isopropyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-methylaminomethyl, *N*-*iso*-butyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-ethylaminomethyl, *N*-isobutyl-*N*-methylaminomethyl, *N*-*t*-butyl-*N*-isopropylaminomethyl, *N,N*-di(isopropyl)aminomethyl, *N,N*-dimethylaminomethyl, *N,N*-diethylaminomethyl, *N,N*-di(*t*-butyl)-aminomethyl, cyclopropylaminomethyl, cyclopropylaminoethyl, cyclopropylmethylaminomethyl, cyclopropylmethylaminoethyl, cyclobutylaminomethyl, cyclobutylaminoethyl, cyclobutylmethylaminomethyl,
 25 cyclobutylmethylaminoethyl, 4,5-dihydro-imidazolyl, 1-piperidinylmethyl, 4-fluoropiperidin-1-ylmethyl, 4,4-difluoropiperidin-1-ylmethyl, 3-hydroxypiperidin-1-ylmethyl, 4-hydroxypiperidin-1-ylmethyl, 4-(piperidin-1-yl)piperidinylmethyl, 4-(dimethylamino)piperidin-1-ylmethyl, 2,6-dimethylpiperidin-1-ylmethyl, 4-morpholinylmethyl, 1-pyrrolidinylmethyl, 2-methylpyrrolidin-1-ylmethyl, 2,5-dimethylpyrrolidin-1-ylmethyl, piperazin-1-ylmethyl,

azocan-1-ylmethyl, azepan-1-ylmethyl, (7-azabicyclo[2.2.1]hept-7-yl)methyl, (1,3,3-trimethyl-6-azaicyclo[3.2.1]oct-6-yl)methyl, 2-piperidinyl or 4-methylpiperazin-1-ylmethyl.

5 The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C₃-C₆ rings. More preferred compounds include cyclopentyl, cyclopropyl, and cyclohexyl.

The term "cycloalkylaminoalkyl" refers to aminoalkyl radicals where the nitrogen atom of the amino group is independently substituted, respectively, with one cycloalkyl radical, or two cycloalkyl radicals and therefore includes "*N*-cycloalkylaminoalkyl" and "*N,N*-dicycloalkylaminoalkyl". More preferred cycloalkylaminoalkyl radicals are "lower
10 cycloalkylaminoalkyl" radicals having alkyl radicals with one to six carbon atoms. Even more preferred are lower cycloalkylaminoalkyl radicals having alkyl radicals with one to three carbon atoms. Examples of such lower alkylaminosulfonyl radicals include *N*-cyclohexylaminomethyl, and *N*-cyclopentylaminoethyl.

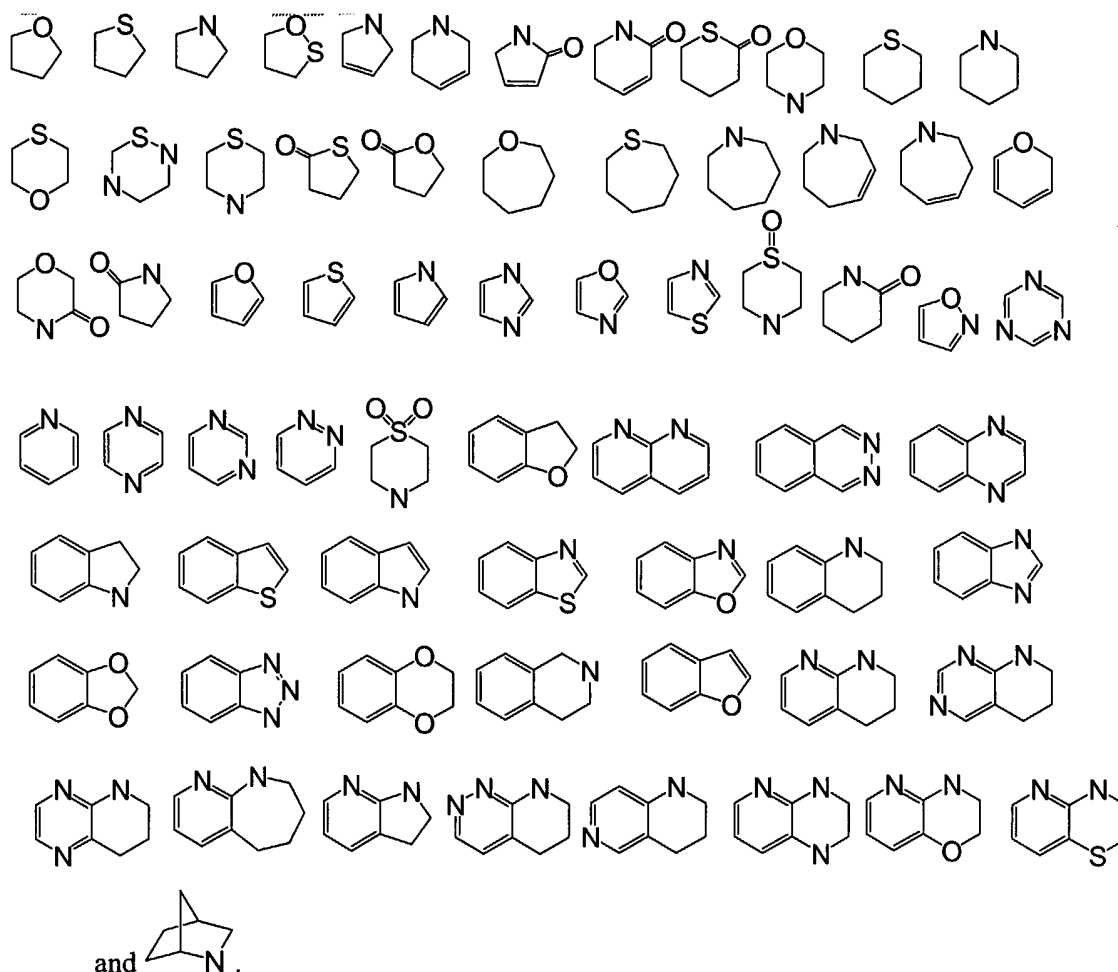
The term "cycloalkylalkylaminoalkyl" embraces cycloalkyl radicals as described above,
15 attached to an alkylaminoalkyl radical. More preferred are lower cycloalkyl-alkylaminoalkyl radicals independently having alkyl radicals of one to three carbon atoms.

"Halo" or "halogen" means a halogen atoms selected from F, Cl, Br and I.

"C_{α-β}haloalkyl" means an alkyl group as described above, unless otherwise indicated, wherein any number--at least one--of the hydrogen atoms attached to the alkyl chain are
20 replaced by F, Cl, Br or I.

"Heterocycle" or "heterocyclyl" means a ring comprising at least one carbon atom and at least one other atom selected from N, O and S. The term heterocycle embraces saturated, partially saturated and unsaturated heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. It does not include rings containing -O-O-
25 or -S-S- portions. Preferably, the heterocycle ring contains 3 to 10 ring atoms. Unsaturated heteroatom-containing ring radicals as used herein means a heterocycle containing at least one aromatic ring. Unsaturated heteroatom-containing ring radicals are also referred to herein as heteroaryl. Partially saturated heteroatom-containing ring radicals as used herein means a heterocycle containing one or more double bonds provided that it is not aromatic.

30 Examples of heterocycles that may be found in the claims include, but are not limited to, the following:



The term "heterocyclaminoalkyl" embraces heterocyclyl radicals as described above, attached to an aminoalkyl radical as defined herein.

- 5 The term "heterocyclalkylaminoalkyl" embraces heterocyclalkyl radicals as described below, attached to an aminoalkyl radical. More preferred are lower heterocyclalkylaminoalkyl radicals having, independently, alkyl radicals of one to three carbon atoms.

10 The term "heterocyclalkyl" embraces heterocyclic-substituted alkyl radicals. More preferred heterocyclalkyl radicals are "5- or 6-membered heteroarylalkyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl radical. Even more preferred are lower heteroarylalkyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as pyridinylmethyl and thienylmethyl.

15 The term "heterocyclalkenyl" embraces heterocyclyl-substituted alkenyl radicals. Preferable heterocyclalkenyl radicals are "lower heterocyclalkenyl" radicals having heterocyclyl radicals attached to alkenyl radicals having two to six carbon atoms. Examples of such radicals include pyridinylethenyl. When the heterocyclyl ring contains 4 to 8 ring atoms

having at least a nitrogen ring atom it is referred to herein as 4-8 membered nitrogen containing heterocyclalkenyl.

The term "heterocycloxy" embraces optionally substituted heterocycl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include piperidyloxy.

5 The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

The terms "oxo" represent the group =O (as in carbonyl).

10 The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals.

The terms "carboxy" or "carboxyl" denotes -CO₂H.

The term "carbonyl" denotes -(C=O)-.

The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

15 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
20 elements or subgroups from the genus.

The term "partially saturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic hydrocarbon ring" means a hydrocarbon ring that is not completely aromatic e.g., tetrahydronaphthyl, tetrahydrochromenyl, dihydroindolyl, and the like.

25 The term "unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic hydrocarbon ring" means a hydrocarbon ring that is aromatic.

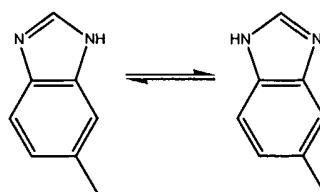
A "pharmaceutically acceptable carrier or excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically
30 acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated

with alternative therapies. For example, effective pain therapeutic agents relieve the pain sensation of the patient. Alternatively, effective therapeutic agents for the treatment of inflammation minimize the damage from the inflammation, and the like.

The term "treatment" includes therapeutic treatment as well as prophylactic treatment (either preventing the onset of disorders altogether or delaying the onset of a pre-clinically evident stage of disorders in individuals).

The compounds of this invention may also be represented in multiple tautomeric forms, for example, as illustrated below:



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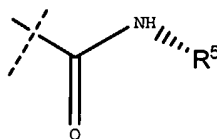
The invention expressly includes all tautomeric forms of the compounds described herein. The compounds may also occur in cis- or trans- or E- or Z- double bond isomeric forms. All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

Substituents on ring moieties (e.g., phenyl, thienyl, etc.) may be attached to specific atoms, whereby they are intended to be fixed to that atom, or they may be drawn unattached to a specific atom, whereby they are intended to be attached at any available atom that is not already substituted by an atom other than H (hydrogen).

The compounds of this invention may contain heterocyclic ring systems attached to another ring system. Such heterocyclic ring systems may be attached through a carbon atom or a heteroatom in the ring system.

Compounds of the present invention can possess, in general, 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. Unless otherwise indicated, the compounds of the present invention, as depicted or named, may exist as the racemate, a single enantiomer, or any uneven (i.e. non 50/50) mixture of enantiomers. All such isomeric forms are within the scope of the invention. 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, ditoluoyltartaric, and camphorsulfonic acid and then

separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column, such as, for example, a CHIRAL-AGP column, optimally chosen to maximize the separation of the enantiomers. Still another
5 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
10 can likewise be obtained by using optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt. Preferred compounds of the invention have an *R* configuration at the carbon that is attached to the amide bond as shown below:



15

Compounds of the present invention can possess, in general, tautomeric forms, including any enolate anions. All such forms are included within the scope of this invention.

Also included in the family of compounds of Formula (I) are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts
20 commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula (I) may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid.
25 Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic,
30 ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic,

hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula (I) include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, *N*-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, *N*-ethylmorpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate acid or base with the compound of Formula (I)

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 HCl, H₂SO₄ and H₃PO₄ 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.

General Synthetic Procedures

Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1994); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers); Organic Reactions, Volumes 1-46 (John Wiley and Sons, 2003), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's

Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

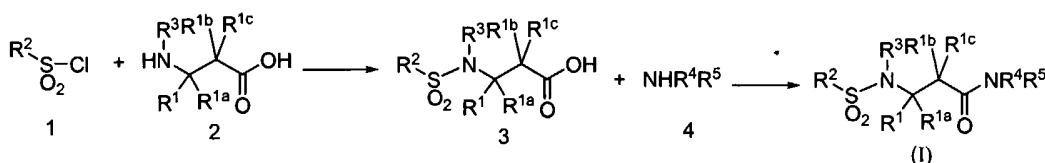
5 The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78°C to about 150°C , more preferably from about 0°C to about 125°C and most preferably at about room (or ambient) temperature, e.g., about 20°C .

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T. W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1999. Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

20 Compounds of Formula (I) where R¹, R², R^{1a}, R^{1b}, R^{1c}, R⁴ and R⁵ are as defined in the Summary of the Invention can be prepared as shown in Scheme A below.

Scheme A



25 Compounds of Formula (I) where R¹, R², R^{1a}, R^{1b}, R^{1c}, R⁴ and R⁵ are as defined in the Summary of the Invention can be prepared as shown in Scheme A above. Reaction of a sulfonyl chloride of formula 1 where R² is as defined in the Summary of the Invention with a β-amino acids of formula 2 provides a compound of formula 3. The reaction is carried out in the presence of a base such as triethylamine, pyridine, and the like and in a suitable organic solvent
30 such as tetrahydrofuran, dimethylformamide and the like, or in the presence of inorganic base such as sodium bicarbonate and sodium carbonate, and the like and in a suitable solvent system such as dioxane/water (1/1, v/v). Alternatively, the reaction can be carried out in neat base.

Compounds of formula 1 are either commercially available or they can be prepared by methods well known in the art. Compounds of formula 2 are either commercially available or they can be prepared by methods well known in the art. Reaction of acid 3 with an amine of formula 4 where R^4 and R^5 are as defined in the Summary of the invention under standard peptidic coupling reaction conditions provide a compound of Formula (I). The reaction is carried out in the presence of a coupling agent such as are coupled with the substituted amine 2 using standard peptide coupling conditions coupling agent (e.g., benzotriazol-1-yloxy-trispyrrolidinophosphonium hexafluorophosphate (PyBOP[®]), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (EDCI), O-(7-azabenzotriazol-1-yl)-1,1,3,3, tetra-

10 methyluronium-hexafluoro- phosphate (HATU), O-benzotriazol-1-yl-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), or the like) and non-nucleophilic base (e.g., triethylamine, *N*-methylmorpholine, and the like, or any suitable combination thereof) at ambient temperature.

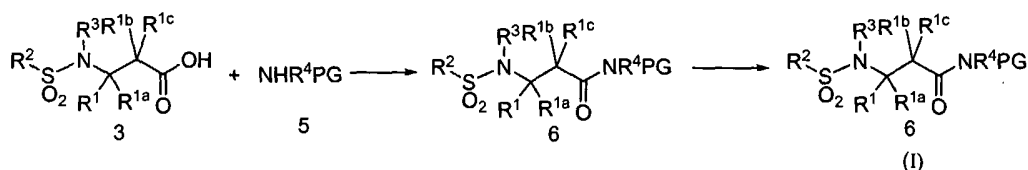
15 Suitable reaction solvents include, but are not limited to, dimethylformamide, methylene chloride, and the like.

Amines of formula 2 are commercially available or may be prepared by methods well known in the art. A detailed description of syntheses of amines is provided in working examples below.

20

Alternatively, the compounds of Formula (I) can be prepared as shown in Scheme B below.

Scheme B



25 Compounds of Formula (I) can also be prepared by reacting compound 3 with a an amine of formula 5 where PG is a precursor group to R^5 group. Conversion of the PG group to R^5 group then provides a compound of Formula (I).

For example, a compound of Formula (I) where R^5 is a saturated, partially saturated or unsaturated 8-, 9-, 10- or 11-membered bicyclic or 12-, 13-, 14- or 15- membered tricyclic ring substituted with cycloalkylamino-(C_1 - C_6)alkyl, cycloalkyl(C_1 - C_6)alkylamino(C_1 - C_6)alkyl, heterocyclylamino(C_1 - C_6)alkyl, heterocyclyl(C_1 - C_6)alkylamino(C_1 - C_6)alkyl, arylamino(C_1 - C_6)alkyl, aryl(C_1 - C_6)alkylamino-(C_1 - C_6)alkyl, (C_1 - C_6)alkylamino(C_1 - C_6)alkoxy,

30

(C₁-C₆)alkylamino(C₁-C₆)alkoxy(C₁-C₆)-alkoxy, amino(C₁-C₆)alkoxy, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, and 5-7 membered nitrogen-containing heterocyclalkyl can be prepared by from a corresponding compound of formula 6 where PG is a saturated, partially saturated or unsaturated 8-, 9-, 10- or 11-membered bicyclic or 12-, 13-, 14- or 15- membered tricyclic ring substituted with a hydroxyalkyl group by treating the hydroxyalkyl compound with an oxidizing agent such as manganese oxide and treating the resulting aldehyde compound with an amine optionally substituted with cycloalkyl, cycloalkylalkyl, heterocycl, alkyl, aryl, aralkyl, or nitrogen containing heterocycl group under reductive amination reaction conditions to provide a compound of Formula (I) with the above listed substituents.

Alternatively, the aldehyde can first treated with an unsubstituted amine and then the amine can be alkylation under standard alkylation reaction conditions or treated with an aldehyde under reductive amination reaction conditions. The above compounds can also be prepared from a corresponding compound of formula 6 carrying an alkene group by first converting the alkyne group to an aldehyde under ozonolysis reaction conditions and then proceeding as described above.

Additionally, the aldehyde can be first converted to a ketone by treating it with a Grignard reagent and then reacted with amine to provide compounds of Formula (I) where the carbon atom alpha to the amino group is substituted.

Compounds of Formula (I) where R⁵ is a saturated, partially saturated or unsaturated 8-, 9-, 10- or 11-membered bicyclic or 12-, 13-, 14- or 15- membered tricyclic ring substituted with 5-6 membered heterocycloxy can be prepared from a corresponding compound of formula 6 where PG is a saturated, partially saturated or unsaturated 8-, 9-, 10- or 11-membered bicyclic or 12-, 13-, 14- or 15- membered tricyclic ring substituted with a hydroxyl group by reacting it with heterocycl halide under alkylating reaction conditions.

It will be well recognized by a person skilled in the art that if one or more functional groups, for example carboxy, hydroxy, amino, or mercapto, need to be protected during the synthesis of a compound of Formula (I) because they should not take part in the reaction such groups should be suitably protected prior to or during the synthesis procedure. A person skilled in the art would be able to easily establish, which protecting groups are suitable with the reactions mentioned above and hereinafter.

Salts of a compound of Formula (I) with a salt-forming group may be prepared in a manner known *per se*. Acid addition salts of compounds of Formula (I) may thus be obtained by treatment with an acid or with a suitable anion exchange reagent. A salt with two acid molecules (for example a dihalogenide of a compound of Formula (I)) may also be converted

into a salt with one acid molecule per compound (for example a monohalogenide); this may be done by heating to a melt, or for example by heating as a solid under a high vacuum at elevated temperature, for example from 130-170 °C, one molecule of the acid being expelled per molecule of a compound of Formula (I).

- 5 Salts can usually be converted to free compounds, e.g. by treating with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogen carbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide.

 The compounds of Formula (I), including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallization (present
10 as solvates). All such forms are within the scope of this invention.

 As can be appreciated by the skilled artisan, the above synthetic schemes are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be
15 performed in an alternate sequence or order to give the desired compounds.

Utility

 The compound of Formula (I) are B1 receptor antagonists and hence are useful in the treatment of a disorder such as acute pain, dental pain, back pain, lower back pain, pain from
20 trauma, surgical pain, pain resulting from amputation or abscess, causalgia, fibromyalgia, demyelinating diseases, trigeminal neuralgia, cancer, chronic alcoholism, stroke, thalamic pain syndrome, diabetes, acquired immune deficiency syndrome ("AIDS"), toxins and chemotherapy, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases, lupus,
25 osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, sunburn, carditis, dermatitis, myositis, neuritis, collagen vascular diseases, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, sympathetically maintained
30 pain, deafferentation syndromes, asthma, vasomotor or allergic rhinitis, epithelial tissue damage or dysfunction, herpes simplex, post-herpetic neuralgia, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritis, vitiligo, general gastrointestinal disorders, colitis,

inflammatory bowel disease, gastric ulceration, duodenal ulcers, thalamic pain syndrome, diabetes, toxins and chemotherapy, septic shock, and bronchial disorders.

Biological Testing

5 The *in vitro* binding affinity of the compounds of the invention to the human B1 and B2 bradykinin receptors can be tested using the radioligand binding assay described in Biological Example 1 below. The antagonistic activity of the compounds of the invention for the human B1 and B2 bradykinin receptors can be tested using the calcium flux assay, Rabbit endothelial cell B1-specific PGI₂ secretion Assay, and umbilical vein Assay described in Biological
10 Examples 2 and 3 below. The antinociceptive activity of the compounds of the invention was determined using the rat and monkey pain models described in Example 4 below. The antiinflammatory activity of the compounds of the invention was determined using the Green Monkey LPS inflammation model described in Example 5 below.

15 Pharmaceutical Compositions and Administration

 The present invention also embraces pharmaceutical compositions comprising the active compounds of Formula (I) in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of the present invention
20 may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly
25 intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

 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.

30 For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg or 5

to 1000 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 amount of compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg, preferably between about 0.1 and about 50 mg/kg, and more preferably about 0.1 and about 20 mg/kg body weight may be appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

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

When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the

cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas.

5 Examples of such dermal penetration enhancers include DMSO and related analogs.

The compounds of this invention can also be administered by a transdermal device. Preferably transdermal administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the
10 active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known
15 ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with
20 the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

25 The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-
30 isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (ie. Captisol), cosolvent solubilization (ie. propylene glycol) or micellar solubilization (i.e., Tween 80).

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-butanediol. 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.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

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.

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. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

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 administered at the same time or sequentially at different times, or the therapeutic agents can be given as a single composition.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

The present compounds may also be used in combination therapies with opioids and other anti-pain analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, COX-2 inhibitors such as celecoxib, rofecoxib, valdecoxib, parecoxib, and darecoxib, NSAID's, and sodium channel blockers, among others. More preferred would be combinations with compounds selected from morphine, meperidine, codeine, pentazocine, buprenorphine, butorphanol, dezocine, meptazinol, hydrocodone, oxycodone, methadone, tetrahydrocannabinol, pregabalin, Tramadol [(+) enantiomer], DuP 747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078, ICI- 204448, acetaminophen (paracetamol), propoxyphene, nalbuphine, E-4018, filenadol, mirtentamil, amitriptyline, DuP631, Tramadol [(-) enantiomer], GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, tramadol racemate, Dynorphine A, E-2078, AXC3742, SNX-111, ADL2-1294, ICI- 204448, CT-3, CP-99,994, and CP-99,994.

Alternatively, the present compounds may also be used in co-therapies with other treatments for inflammation, e.g. steroids, NSAIDs, iNOS inhibitors, p38 inhibitors, TNF inhibitors, 5-lipoxygenase inhibitors, LTB₄ receptor antagonists and LTA₄ hydrolase inhibitors.

Examples

In order that the invention described herein may be more readily understood, the following references (intermediates) and examples (final compound) are set forth. These detailed descriptions fall within the scope, and serve to exemplify the above-described General Synthetic Procedures which form part of the invention. These detailed descriptions are

presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All parts are by weight unless otherwise indicated. 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 > 95% purity as determined by high-performance liquid chromatography. Unless otherwise stated, reactions were run at RT.

The following abbreviations are used:

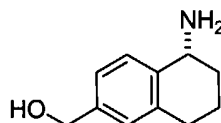
10	AcOH, HOAc	-	acetic acid
	CH ₃ CN	-	acetonitrile
	NH ₃	-	ammonia
	NH ₄ Cl	-	ammonium chloride
	NH ₄ OH	-	ammonium hydroxide
15	HATU	-	O-(7-Azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
	AIBN	-	2,2'-azobisisobutyronitrile
	(PPh ₃) ₂ NiBr ₂	-	bis(triphenylphosphine)nickel(II) bromide
	BH ₃	-	borane
20	BH ₃ SMe ₂	-	borane-methyl sulfide complex
	Br ₂	-	bromine
	NBS	-	<i>N</i> -bromosuccinimide
	CCl ₄	-	carbon tetrachloride
	CHCl ₃	-	chloroform
25	DBU	-	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCE	-	1,2-dichloroethane
	CH ₂ Cl ₂	-	dichloromethane; DCM
	Et ₂ O	-	diethyl ether
	IP ₂ NEt, DIEA	-	diisopropylethylamine
30	Me ₂ NH	-	dimethylamine
	EDC	-	(3-dimethylamino-propyl)-ethyl carbodiimide-HCl salt
	DMAP	-	4-(dimethylamino)pyridine
	DMF	-	dimethylformamide

	DMSO	-	dimethyl sulfoxide (also known as methyl sulfoxide)
	DPPA	-	diphenylphosphoryl azide
	EtOH	-	ethanol
5	EtOAc	-	ethyl acetate
	HCO ₂ H	-	formic acid
	g	-	gram
	h	-	hour
	HCl	-	hydrochloric acid
10	H ₂	-	hydrogen
	HOAt	-	1-hydroxy-7-azabenzotriazole
	HOBt	-	1-hydroxybenzotriazole
	IPA	-	isopropanol
	<i>i</i> PrOH	-	isopropanol
15	ISCO	-	ISCO liquid chromatography system
	LAH	-	lithium aluminum hydride
	LDA	-	lithium diisopropylamide
	LiOH	-	lithium hydroxide
	MgSO ₄	-	magnesium sulfate
20	MeOH	-	methanol
	NMM	-	<i>N</i> -methylmorpholine
	NMP	-	1-methyl-2-pyrrolidone
	mL	-	milliliter
	min	-	minutes
25	N ₂	-	nitrogen
	Pd/C	-	palladium on carbon
	Pd(OH) ₂	-	palladium hydroxide
	H ₃ PO ₄	-	phosphoric acid
	K ₂ CO ₃	-	potassium carbonate
30	KCN	-	potassium cyanide
	KOH	-	potassium hydroxide
	RT	-	room temperature
	SiO ₂	-	silica
	NaOAc	-	sodium acetate

	NaN ₃	-	sodium azide
	NaHCO ₃	-	sodium bicarbonate
	NaBH ₄	-	sodium borohydride
	NaOH	-	sodium hydroxide
5	NaBH(OAc) ₃	-	sodium triacetoxyborohydride
	H ₂ SO ₄	-	sulfuric acid
	SOCl ₂	-	thionyl chloride
	THF	-	tetrahydrofuran
	TsCl	-	<i>p</i> -tosyl chloride
10	TsOH	-	<i>p</i> -toluene sulfonic acid
	TEA, Et ₃ N	-	triethylamine
	TFA	-	trifluoroacetic acid
	PPh ₃	-	triphenylphosphine
	H ₂ O	-	water

15

Reference 1

Synthesis of (5*R*)-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol20 Step A: Synthesis of 5(*S*)-hydroxy-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid methyl ester

To an oven-dried 2 L round-bottomed flask equipped with an argon inlet/outlet and magnetic stirring was added (*R*)-2-methyl-CBS-oxazaborolidine (7.4 mL of a 1M soln in toluene, 7.4 mmol, Aldrich). Toluene (190 mL) was added and the reaction mixture was cooled in an ice-salt bath (bath temp. = -10 °C). BH₃-SMe₂ was added (17 mL, 180 mmol, Aldrich), followed by a solution of 5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid methyl ester (30 g, 150 mmol, Albany Molecular) in THF (200 mL) was added over 5 h using a syringe pump. After the addition was complete, the reaction mixture was stirred for an additional 1 h. The reaction mixture was poured into an addition funnel, and the reaction mixture was added to MeOH (200 mL), cooled in a ice-salt bath, over 30 min at such a rate that the internal temp. was kept below 0 °C. The reaction mixture was concentrated *in vacuo*. Et₂O (1 L) was added, and the mixture was washed with 1M H₃PO₄ (3×), satd NaHCO₃, and

brine (ca. 400 mL each wash). The organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was dissolved in Et_2O again (500 mL), and the mixture was washed with 1M H_3PO_4 (3×200 mL), satd NaHCO_3 , and brine. After drying the organic layer over MgSO_4 , the mixture was filtered and concentrated *in vacuo*, which gave the title compound as a white-yellow solid. MS (+ ion ESI) $m/z = 207$ (MH^+), 189 ($\text{MH}^+ - \text{H}_2\text{O}$).

Step B: Synthesis of 5(*R*)-azido-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid methyl ester

To a 500 mL three-neck round-bottomed flask equipped with argon inlet/outlet, thermometer, and magnetic stirring was added 5(*S*)-hydroxy-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid methyl ester (29 g, 140 mmol) in toluene (280 mL). The reaction mixture was cooled in a ice-salt bath, and DPPA (36 mL, 170 mmol, Aldrich) was added (internal temp. = -4°C). DBU (25 mL, 170 mmol, Aldrich) was added over 10 min at such a rate that the internal temp. of the reaction was kept below 1°C . The ice in the bath was allowed to melt, and the reaction continued for 12 h during which time the reaction mixture stopped stirring because a precipitate had formed. Stirring was resumed, and the reaction mixture was stirred at RT for another 11 h. The reaction contents were poured into a 2 L sep funnel, and the lower dark-brown layer was removed. Water (250 mL) was added to the remaining top layer, and the reaction mixture was extracted with Et_2O (3×250 mL). The combined organic layers were washed with 1M H_3PO_4 , water, satd NaHCO_3 , and brine. The organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification by silica gel chromatography (330 g Isco Redise[®] column, 1:1 hexane- CH_2Cl_2) of the crude material provided the title compound. MS (+ ion ESI) $m/z = 232$ (MH^+).

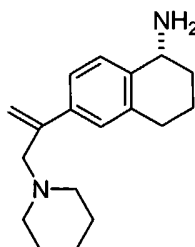
Step C: Synthesis (5(*R*)-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol

To an oven-dried, 3-neck, 2 L round-bottomed flask equipped with argon inlet/outlet, addition funnel, thermometer, and overhead stirring was added THF (700 mL) and LAH (470 mL of a 1M soln in THF, 470 mmol, Aldrich). The reaction mixture was cooled in a ice-salt bath, and 5-azido-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid methyl ester (27 g, 120 mmol) in THF (100 mL) was added over ca. 30 min. The reaction mixture was warmed to RT overnight, then cooled in an ice-salt bath the next morning. Water (18 mL) in THF (20 mL) was added to the reaction mixture over 4 h. Vigorous gas evolution occurred. 5N NaOH (18 mL) was added over 30 min followed by water (54 mL). After stirring for an additional 1 h, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was reconstituted in MeOH and CH_3CN , and concentrated *in vacuo* again to provide the title compound as light-brown solid. MS (+ ion ESI) $m/z = 161$ ($\text{M} - \text{NH}_3$).

Similarly (4-(*R*)-aminochroman-7-yl)-methanol and (1-(*R*)-aminoindan-5-yl)methanol were prepared.

Reference 2

- 5 Synthesis of (*R*)-6-(1-piperidin-1-ylmethylvinyl)-1,2,3,4-tetrahydronaphthalen-1-ylamine



Step A: Synthesis of 2-trifluoromethanesulfonic acid 5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl ester

- 10 To a 1-L round-bottomed flask charged with 6-hydroxy-1-tetralone (Aldrich, 21.97 g, 0.136 mol) at 0 °C was added CH₂Cl₂ (500 mL) and pyridine (Aldrich, 11 mL, 0.136 mol). Triflic anhydride (Aldrich, 23 mL, 0.136 mol) was added through an additional funnel over a period of 12 min. The reaction mixture was gradually warmed to room temperature and stirred at room temperature overnight. The residue was diluted with water and the two phases were
- 15 separated. The organic phase was washed with 1N HCl (100 mL x 2), saturated NaHCO₃, and brine, dried over Na₂SO₄. After filtration and concentration *in vacuo*, the crude was purified by flash chromatography (5-11% EtOAc-hexane) to provide the title product as yellow oil. MS (ESI): 295 (M+H)⁺.

- Step B: Synthesis of 2-trifluoromethanesulfonic acid 5(*S*)-hydroxy-5,6,7,8-tetrahydro-
- 20 naphthalen-2-yl ester

- To a dry three-necked flask containing (*R*)-2-methyl-CBS-oxazaborolidine (Aldrich, 1.94 mL, 1.0M in toluene, 1.93 mmol, 0.05 eq) under N₂ was added a solution of borane-methylsulfide (BMS) (Aldrich, 3.30 mL, 34.80 mmol, 0.9 eq) in toluene (200 mL) through an additional funnel. After the addition was complete, the reaction mixture was allowed to cool to
- 25 0 °C. A solution of 2-trifluoromethanesulfonic acid 5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl ester (11.37 g, 38.67 mmol, 1.0 eq) in THF (180 mL) was added dropwise through an additional funnel. Following the addition, the reaction mixture was stirred at RT for additional 40 min, quenched with MeOH. The solvent was removed *in vacuo* and the crude was diluted with H₂O (50 mL). The aqueous phase was extracted with ether (3 x 150 mL). The combined
- 30 organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The title

compound was obtained as an off-white solid by flash chromatography (16-22% EtOAc-hexane).

Step C: Synthesis of 2-trifluoromethanesulfonic acid 5(R)-azido-5,6,7,8-tetrahydro-naphthalen-2-yl ester

- 5 To a solution of 2-trifluoromethanesulfonic acid 5(S)-hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl ester (11.2 g, 37.9 mmol, 1.0 eq) in THF (150 mL) at RT was added DPPA (Aldrich, 11.1 mL, 51.6 mmol, 1.36 eq). The resulting mixture was allowed to cool to 0 °C and DBU (Aldrich, 7.7 mL, 51.6 mmol, 1.36 eq) was added slowly through a syringe. The reaction mixture was allowed to warm to RT and stirred over the weekend. The reaction
- 10 mixture was concentrated *in vacuo*. The crude product was dissolved in EtOAc (400 mL). The organic layer was washed with NH₄Cl (twice), H₂O, and brine, dried over Na₂SO₄. After filtration and concentration *in vacuo*, the crude was purified by flash chromatography (5% EtOAc-hexane) to provide the title compound.

- Step D: Synthesis of 2-trifluoromethanesulfonic acid 5(R)-amino-5,6,7,8-tetrahydro-naphthalen-2-yl ester
- 15

- A solution of 2-trifluoromethanesulfonic acid 5(R)-azido-5,6,7,8-tetrahydronaphthalen-2-yl ester (10.3 g, 32.1 mmol, 1.0 eq) in THF (70 mL) was added PPh₃ (Aldrich, 8.4 g, 32.1 mmol, 1.0 eq), and H₂O (30 mL) at 0 °C. The reaction mixture was allowed to warmed to RT and stirred overnight. 2N HCl was added until the mixture was
- 20 acidic (PH = 1-2). The mixture was extracted with toluene (3 x 100 mL). The aqueous phase was neutralized with 5N NaOH until the pH is 12-13, and the product was extracted with ether (3 x 150 mL). The ether solution was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (6% MeOH-CH₂Cl₂) to provide the title compound.

- 25 Step E: Synthesis of 2-trifluoromethanesulfonic acid 5(R)-tert-butoxycarbonyl-amino-5,6,7,8-tetrahydro-naphthalen-2-yl ester

- A solution of 2-trifluoromethanesulfonic acid 5(R)-amino-5,6,7,8-tetrahydro-naphthalen-2-yl ester (2.0 g, 6.8 mmol, 1.0 eq) in CH₂Cl₂ (20 mL) was added Et₃N (1.9 mL, 13.6 mmol, 2.0 eq) and di-tert-butyl carbonate (Aldrich, 1.8 g, 8.1 mmol, 1.2 eq). The reaction
- 30 mixture was stirred at RT overnight, washed with saturated NaHCO₃ (2 x 20 mL), brine, dried over Na₂SO₄. After filtration and concentration *in vacuo*, the crude was purified by flash chromatography (4-10% EtOAc-hexane) to provide the title compound as a white solid.

Step F: Synthesis of [6-(1-piperidin-1-ylmethylvinyl)-1(*R*)-1,2,3,4-tetrahydro-naphthalen-1-yl]-carbamic acid tert-butyl ester

A solution of 2-trifluoromethanesulfonic acid 5(*R*)-tert-butoxycarbonylamino-5,6,7,8-tetrahydronaphthalen-2-yl ester (1.89 g, 4.79 mmol, 1.0 eq) in CH₃CN (25 mL) purged with N₂ was added palladium (II) acetate (Strem Chemicals, 65 mg, 0.29 mmol, 0.06 eq), 1,1'-bis(diphenylphosphino)ferrocene (Aldrich, 0.70 g, 1.26 mmol, 0.26 eq), K₂CO₃ (0.99 g, 7.18 mmol, 1.5 eq) and *N*-allylpiperidine (Lancaster, 3.00 g, 23.96 mmol, 5.0 eq). The reaction mixture sealed with a septum was heated to 80 °C overnight, cooled to RT, diluted with H₂O, and extracted with ether. The ether solution was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (14-21% EtOAc-Hexane) to provide the title compound. MS (ESI): 371(M+H)⁺.

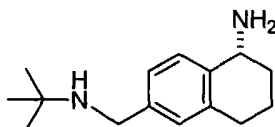
Step G: Synthesis of 6-(1-piperidin-1-ylmethylvinyl)-1,2,3,4-tetrahydronaphthalen-1-ylamine

To a solution of [6-(1-piperidin-1-ylmethylvinyl)-1(*R*)-1,2,3,4-tetrahydro-naphthalen-1-yl]-carbamic acid tert-butyl ester in CH₂Cl₂ (3 mL) was added TFA (3 mL). The reaction mixture was stirred at RT for 4 h and then concentrated in *vacuo*. The crude was neutralized with 10% Na₂CO₃ until the aqueous phase is basic, extracted with CH₂Cl₂. The organic solution was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide the title compound. MS (ESI): 271 (M+H)⁺.

20

Reference 3

Synthesis of (*R*)-6-((tert-butylamino)methyl)-1,2,3,4-tetrahydronaphthalen-1-ylamine



25

Step A: Synthesis of (*R*)-tert-butyl 6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl-carbamate

Triethylamine (27.7 mL, 199 mmol) and di-*tert*-butyl-dicarbonate (17.4 g, 79.6 mmol) were added consecutively to a solution of (5(*R*)-amino-5,6,7,8-tetrahydronaphthalen-2-yl)-methanol (7.05 g, 39.8 mmol) in a mixed solvent of ethyl acetate (100 mL), methanol (100 mL), and dichloromethane (100 mL) and the reaction mixture was stirred at RT for 2 h. The solvents were removed in *vacuo*, the residue was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic portion was separated, washed with brine, the solvents were removed to afford a white solid, used in the following reaction without purification.

Step B: Synthesis of *(R)*-tert-butyl 6-formyl-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate

A mixture of *(R)*-tert-butyl 6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate (11.0 g, 39.8 mmol) and MnO₂ (Aldrich, <5 micron, 85%, 20.3 g, 198 mmol) in dichloromethane (500 mL) was stirred at r.t. overnight, filtered through a pad of Celite and the solvents were removed to afford a light yellowish viscous oil which was used in the following reaction without purification.

Step C: Synthesis of *(R)*-tert-butyl 6-((tert-butylamino)methyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate

A mixture of *(R)*-tert-butyl 6-formyl-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate (39.8 mmol), *tert*-butylamine (21.0 mL, 199 mmol), and acetic acid (2.4 mL, 36.0 mmol) in DMF (50 mL) in a sealed vessel was stirred at 60 °C for 1 h, cooled to r.t. and diluted with MeOH. NaBH₄ (3.0 g, 80 mmol) was added portion wise and the reaction mixture was stirred at RT for 10 min. MeOH was removed under reduced pressure and the DMF solution was partitioned between ethyl acetate and water. The organic portion was separated and the solvents were removed to afford a viscous oil which was used in the following reaction without purification.

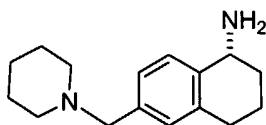
Step D: Synthesis of *(R)*-6-((tert-butylamino)methyl)-1,2,3,4-tetrahydronaphthalen-1-ylamine

A solution of *(R)*-tert-butyl 6-((tert-butylamino)methyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate (13.3 g, 39.8 mmol) in 300 mL of a saturated hydrogen chloride solution in ethyl acetate was stirred at RT overnight in a sealed flask and the solids were collected by filtration.

Similarly, *(R)*-7-((tert-butylamino)methyl)chroman-4-amine and *(R)*-5-((tert-butylamino)methyl)-2,3-dihydro-1H-inden-1-amine were prepared.

Reference 4

Synthesis of *(R)*-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamine



Step A: Synthesis of *(R)*-tert-butyl 6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate.

(R)-tert-Butyl 6-formyl-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate (12.2 g, 44.33 mmol) and piperidine (22 mL, 221.6 mmol, 5.0 equiv) were dissolved in 1,2-dichloroethane (400 mL). Acetic acid (10 drops) and sodium triacetoxyborohydride (23.4 g, 110.82 mmol, 2.5 equiv) were added and the reaction mixture was heated at 50 °C for 15 h. The reaction mixture

was cooled to room temperature, diluted with EtOAc (600 mL), washed with saturated sodium bicarbonate solution (2×250 mL), saturated ammonium chloride solution (200 mL), brine (200 mL), dried (MgSO₄) and purified on silica gel using 5% methanol in dichloromethane as eluant, affording (*R*)-*tert*-butyl-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate. MS: 345.2 (M+H).

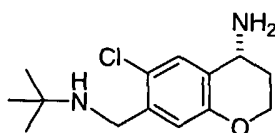
Step B: Synthesis of (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine

A solution of (*R*)-*tert*-butyl 6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate (15.0 g, 43.57 mmol) in methanol (325 mL) was treated with a 1.0M solution of HCl in diethyl ether (300 mL, 300 mmol, 6.8 equiv), capped and stirred at room temperature for 14 h. The reaction mixture was concentrated *in vacuo* and partitioned in dichloromethane (300 mL) and 1.0N NaOH (300 mL). The aqueous layer was separated and extracted with dichloromethane (2×250 mL). The combined organic layers were washed with brine (200 mL), dried (MgSO₄) and concentrated, affording (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine as a dark yellow oil. MS: 245.2 (M+H).

Similarly, (*R*)-7-(piperidin-1-ylmethyl)chroman-4-amine, (*R*)-5-(piperidin-1-ylmethyl)-2,3-dihydro-1H-inden-1-amine and (*R*)-6-((4-methylpiperidin-1-yl)methyl)-1,2,3,4-tetrahydronaphthalen-1-amine were prepared.

Reference 5

Synthesis of 7-(*tert*-butylaminomethyl)-6-chloro-chroman-(4*R*)-ylamine



Step A: Synthesis of 7-bromomethyl-6-chlorochroman-4-one

A mixture of 6-chloro-7-methylchroman-4-one (20 g, 102 mmol), NBS (19.9 g, 112 mmol), and AIBN (4.17 g, 25.4 mmol) in anhydrous CCl₄ (300 mL) was heated at reflux for 24 h. The reaction mixture was cooled and the solid was filtered off. The filtrate was concentrated and used in the next step without purification.

Step B: Synthesis of 7-(*tert*-butylamino-methyl)-6-chloro-chroman-4-one

To a stirred mixture of *tert*-butylamine (7.3 g, 100. Mmol) and Et₃N (10.1 g, 99.8 mmol) in anhydrous CH₂Cl₂ (50 ml) was added a solution of 7-bromomethyl-6-chloro-chroman-4-one (25 g, 91 mmol) in CH₂Cl₂ (150 ml) dropwise. Stirring was continued for 16 h after which the mixture was concentrated, taken up in H₂O, acidified with 10% HCl until pH 1, and extracted with Et₂O (discarded). The acidic aqueous layer was neutralized with 5N NaOH,

and extracted with CH₂Cl₂ (3x). The combined extracts were dried over MgSO₄, concentrated to give a yellow solid.

Step C: Synthesis of 7-(tert-butylamino-methyl)-6-chloro-chroman-(4S)-ol

To a stirred solution of (1S,2S)-(+)-*N*-(4-toluene-sulfonyl)-1,2-diphenylethylene-diamine (0.29 g, 8.1 mmol) in *i*-PrOH (15 ml) was added [RuCl₂(N6-*p*-cymene)]₂, and Et₃N under argon. The reaction mixture was heated at 80 °C for 1 h, cooled, and concentrated to dryness. To this mixture was added a solution of 7-(tert-butylamino-methyl)-6-chloro-chroman-4-one (12 g, 45 mol) in anhydrous CH₃CN (150 ml), followed by 5:2 formic acid/TEA (6 ml). The reaction was stirred at rt for 24 h and then concentrated, taken up in H₂O, neutralized with 10% Na₂CO₃, extracted with CH₂Cl₂ (3x), dried over MgSO₄, concentrated to give a brown foam which was stirred in hexane/ether (1:1), and filtered. The filtrate was concentrated to give a light brown foam.

Step D: Synthesis of 4(*R*)-azido-6-chloro-chroman-7-ylmethyl)-tert-butylamine

To a stirred, cooled (0 °C) solution of 7-(tert-butylaminomethyl)-6-chlorochroman-(4S)-ol (11.55 g, 42.91 mmol) in anhydrous toluene (150 mL) was added DPPA (23.6 g, 85.8 mmol) dropwise in 0.5 h and DBU (13.1 g, 85.9 mmol). The reaction mixture was stirred at rt for 24 h. The reaction mixture was concentrated, taken up in H₂O, extracted with CH₂Cl₂ (3x), dried over MgSO₄, concentrated and purified by ISCO (3% MeOH/CH₂Cl₂) to give a brown oil. MS (APCI) *m/z* 296 (M+2).

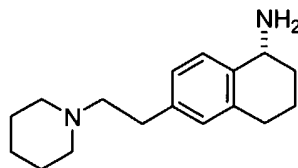
Step E: Synthesis of 7-(tert-butylaminomethyl)-6-chlorochroman-(4*R*)-ylamine

A mixture of (4*R*)-azido-6-chlorochroman-7-ylmethyl)-tert-butylamine (12 g, 41 mmol) and Ph₃P (16 g, 61 mmol) in anhydrous THF (100 mL) was stirred at RT in 3 h. H₂O (100 mL) was added and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled, concentrated, taken up in toluene, extracted with 5N HCl. The aqueous layer was neutralized with 10N NaOH, extracted with CHCl₃ (3x), dried over MgSO₄, concentrated to give a brown oil. MS (APCI) *m/z* 270 (M+2).

Similarly, (*R*)-6-chloro-7-(piperidin-1-ylmethyl)chroman-4-amine was prepared.

Reference 6

Synthesis of (*R*)-6-(2-(piperidin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-amine



Step A: Synthesis of (R)-tert-butyl 6-(iodomethyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate

To a solution of (R)-tert-butyl 6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate (415.5 mg, 1.5 mmol) in dichloromethane/ether (1:1, 30 mL) at room temperature were added triphenylphosphine (590 mg, 2.25 mmol) and imidazole (153 mg, 2.25 mmol). To this stirred solution was then added iodine (571 mg, 2.25 mmol). After stirring for 20 min, the reaction was quenched with 10% Na₂S₂O₃ (15 mL) until it became a clear two-phase solution. The aqueous phase was extracted with ether. The combined organic phase was dried over Na₂SO₄, filtered, and evaporated to dryness. Flash chromatography (SiO₂, hexane/CH₂Cl₂ = 3:1 to pure CH₂Cl₂) afforded the desired product as a white solid.

10 Step B: Synthesis of (R)-tert-butyl 6-((1,3-dithian-2-yl)methyl)-1,2,3,4-tetrahydronaphthyl-1-ylcarbamate

To a solution of 1,3-dithiane (1.01 g, 8.4 mmol) in 10 mL of dry THF at -30 °C was added dropwise 2.5M n-butyllithium in hexane (3.36 mL, 8.4 mmol). After stirring at -20 °C for 1.5 h, a solution of the iodide obtained in Step A (542 mg, 1.4 mmole, azeotroped with benzene) in dry THF (10 mL) was added dropwise at -20 °C. The reaction mixture was stirred at -5 °C to 0 °C for 1 h. The reaction mixture was quenched with sat. NH₄Cl solution, extracted with EtOAc, dried over Na₂SO₄, filtered, and evaporated to dryness. Flash chromatography (SiO₂, CH₂Cl₂/hexane = 1:1 to 2:1 to CH₂Cl₂/EtOAc = 100:3) afforded the title compound as a white solid.

20 Step C: Synthesis of (R)-tert-butyl 6-(2-oxoethyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate
(R)-tert-Butyl 6-((1,3-dithian-2-yl)methyl)-1,2,3,4-tetrahydronaphthyl-1-ylcarbamate (6.1 g, 16.1 mmol) and CaCO₃ (3.23 g, 32.3 mmol) were suspended in THF/water (120 mL, 5:1 ratio) and Hg(ClO₄)₂ (9.65 g, 24.15 mmol) was added portion wise. After stirring at room temperature for 2 h, the reaction mixture was filtered through a celite pad with the help of EtOAc. The filtrate was evaporated to dryness and the residue was purified by flash chromatography (SiO₂, DCM to DCM/EtOAc = 3:1 to 2:1) gave the title compound as a colorless sticky oil.

25 Step D: Synthesis of (R)-tert-butyl 6-(2-(piperidin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate

30 To a solution of (R)-tert-butyl 6-(2-oxoethyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate (2.02 g, 7 mmol) and piperidine (1.79 g, 21 mmol) in dichloroethane (10 mL) was added sodium triacetoxyborohydride (2.97 g, 14 mmol). After stirring overnight at room temperature, the reaction solution was diluted with EtOAc and washed with sat. NaHCO₃ and brine. The organic phase was dried over Na₂SO₄ and evaporated to dryness in vacuo. The crude

was purified by flash chromatography (SiO₂, DCM to EtOAc to EtOAc/MeOH = 100:20) to give the title compound as a sticky oil.

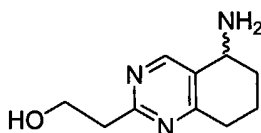
Step E: Synthesis of (*R*)-6-(2-(piperidin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-amine

To a solution of (*R*)-tert-butyl-6-(2-(piperidin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate (2.0 g, 5.35 mmol) in DCM (25 mL) at room temperature was added TFA (3.66 g, 32 mmol). After stirring at room temperature overnight, the reaction mixture was evaporated to dryness. The residue was treated with 2.5 mL of triethylamine and it was evaporated again in vacuo. The crude product was azeotroped with benzene and was directly used in the next step.

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Reference 7

Synthesis of 2-(5(*R/S*)-amino-5,6,7,8-tetrahydroquinazolin-2-yl)ethanol



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Step A: Synthesis of 3-(tert-butyldiphenylsilyloxy)-propanenitrile

To a solution of 3-hydroxypropanenitrile (7.1 g, 0.1 mol) and DMAP (1.22 g, 0.01 mmol) in dry DCM (30 mL) at room temperature was added Et₃N (30.3 g, 0.3 mol), followed by TBDPSCI (27.5 g, 0.1 mol). A lot of white solid were formed. After stirring at room temperature overnight, the reaction mixture was quenched with sat. NH₄Cl solution, extracted with DCM, dried over Na₂SO₄, and evaporated in vacuo. Flash chromatography (SiO₂, hexane/EtOAc = 100:2 to 100:5 to 100:10) of the crude gave of 3-(tert-butyldiphenylsilyloxy)propanenitrile as a white solid.

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Step B: Synthesis of 3-(tert-butyldiphenylsilyloxy)-propanamidine

To a suspension of NH₄Cl (5.35 g, 0.1 mol) in dry benzene (60 mL) at 0 °C was slowly added a solution of trimethylaluminum in toluene (50 mL, 2M). After the addition was complete, the reaction mixture was allowed to warm up to room temperature and was stirred for 2 h until gas evolution had ceased. A solution of 3-(tert-butyldiphenylsilyloxy)propanenitrile (9.27 g, 0.03 mol) in dry benzene (20 mL) was added to the aluminum amide reagent and the resulting mixture was heated up to 80 °C for 20 h. The reaction mixture was slowly cooled to room temperature and then carefully poured into a slurry of 300 mL of DCM and 200 g of silica gel. It was then filtered and washed thoroughly with MeOH/DCM (1:2). After concentration,

25

30

flash chromatography (SiO₂, EtOAc to EtOAc/MeOH = 100:20 to 100:30 to EtOAc/2M NH₃ in MeOH = 100:30) gave the title compound as a white solid.

Step C: Synthesis of 2-(2-(tert-butyldiphenylsilyloxy)ethyl)-7,8-dihydroquinazolin-5(6H)-one

A solution of 3-(tert-butyldiphenylsilyloxy)-propanamidine (25 g, 77 mmol) and 2-
5 ((dimethylamino)methylene)cyclohexane-1,3-dione (12.8 g, 77 mmol) in dry EtOH (400 mL) was heated at 80 °C for 3 h. After cooling to room temperature, the solvent was evaporated. Flash chromatography (SiO₂, EtOAc/hexane = 1:1) gave the title compound as a white solid.

Step D: Synthesis of 2-(2-(tert-butyldiphenylsilyloxy)ethyl)-5,6,7,8-tetrahydroquinazolin-5-ol

A solution of 2-(2-(tert-butyldiphenylsilyloxy)ethyl)-7,8-dihydroquinazolin-5(6H)-one
10 (2.16 g, 5 mmol) in dry MeOH (30 mL) was treated with NaBH₄ (189 mg, 5 mmol). After 5 min, the reaction was quenched with 5 mL of sat. NH₄Cl solution. The MeOH was evaporated and the residue was extracted with DCM, dried over Na₂SO₄ and evaporated. Flash chromatography (SiO₂, DCM to EtOAc) gave the title compound as a white solid.

Step E: Synthesis of 5-azido-2-(2-(tert-butyldiphenylsilyloxy)ethyl)-5,6,7,8-tetrahydro-
15 quinazoline

To a solution of 2-(2-(tert-butyldiphenylsilyloxy)ethyl)-5,6,7,8-tetrahydroquinazolin-5-ol
(2.0 g, 4.63 mmol) in toluene (25 mL) at -10 °C was added DPPA (1.2 mL, 5.56 mmol). To this stirred solution was then added DBU (0.83 mL, 5.56 mmol) dropwise while keeping the temperature below 0 °C. After stirring at room temperature for 16 h, the reaction was evaporated
20 to dryness and directly submitted to flash chromatography (SiO₂, hexane/DCM = 1:2) to afford the title compound as a white solid.

Step F: Synthesis of 2-(2-(tert-butyldiphenylsilyloxy)ethyl)-5,6,7,8-tetrahydroquinazolin-5-amine

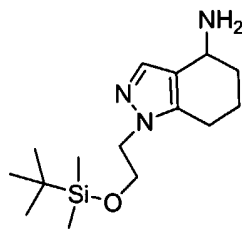
A suspension of Pd/C (80 mg, 10% w/w) in a solution of 5-azido-2-(2-(tert-
25 butyldiphenylsilyloxy)ethyl)-5,6,7,8-tetrahydroquinazoline (800 mg, 1.75 mmol) in EtOAc (30 mL) was stirred under H₂ atmosphere overnight. The reaction mixture was then directly submitted to flash chromatograph (SiO₂, EtOAc to EtOAc/MeOH = 100:15 to EtOAc/2M NH₃ in MeOH = 2:1) to give the title compound as a white solid.

Step G: Synthesis of 2-(5-amino-5,6,7,8-tetrahydroquinazolin-2-yl)ethanol

A solution of 2-(2-(tert-butyldiphenylsilyloxy)ethyl)-5,6,7,8-tetrahydroquinazolin-5-
30 amine (570 mg, 1.32 mmol) in THF (10 mL) at 0 °C was treated with a 1M TBAF solution in THF (1.56 mL, 1.56 mmol). After stirring at room temperature overnight, the reaction mixture was directly submitted to flash chromatograph (SiO₂, EtOAc to EtOAc/MeOH = 100:15 to EtOAc/2M NH₃ in MeOH = 1:1) to give crude product as a white solid.

Reference 8

Synthesis of 1-(2-(tert-butyldimethylsilyloxy)ethyl)-4,5,6,7-tetrahydro-1H-indazol-4-ylamine



5

Step A: Synthesis of 1-(2-hydroxyethyl)-6,7-dihydro-1H-indazol-4(5H)-one

2-Hydroxyethyl hydrazine (1.36 mL, 20 mmol) was slowly added to an ice-cooled solution of 2-((dimethylamino)methylene)cyclohexane-1,3-dione (3.34 g) in methanol (50 mL). After stirring the reaction mixture at room temperature for 20 min, the solvent was
10 evaporated. Flash chromatography (SiO₂, EtOAc/MeOH = 100:5 to 100:7 to 100:10) on the crude product gave the title compound as a white solid.

Step B: Synthesis of 1-(2-(tert-butyldimethylsilyloxy)ethyl)-6,7-dihydro-1H-indazol-4(5H)-one

To a solution of 1-(2-hydroxyethyl)-6,7-dihydro-1H-indazol-4(5H)-one (14 g, 77.8
15 mmol) in dry DCM (100 mL) was added Et₃N (22 mL, 155.6 mmol), followed by TBSCl (14 g, 93.3 mmol) and DMAP (95 mg, 0.78 mmol). After stirring at room temperature overnight, the reaction mixture was quenched with brine and extracted with EtOAc. Flash
chromatography (SiO₂, EtOAc/hexane = 1:1) of the crude product gave the title compound as a white solid.

20 Step C: Synthesis of 1-(2-(tert-butyldimethylsilyloxy)ethyl)-4,5,6,7-tetrahydro-1H-indazol-4-ol

A solution of 1-(2-(tert-butyldimethylsilyloxy)ethyl)-6,7-dihydro-1H-indazol-4(5H)-one (21 g, 71.4 mmol) in dry MeOH (200 mL) was treated with NaBH₄ (2.7 g, 71.4 mmol). After 30 min, the reaction mixture was quenched with 15 mL of Sat. NH₄Cl solution. The MeOH was evaporated and the residue was extracted with EtOAc, dried over Na₂SO₄ and
25 evaporated. Flash chromatography (SiO₂, EtOAc/hexane = 1:1 to EtOAc) of the crude product gave the title compound as a white solid.

Step D: Synthesis of 4-azido-1-(2-(tert-butyldimethyl silyloxy)ethyl)-4,5,6,7-tetrahydro-1H-indazole

To a solution of 1-(2-(tert-butyldimethylsilyloxy)ethyl)-4,5,6,7-tetrahydro-1H-indazol-
30 4-ol (23 g, 77.7 mmol) in 200 mL of toluene at -10 °C was added DPPA (20 mL, 93.2 mmol). DBU (13.9 mL, 93.2 mmol) was added dropwise while keeping the temperature below 0 °C.

After stirring at room temperature for 18 h, the reaction mixture was evaporated to dryness and directly submitted to flash chromatography (SiO₂, hexane/EtOAc = 2:1 to EtOAc) to afford the title compound as a colorless liquid, together with 12 g of recovered starting alcohol.

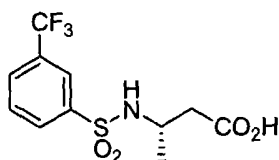
Step E: Synthesis of 1-(2-(tert-butyldimethylsilyloxy)ethyl)-4,5,6,7-tetrahydro-1H-indazol-4-

5 amine

A suspension of 150 mg of Pd/C (10% w/w) in a solution of 4-azido-1-(2-(tert-butyl-dimethylsilyloxy)ethyl)-4,5,6,7-tetrahydro-1H-indazole (2.0 g, 6.23 mmol) in EtOAc (100 mL) was stirred under H₂ atmosphere overnight. The reaction mixture was then directly submitted to flash chromatograph (SiO₂, EtOAc to EtOAc/MeOH = 100:20 to EtOAc/2M NH₃ in MeOH =
10 100:20 to 100:30 to 100:40) to give the title compound as a white solid.

Reference 9

Synthesis of (*S*)-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid



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A mixture of L-homoalanine hydrogen chloride (1.0 g, 7.16 mmol) and sodium hydroxide (0.63 g, 15.8 mmol) in water (15 mL) was stirred at r.t. for 5 min. The reaction mixture was cooled to 0 °C, diluted with 1,4-dioxane (15 mL), and triethyl amine (1.2 mL, 8.60 mmol) and 3-trifluoromethylbenzenesulphonyl chloride (95%, 1.2 mL, 7.16 mmol) were
20 added sequentially. The reaction mixture was gradually warmed to r.t., 1,4-dioxane was removed in vacuo and the aqueous portion was acidified to pH 4 with 1.0N HCl. The product was extracted with EtOAc. Removal of the solvents afforded the titled compound as a colorless oil, which was used in the following reaction without purification.

Similarly, the following acids were made:

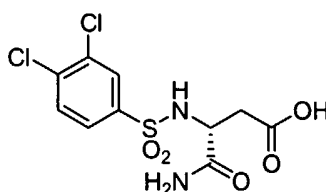
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- (*S*)-3-(naphthalene-3-sulfonamido)butanoic acid;
- (*S*)-3-(4-chloro-2,5-dimethylphenyl-sulfonamido)butanoic acid;
- (*S*)-3-(2-chloro-5-(trifluoromethyl)phenylsulfonamido)butanoic acid;
- (*S*)-3-(2-fluoro-5-(trifluoromethyl)phenylsulfonamido)butanoic acid;
- (*S*)-3-(2,5-dichlorophenylsulfonamido)butanoic acid;
- 30 (*S*)-3-(2,3-dichlorophenyl-sulfonamido)butanoic acid;
- (*S*)-3-(3,4-dichlorophenylsulfonamido)butanoic acid;
- (*S*)-3-(3,5-dichlorophenyl-sulfonamido)butanoic acid;
- (*S*)-3-(2,6-dichlorophenylsulfonamido)butanoic acid;

(*S*)-3-(5-chloro-2-fluorophenylsulfonamido)butanoic acid;
 (*S*)-3-(3-chloro-2-fluorophenylsulfonamido)butanoic acid;
 (*S*)-3-(3-methylphenyl-sulfonamido)butanoic acid;
 (*S*)-3-(4-tert-butylphenylsulfonamido)butanoic acid;
 5 (*S*)-3-(3-(trifluoromethyl)phenyl-sulfonamido)hex-5-ynoic acid; and
 (*R*)-4-methyl-3-(3-(trifluoromethyl)phenylsulfonamido)pentanoic acid.

Reference 10

Synthesis of (*R*)-4-amino-4-oxo-3-(3,4-dichlorophenylsulfonamido)butanoic acid



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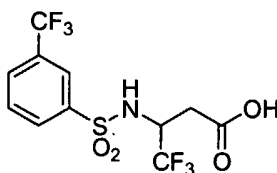
To (*R*)-3,4-diamino-4-oxobutanoic acid (Chem-impex, 5g) in dioxane (36 mL) and water (36 mL) was added sodium carbonate (9.2 g) at RT. 3,4-Dichlorobenzenesulfonyl chloride (Aldrich; 7.1 mL) was added and the reaction mixture was stirred overnight. EtOAc (500 mL)
 15 was added and the reaction mixture was acidified with 10% HCl and brine. The organic layer was separated and washed with brine three times, dried and evaporated to give the crude product which was used directly in the next step.

Similarly the following acids were prepared:

(*R*)-4-amino-4-oxo-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid; (*R*)-4-amino-
 20 4-oxo-3-(4-methylphenylsulfonamido)butanoic acid;
 (*R*)-3-(4-chloro-2,5-dimethylphenylsulfonamido)butanoic acid; (*R*)-4-(benzyloxy)-3-(3,4-dichlorophenylsulfonamido)-4-oxobutanoic acid;
 (*R*)-4-tert-butoxy-3-(3,4-dichlorophenylsulfonamido)-4-oxobutanoic acid; (*R*)-3-(3,4-dichlorophenylsulfonamido)-4-methoxy-4-oxobutanoic acid;
 25 (*R*)-3-(3,4-dichlorophenylsulfonamido)-4-ethoxy-4-oxobutanoic acid.

Reference 11

Synthesis of 4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid



Step A: Synthesis of ethyl 4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanoate

3-Trifluoromethylbenzenesulphonyl chloride (From Lancaster, 98%, 5.10 mL, 31.3 mmol) was added to a solution of ethyl 3-amino-4,4,4-trifluorobutyrate (From Lancaster, 95%,
5 6.10 g, 31.3 mmol) in anhydrous pyridine (10 mL) at r.t. After 1 h, the reaction mixture was partitioned between diethyl ether and 5% of HCl (aq). The organic portion was separated, washed with water, brine, and concentrated to afford the title compound as a yellow oil, used in the following reaction without purification.

Step B: Synthesis of 4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid

10 A mixture of ethyl 4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanoate (13.5 g) and lithium hydroxide monohydrate (4.32 g, 103 mmol) in a methanol:THF:water solvent mixture (60 mL, 1:1:1) was stirred at r.t. overnight. After removing about two thirds of the solvents in vacuo, the aqueous residue was diluted with water, washed with diethyl
15 ether, then acidified to pH 4 with 5% of HCl, and extracted with EtOAc. The organic portion was washed with brine, removal of the solvents afforded the title compound as a light pinkish solid.

Similarly, (*R*)-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid was prepared from (*R*)-ethyl 3-amino-4,4,4-trifluorobutanoate (prepared according to literature procedure: Soloshonok, V.A.; Ono, T.; Soloshonok, I.V. *J. Org. Chem.* 1997, 62, 7538-39).

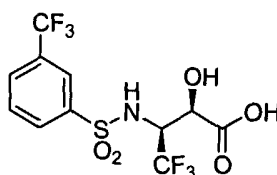
20 The following sulfonylated acids were prepared similarly:

- (*R*)-4,4,4-trifluoro-3-(3-methylphenylsulfonamido)butanoic acid;
- (*R*)-4,4,4-trifluoro-3-(naphthalene-3-sulfonamido)butanoic acid;
- (*R*)-3-(4-chloro-2,5-dimethylphenylsulfonamido)-4,4,4-trifluorobutanoic acid;
- (*R*)-3-(2-chloro-5-(trifluoromethyl)phenylsulfonamido)-4,4,4-trifluorobutanoic acid;
- 25 (*R*)-3-(4-chloro-3-(trifluoromethyl)phenylsulfonamido)-4,4,4-trifluorobutanoic acid;
- (*R*)-3-(2,5-dichlorophenylsulfonamido)-4,4,4-trifluorobutanoic acid;
- (*R*)-3-(2,6-dichlorophenylsulfonamido)-4,4,4-trifluorobutanoic acid;
- (*R*)-3-(2,3-dichlorophenylsulfonamido)-4,4,4-trifluorobutanoic acid;
- (*R*)-3-(3,4-dichlorophenylsulfonamido)-4,4,4-trifluorobutanoic acid;
- 30 (*R*)-3-(3,5-dichlorophenylsulfonamido)-4,4,4-trifluorobutanoic acid;
- (*R*)-3-(5-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluorobutanoic acid;
- (*R*)-3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluorobutanoic acid;
- (*R*)-3-(2,3-dihydrobenzo[b][1,4]dioxine-6-sulfonamido)-4,4,4-trifluorobutanoic acid;
- (*R*)-3-(4-chlorobenzo[c][1,2,5]oxadiazole-7-sulfonamido)-4,4,4-trifluorobutanoic acid;
- 35 (*R*)-3-(5-chloro-2-methoxyphenylsulfonamido)-4,4,4-trifluorobutanoic acid;

- (*S*)-4,4,4-trifluoro-3-(quinoline-8-sulfonamido)butanoic acid;
 (*R*)-3-(3,5-dichloro-2-hydroxyphenylsulfonamido)-4,4,4-trifluorobutanoic acid;
 (*R*)-3-(2,3-dihydrobenzofuran-5-sulfonamido)-4,4,4-trifluorobutanoic acid;
 (*R*)-3-(3,4-difluorophenylsulfonamido)-4,4,4-trifluorobutanoic acid;
 5 (*R*)-3-(3,5-difluorophenylsulfonamido)-4,4,4-trifluorobutanoic acid; and
 (*R*)-3-(2,3-difluorophenylsulfonamido)-4,4,4-trifluorobutanoic acid.

Reference 12

10 Synthesis of (2*R*,3*R*)-4,4,4-trifluoro-2-hydroxy-3-(3-(trifluoromethyl)-phenylsulfonamido)butanoic acid

Step A: Synthesis of (*S,E*)-1-phenyl-*N*-(2,2,2-trifluoroethylidene)ethanamine

15 A solution of (*S*)-1-phenylethanamine (26.9 g, 222 mmol), 2,2,2-trifluoro-1-methoxyethanol (40.2 g, 309 mmol) and *p*-toluenesulfonic acid monohydrate (4.23 g, 0.222 mmol) in toluene (300 mL) was refluxed in Dean-Stark apparatus for 3 h. Et₂O (250 mL) was added and washed with sat NaHCO₃ aq. (500 mL x 3) and sat NaCl aq. (500 mL x 2), and then dried over Na₂SO₄. The solvents were removed under reduced pressure (40 °C, 28 mmHg), and the resulting crude product was used without further purification.

20 Step B: Synthesis of (2*R*,3*R*)-2-(benzyloxy)-4-((*R*)-1-phenylethyl)-3-(trifluoromethyl)-cyclobutanone

A solution of (*S,E*)-1-phenyl-*N*-(2,2,2-trifluoroethylidene)ethanamine (9.97 g, 49.6 mmol) and 2-(benzyloxy)acetyl chloride (15.4 mL, 99.2 mmol) in CH₂Cl₂ (64 mL) was stirred at 0 °C under N₂. Triethylamine (20.0 mL, 143 mmol) was added dropwise and the resulting
 25 mixture was then stirred at 40 °C for 18 h. H₂O (150 mL) was added to the reaction mixture and extracted with AcOEt (150 mL x 2). The combined organic phase was washed with sat NaCl aq. (200 mL with 1*N* HCl 10 mL x 3, 200 mL with sat NaHCO₃ aq. 10 mL x 3), and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the crude product was chromatographed on silica (CH₂Cl₂) and recrystallized twice from EtOH and isopropanol,
 30 respectively, to yield the title compound. MS (M+1): 350.1

Step C: Synthesis of (2*R*,3*R*)-methyl 2-(benzyloxy)-4,4,4-trifluoro-3-((*S*)-1-phenylethyl-amino)butanoate

A solution of (2*R*,3*R*)-2-(benzyloxy)-4-((*R*)-1-phenylethyl)-3-(trifluoromethyl)-cyclobutanone (9.53 g, 27.3 mmol) and HCl gas (23.3 g, 638 mmol) in methanol (300 mL) was stirred at 50 °C for 2 days. The solvent was removed under reduced pressure and residue was dissolved in CH₂Cl₂ (400 mL) and washed with sat NaHCO₃ aq. (400 mL x 2) and sat NaCl aq. (400 mL x 2), and then dried over Na₂SO₄. The solvent was removed under reduced pressure, and the crude product was chromatographed on silica (hexane→hexane/CH₂Cl₂ = 1/1) to yield the title compound. MS (M+1): 382.2

10 Step D: Synthesis of (2*R*,3*R*)-methyl 3-amino-4,4,4-trifluoro-2-hydroxybutanoate

The title compound was synthesized by modification of the reported procedure (Abouabdellah, A.; Bégué, J. P.; Bonnet-Delpon, D.; Nga, T. T. T. *J. Org. Chem.* 1997, 62, 8826-8833). A solution of (2*R*,3*R*)-methyl 2-(benzyloxy)-4,4,4-trifluoro-3-((*S*)-1-phenylethylamino)butanoate (9.74 g, 25.5 mmol) and 10% Pd/C (1.93 g) in anhydrous AcOEt (300 mL) was stirred under H₂ atmosphere for 27 h. To the filtrate of the mixture on Celite 1*N* HCl in Et₂O (100 mL) was added and stirred for 2.5 h. The solvent was removed under reduced pressure and dried in vacuo to yield the title compound as hydrochloride salt. MS (M+1): 188.2

20 Step E: Synthesis of (2*R*,3*R*)-methyl 4,4,4-trifluoro-2-hydroxy-3-(3-(trifluoromethyl)-phenylsulfonamido)butanoate

To a solution of (2*R*,3*R*)-methyl 3-amino-4,4,4-trifluoro-2-hydroxybutanoate (0.436 g, 1.95 mmol) in pyridine (4.0 mL) was added 3-(trifluoromethyl)benzene-1-sulfonyl chloride (0.449 g, 1.84 mmol), and stirred at r.t. for 1.5 h. Et₂O (100 mL) was added and washed with 2.5*N* HCl aq. (100 mL x 4) and sat NaHCO₃ aq. (100 mL x 2), and then dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was chromatographed on silica (CH₂Cl₂→CH₂Cl₂/MeOH= 40/1) to yield the title compound. MS (M+1): 396.2

Step F: Synthesis of (2*R*,3*R*)-4,4,4-trifluoro-2-hydroxy-3-(3-(trifluoromethyl)phenyl-sulfonamido)butanoic acid

A solution of (2*R*,3*R*)-methyl 4,4,4-trifluoro-2-hydroxy-3-(3-(trifluoromethyl)-phenylsulfonamido)butanoate (0.414 g, 1.05 mmol) and lithium hydroxide mono hydrate (0.353 g, 8.41 mmol) in H₂O/MeOH/THF (4.0 mL/4.0ml/4.0ml) was stirred at r.t. for 3 h. The solvent was evaporated down to 20 mL under reduced pressure, and the resulting solution was acidified to pH 1 with 5*N* HCl aq. The product was extracted with AcOEt (40 mL x 4) and the combined organic phase was washed with sat NaCl aq. (20 mL x 2) and dried over Na₂SO₄. The solvent

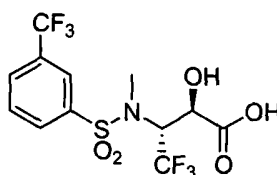
was removed under reduced pressure and dried in vacuo to yield the title compound. MS (M-1): 380.2.

Similarly, the following acids are made:

- (2R,3S)-3-(5-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-2-hydroxybutanoic acid;
 (2R,3S)-3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-2-hydroxybutanoic acid;
 (2R,3S)-3-(2,3-dichlorophenylsulfonamido)-4,4,4-trifluoro-2-hydroxybutanoic acid;
 (2R,3S)-3-(3,4-dichlorophenylsulfonamido)-4,4,4-trifluoro-2-hydroxybutanoic acid;
 (2R,3S)-3-(2,5-dichlorophenylsulfonamido)-4,4,4-trifluoro-2-hydroxybutanoic acid; and
 (2R,3S)-4,4,4-trifluoro-2-hydroxy-3-(naphthalene-2-sulfonamido)butanoic acid.

Reference 13

Synthesis of (2R,3S)-4,4,4-trifluoro-2-hydroxy-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)butanoic acid



- Step A: Synthesis of (2R,3S)-methyl 4,4,4-trifluoro-2-hydroxy-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)butanoate

To (2R,3R)-methyl 4,4,4-trifluoro-2-hydroxy-3-(3-(trifluoromethyl)phenylsulfonamido)butanoate (1.1 g) prepared in Reference 12, Step E in dry DMF (10 mL) was added potassium carbonate (1.14 g) and iodomethane (0.52 mL). The reaction mixture was stirred at RT for 2 h. EtOAc (200 mL) was added and washed with brine (3x100 mL), dried and evaporated to give the title compound.

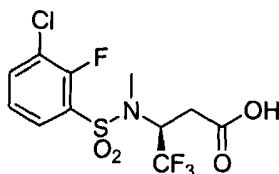
Step B: Synthesis of (2R,3S)-4,4,4-trifluoro-2-hydroxy-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)butanoic acid

(2R,3S)-Methyl 4,4,4-trifluoro-2-hydroxy-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)butanoate was converted to the title compound according to Reference 12, Step F.

Similarly, (2R,3S)-3-(3-chloro-2-fluoro-*N*-methylphenylsulfonamido)-4,4,4-trifluoro-2-hydroxybutanoic acid was prepared.

Reference 14

Synthesis of (*S*)-3-(3-chloro-2-fluoro-*N*-methylphenylsulfonamido)-4,4,4-trifluorobutanoic acid



Step A: Synthesis of (*S*)-ethyl 3-(3-chloro-2-fluoro-*N*-methylphenylsulfonamido)-4,4,4-trifluorobutanoate

(*S*)-Ethyl 3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluorobutanoate, prepared according to Reference 11, Step A, was converted to the title compound according to Reference 13, Step A.

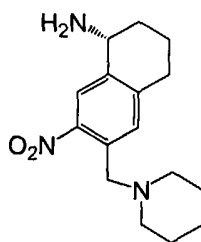
Step B: Synthesis of (*S*)-3-(3-chloro-2-fluoro-*N*-methylphenylsulfonamido)-4,4,4-trifluorobutanoic acid

(*S*)-Ethyl 3-(3-chloro-2-fluoro-*N*-methylphenylsulfonamido)-4,4,4-trifluorobutanoate (1.5 g) was dissolved in 25 mL of dioxane. 25 mL of 10% hydrochloric acid solution was added and the reaction mixture was heated at 90 °C for 9 h. The solvents were concentrated and extracted with EtOAc to give the title compound.

Similarly, (*S*)-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid was prepared.

Reference 15

Synthesis of (*R*)-7-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamine



Step A: Synthesis of (*R*)-2,2,2-trifluoro-*N*-(6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide

To a solution of (*R*)-(5-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (5.32 g, 30 mmol) and trifluoroacetic anhydride (4.66 mL, 33 mL) in 20 mL of dry THF at RT was added

dropwise triethylamine (5.0 mL, 36 mmol). After stirring at RT for 2 h, the reaction was quenched with sat. NaHCO₃, extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and evaporated to dryness. Flash chromatography (SiO₂, DCM/EtOAc = 1:1 to pure EtOAc) afforded the title compound (7.2 g) as a white solid.

- 5 Step B: Synthesis of (*R*)-(5-(2,2,2-trifluoroacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)-methylacetate

To a solution of (*R*)-2,2,2-trifluoro-*N*-(6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (546 mg, 2 mmol) in 10 mL of dry DCM was added acetic anhydride (0.30 mL, 3 mmol) and triethylamine (0.8 mL, 6 mmol), followed by DMAP (10
10 mg). After stirring for 2 h at RT, the solution was evaporated to dryness and directly submitted to flash chromatography (SiO₂, DCM) to give the title compound (610 mg) as a white solid.

Step C: Synthesis of (*R*)-(1-nitro-5-(2,2,2-trifluoroacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)methyl acetate and (*R*)-(3-nitro-5-(2,2,2-trifluoroacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)methyl acetate

- 15 To a solution of (*R*)-(5-(2,2,2-trifluoroacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)-methyl acetate (160 mg, 0.508 mmol) in MeCN (2 mL) was added NO₂⁺BF₄⁻ (66 mg, 0.508 mmol). After stirring at RT for 20 min, the reaction was quenched with 0.5 mL of Sat. NaHCO₃, and the solvent was evaporated to dryness. Flash chromatography (SiO₂, DCM/hexane = 5:1 to pure DCM) gave (*R*)-(1-nitro-5-(2,2,2-trifluoroacetamido)-5,6,7,8-
20 tetrahydronaphthalen-2-yl)methyl acetate (40 mg) as a white solid and (*R*)-(3-nitro-5-(2,2,2-trifluoroacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)methyl acetate (90 mg) as a white solid.

Step D: Synthesis of (*R*)-2,2,2-trifluoro-*N*-(6-(hydroxymethyl)-7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide

- To a solution of (*R*)-(3-nitro-5-(2,2,2-trifluoroacetamido)-5,6,7,8-tetrahydronaphthalen-
25 2-yl)methyl acetate (17 mg) in 10 mL of MeOH was added one drop of 96% H₂SO₄ and the resulting mixture was stirred at 50 °C for 3 h. After cooling to RT, the reaction was quenched with Sat. NaHCO₃ (0.5 mL). The MeOH was evaporated and the residue was directly loaded on column chromatography (SiO₂, DCM to DCM/EtOAc = 2:1 to 1:1) to give the title compound (15 mg) as a white solid.

- 30 Step E: Synthesis of (*R*)-2,2,2-trifluoro-*N*-(6-formyl-7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide

To a solution of (*R*)-2,2,2-trifluoro-*N*-(6-(hydroxymethyl)-7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (350 mg, 1.1 mmol) in DCM (100 mL) was added portionwise MnO₂ (957 mg, 11 mmol). After stirring at RT for 3 h, the reaction mixture was

filtered through silica gel with the help of hexane/EtOAc = 1:1 to give the title compound (350 mg) as a white solid.

Step F: Synthesis of (*R*)-2,2,2-trifluoro-*N*-(7-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide

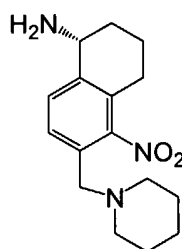
- 5 To a solution of (*R*)-2,2,2-trifluoro-*N*-(6-formyl-7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (350 mg, 1.1 mmol) in 1,2-dichloroethane (6 mL) was added piperidine (187 mg, 2.2 mmol) and NaBH(OAc)₃ (350 mg, 1.65 mmol). After stirring at RT overnight, the reaction was quenched with Sat. NaHCO₃, extracted with EtOAc, dried over Na₂SO₄, filtered, and evaporated to dryness. Flash chromatography (SiO₂, EtOAc/hexane = 1:1) afforded the
- 10 title compound (270 mg) as a white solid.

Step G: Synthesis of (*R*)-7-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine

- A solution of (*R*)-2,2,2-trifluoro-*N*-(7-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (230 mg, 0.6 mmol) and NaOH (108 mg, 2.7 mmol) in a
- 15 mixed solvent (THF/MeOH/H₂O = 5mL/5mL/1mL) was heated at 70 °C for 3 h. After cooling to RT, the solvent was evaporated to dryness and the residue was directly loaded on column chromatography (SiO₂, EtOAc to EtOAc/2M NH₃ in MeOH = 100:15 to 100:20) to give the title (200 mg) as a white solid.

20 Reference 16

Synthesis of (*R*)-5-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamine



- 25 Step A: Synthesis of (*R*)-2,2,2-trifluoro-*N*-(6-(hydroxymethyl)-5-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide

- To a solution of (*R*)-(1-nitro-5-(2,2,2-trifluoroacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)methyl acetate (560 mg) in 10 mL of MeOH was added one drop of 96% H₂SO₄ and the resulting mixture was stirred at 50 °C for 3 h. After cooling to RT, the reaction was quenched
- 30 with Sat. NaHCO₃ (0.5 mL). The MeOH was evaporated and the residue was directly loaded

on column chromatography (SiO₂, hexane/EtOAc = 2:1) to give the title compound (15 mg) as a white solid.

Step B: Synthesis of (*R*)-2,2,2-trifluoro-*N*-(6-formyl-5-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide

5 To a solution of (*R*)-2,2,2-trifluoro-*N*-(6-(hydroxymethyl)-5-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (440 mg, 1.38 mmol) in DCM (50 mL) was added portionwise MnO₂ (1.20 g, 13.8 mmol). After stirring at RT for 1 h, the reaction mixture was filtered through silica gel with the help of hexane/EtOAc = 1:1 to give the title compound (250 mg) as a white solid.

10 Step C: Synthesis of (*R*)-2,2,2-trifluoro-*N*-(5-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide

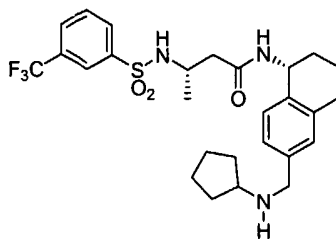
To a solution of (*R*)-2,2,2-trifluoro-*N*-(6-formyl-5-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (250 mg, 0.79 mmol) in 1,2-dichloroethane (2 mL) and 0.5 mL of HOAc was added piperidine (135 mg, 1.58 mmol) and NaBH(OAc)₃ (251 mg, 1.19 mmol). After stirring at RT overnight, the reaction was quenched with sat. NaHCO₃, extracted with EtOAc, dried over Na₂SO₄, filtered, and evaporated to dryness. Flash chromatography (SiO₂, EtOAc/hexane = 1:4 to 1:3 to 1:2) afforded the title compound (240 mg) as a white solid.

Step D: Synthesis of (*R*)-5-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine

20 A solution of (*R*)-2,2,2-trifluoro-*N*-(5-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (230 mg, 0.6 mmol) and NaOH (48 mg, 1.2 mmol) in a mixed solvent (MeOH/H₂O = 10mL/1mL) was heated at 70 °C for 3 h. After cooling to RT, the solvent was evaporated to dryness and the residue was directly loaded on column chromatography (SiO₂, EtOAc to EtOAc/2M NH₃ in MeOH = 100:10 to 100:20 to 100:30) to give the title compound (130 mg) as a white solid.

Example 1

Synthesis of (*S*)-*N*-((*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide



Step A: Synthesis of (*S*)-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide

A mixture of (*S*)-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid (2.05 g, 6.59 mmol described in Reference 9), (*R*)-(5-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol, (1.17 g, 6.59 mmol), TBTU (from Advanced ChemTech, 2.33 g, 7.25 mmol), and Hunig's base (1.73 mL, 9.89 mmol) in DMF (20 mL) was stirred at r.t. for 2 h. The reaction mixture was partitioned between ethyl acetate and aqueous Na₂CO₃. The organic portion was separated, washed with water, brine, and the solvents were removed to afford the title compound as an off-white solid which was used in the following reaction without purification.

Step B: Synthesis of (*S*)-*N*-((*R*)-6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide

A mixture of (*S*)-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide (3.41 g, 7.25 mmol) and MnO₂ (from Aldrich, <5 micron, activated, ~85%, 3.5 g, 34.2 mmol) in 300 mL of methylene chloride was stirred at r.t. overnight. The reaction mixture was filtered through a pad of silica gel, eluted with 0 to 30% of ethyl acetate in methylene chloride, the title compound was obtained as an off-white waxy solid.

Step C: Synthesis of (*S*)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide

A mixture of (*S*)-*N*-((*R*)-6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide (0.28 g, 0.60 mmol), cyclopentylamine (0.59 mL, 6.0 mmol), and acetic acid (0.036 mL, 0.60 mmol) in 2 mL of DMF in a sealed tube was stirred at 60 °C for 16 h. The reaction mixture was cooled to r.t., diluted with MeOH and NaBH₄ (0.068 g, 1.8 mmol) was added. After for 10 min, the volatiles were removed in vacuo and the residue was partitioned between EtOAc and water. The organic portion was separated, washed with brine and the solvents were removed. The crude product was purified by flash column chromatography (0 – 10% of MeOH-NH₄OH (aq, 28 ~ 30 %) (volume ratio 3:1) in methylene chloride in 21 min, 10 – 15% of MeOH-NH₄OH (aq, 28 ~ 30 %) (volume ratio 3:1)

in methylene chloride in 6 min) to give the titled compound was obtained as a white solid. MS m/z : 538.3 (M+H)⁺. Calc'd for C₂₇H₃₄F₃N₃O₃S – 537.64.

Proceeding as described above, the following compounds were prepared:

- (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*S*)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 10 (3*S*)-*N*-((1*R*)-6-(((2-(methyloxy)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((cyclopropylmethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*S*)-*N*-((1*R*)-6-(((2-methylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 20 (3*S*)-*N*-((4*R*)-7-(((1,1-dimethylethyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-((cyclopentylamino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-((cyclopropylamino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 25 (3*S*)-*N*-((4*R*)-7-(((1-methylethyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-((4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3*S*)-*N*-((4*R*)-7-(((3*S*)-3-hydroxy-1-piperidinyl)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

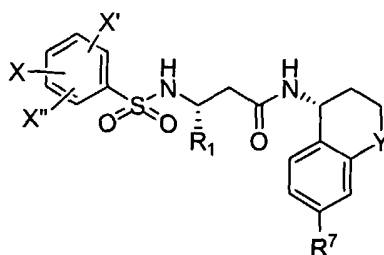
- (3*S*)-*N*-((4*R*)-7-(((2-(methyloxy)ethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((cyclopropylmethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*S*)-*N*-((4*R*)-7-(((2-methylpropyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(1-(1-piperidinylmethyl)ethenyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethyl-ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 10 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((1,1-dimethyl-ethyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclopentyl-amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 15 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-((cyclopentyl-amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 20 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(1-piperidinyl-methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((2-methylpropyl)-amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((2-methylpropyl)-amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- 25 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1-methylethyl)-amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((1-methylethyl)-amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((cyclopropyl-methyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 30 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((cyclopropyl-methyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclobutyl-amino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-((cyclobutyl-amino)-methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((3*S*)-3-hydroxy-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((3*R*)-3-hydroxy-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((3*S*)-3-hydroxy-1-piperidinyl)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((3*R*)-3-hydroxy-1-piperidinyl)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- 10 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-pyrrolidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(1-pyrrolidinyl-methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- 15 (3*S*)-3-(((4-(1,1-dimethylethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-bromo-3-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((2-fluoro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 20 (3*S*)-3-(((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3*S*)-*N*-((1*R*)-6-((3-pyridinylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-3-(((6-chloro-2-naphthalenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2-fluoro-5-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3*S*)-3-(((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclopentyl-amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((6-chloro-2-naphthalenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclopentylamino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

- (3*S*)-3-(((2-chloro-1-naphthalenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclopentyl-amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(methyl((3-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*S*)-3-(((2-nitro-4-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((2,6-dichloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-((1,1'-biphenyl-4-ylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-
- 10 tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2-nitro-4-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-3-(((2,6-dichloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 15 (3*S*)-3-((1,1'-biphenyl-4-ylsulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)-amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-((1,1'-biphenyl-3-ylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide; and
- (3*S*)-3-(((4-(1,3-oxazol-5-yl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-methyl)-
- 20 1,2,3,4-tetrahydro-1-naphthalenyl)butanamide.

The following compounds in Table 1 can be prepared similarly.

Table 1

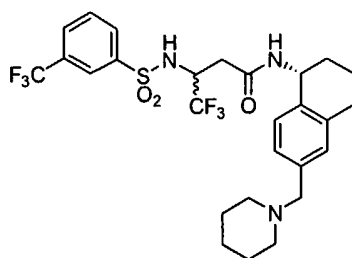


X	X'	X''	R ¹	Y	R'
3-CF ₃	H	H	CH ₃	CH ₂	-CH ₂ NHPr- <i>i</i>
3-CF ₃	H	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ - <i>c</i>
3-Cl	H	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ - <i>c</i>
2-F	5-CF ₃	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ - <i>c</i>
2-Cl	5-CF ₃	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ - <i>c</i>

X	X'	X''	R ¹	Y	R ⁷
2-Napthyl	H	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-Cl	3-Cl	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-Cl	5-Cl	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
3-Cl	4-Cl	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-Cl	6-Cl	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-F	5-Cl	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-F	3-Cl	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-Me	4-Cl	5-Me	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
4-Bu- <i>tert</i>	H	H	CH ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-Me	4-Cl	5-Me	CH ₃	O	-CH ₂ NHC ₄ H ₇ -c
2-Me	4-Cl	5-Me	CH ₃	direct bond	-CH ₂ NHC ₄ H ₇ -c
2Me	4-Cl	5-Me	CF ₃	direct bond	-CH ₂ NHC ₄ H ₇ -c
4-Cl	H	H	CF ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-Cl	5-Cl	H	CF ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
3-Me	H	H	CF ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
3-Cl	H	H	CF ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-F	4-Cl	H	CF ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-F	3-Cl	H	CF ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-F	5-Cl	H	CF ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-Cl	3-Cl	H	CF ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-Cl	6-Cl	H	CF ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
3-Cl	4-Cl	H	CF ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-Napthyl	H	H	CF ₃	CH ₂	-CH ₂ NHC ₄ H ₇ -c
2-Napthyl	H	H	CF ₃	O	-CH ₂ NHC ₅ H ₉ -c

Example 2

Synthesis of (*R*)-4,4,4-trifluoro-*N*-(6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide



Step A: Synthesis of (*R*)-4,4,4-trifluoro-*N*-(6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenyl)sulfonamido)butanamide

5 A mixture of 4,4,4-trifluoro-3-(3-(trifluoromethyl)phenyl)sulfonamido)butanoic acid (described in Reference 11, 2.84 g, 7.78 mmol), (*R*)-(5-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (1.38 g, 7.78 mmol), TBTU (from Advanced ChemTech, 2.75g, 8.55 mmol), and Hunig's base (2.0 mL, 11.7 mmol) in 20 mL of DMF was stirred at r.t. for 3 h. The reaction mixture was partitioned between ethyl acetate and water. The organic portion was separated,
10 washed with water, and brine. The solvents were removed to give the title compound as an off-white solid which was used in the following reaction without purification. The product was contaminated with benzotriazol-1-ol which was easily separated from the product in the following reaction.

Step B: Synthesis of (*R*)-4,4,4-trifluoro-*N*-(6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenyl)sulfonamido)butanamide
15

A mixture of (*R*)-4,4,4-trifluoro-*N*-(6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenyl)sulfonamido)butanamide (crude, ~7.8 mmol) and MnO₂ (From Aldrich, <5 micron, activated, ~85%, 6.0 g, 58.6 mmol) in 500 mL of methylene chloride was stirred at r.t. overnight. The reaction mixture was filtered through a pad of silica gel, eluted
20 with 10 – 15 % of ethyl acetate in methylene chloride and concentrated to give the title compound was obtained as a light yellowish solid.

Step C: Synthesis of (*R*)-4,4,4-trifluoro-*N*-(6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenyl)sulfonamido)butanamide

A mixture of (*R*)-4,4,4-trifluoro-*N*-(6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenyl)sulfonamido)butanamide (0.56 g, 1.07 mmol), piperidine (0.16 mL, 1.61 mmol) and acetic acid (0.10 mL, 1.61 mmol) in 1 mL of DMF and 2 mL of 1,2-dichloroethane was stirred at r.t. for 2 h. Sodium triacetoxy borohydride (From Aldrich, 95%, 0.48 g, 2.14 mmol) was added and the reaction mixture was then stirred at 60 °C overnight. The reaction mixture was cooled to r.t., diluted with EtOAc/H₂O, acidified with 10% of HCl
30 to pH 2, and stirred for 30 min. NaHCO₃ (aq) was added to bring pH to 8~9 and the organic

portion was separated, and washed with brine. The solvents were removed and the crude product was purified by flash column chromatography (0-13% of MeOH-NH₄OH (aq, 28 ~ 30 %) (volume ratio 3:1) in methylene chloride in 20 min, 13 – 15% of MeOH-NH₄OH (aq, 28 ~ 30 %) (volume ratio 3:1) in methylene chloride in 8 min) to give the title compound as a white solid. MS m/z: 592.2 (M+H)⁺. Calc'd for C₂₇H₃₁F₆N₃O₃S – 591.61.

Similarly the following compounds were prepared.

- (3*R/S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-*N*-((4*R*)-7-(((1,1-dimethylethyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-*N*-((4*R*)-6-chloro-7-(((1,1-dimethylethyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-*N*-((4*R*)-7-((cyclopentylamino)methyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- (3*R/S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)butanamide;
- (3*R/S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((2,4,6-trimethylphenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((4-methylphenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-3-(((4-chlorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide

- (3*R/S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- (3*R/S*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*R/S*)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2,4,6-trimethylphenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 10 (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((1-methylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((1-methylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((1-methylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(1-azepanylmethyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-*N*-((4*R*)-7-(1-azepanylmethyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 20 ((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((4*R*)-7-(4-morpholinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((3*S*)-3-hydroxy-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 25 (3*R/S*)-*N*-((1*R*)-6-((cyclohexylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((4*R*)-7-((4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((4*R*)-7-(((3*R*)-3-hydroxy-1-piperidinyl)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3*R/S*)-3-(((3-chloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-(6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-methylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*R/S*)-*N*-((1*R*)-6-((cyclobutylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*R/S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-*N*-((1*R*)-6-(((2,2-dimethylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 10 (3*R/S*)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(4-morpholinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-methyl-1-piperazinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-*N*-((4*R*)-7-(((2,2-dimethylpropyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 20 (3*R/S*)-*N*-((4*R*)-7-((cyclohexylamino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-(1-pyrrolidinyl)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 25 (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-(1-piperidinyl)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-(4-morpholinyl)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-*N*-((1*R*)-6-(((2-(acetyl)amino)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3*R/S*)-*N*-((1*R*)-6-(((2-(dimethylamino)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-*N*-((1*R*)-6-(((2-(diethylamino)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*R/S*)-*N*-((1*R*)-6-(((2*R*,6*S*)-2,6-dimethyl-1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-hydroxy-1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-hydroxy-1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((4-chloro-10 2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- (3*R/S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-((3-hydroxy-1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-(1-pyrrolidiny)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 15 (3*R/S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidiny)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*R/S*)-*N*-((4*R*)-7-(1-azepanylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- (3*R/S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-((3-20 hydroxy-1-piperidiny)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*R/S*)-4,4,4-trifluoro-3-((6-isoquinoliny)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-3-(((3-chloro-4-methylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3*R/S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-chloro-4-methylphenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- (3*S*)-3-(((3,4-bis(methyloxy)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-3-(((3,4-bis(methyloxy)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-30 piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3,4-bis(methyloxy)phenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- (3*R*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

- (3*S*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-4,4,4-trifluoro-3-(methyl((3-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-hydroxy-1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2*S*)-tetrahydro-2-furanylmethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2*R*)-tetrahydro-2-furanylmethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 10 (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-((8-quinolinylsulfonyl)amino)butanamide;
- (3*R/S*)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 15 (3*R/S*)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-3-(((5-chloro-2-(methyloxy)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-3-(((2,6-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 20 (3*S*)-3-(((4-chloro-3-(trifluoromethyl)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-3-(((4-chloro-3-(trifluoromethyl)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3*R/S*)-3-(((5-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-3-(((3-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 30 (3*R*)-4,4,4-trifluoro-3-(((8-(methyloxy)-5-quinolinyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-4,4,4-trifluoro-3-(((8-(methyloxy)-5-quinolinyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

- (3*R/S*)-3-((2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- 5 (3*R*)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- (3*R*)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-methyl-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 10 (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-fluoro-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;
- 15 (3*R*)-*N*-(6-chloro-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((7*R*)-1,2,3,4,7,8,9,10-octahydrobenzo[*f*]isoquinolin-7-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;
- 20 (3*R*)-3-(((2,5-difluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;
- (3*R*)-4,4,4-trifluoro-3-(((5-methyl-2-(methyloxy)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3*R*)-3-(((5-chloro-2-(methyloxy)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- (3*R*)-3-(((3,5-difluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((2,5-difluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 30 (3*R*)-4,4,4-trifluoro-3-(((3-methylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((3,5-difluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;

- (3R)-N-((1R)-6-((4aR,8aR)-octahydro-2(1H)-isoquinolinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3R)-4,4,4-trifluoro-N-((1R)-6-((4-(2-hydroxyethyl)-1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3R)-N-((1R)-6-(((cyclopropylmethyl)(propyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3R)-N-((1R)-6-((3,3-dimethyl-1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3R)-3-(((3-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-N-((1R)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 10 (3R)-3-(((5-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-N-((1R)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3R)-3-(((5-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-N-((4R)-7-(1-piperidiny)methyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;
- 15 (3R)-3-(((3-chloro-2-fluorophenyl)sulfonyl)amino)-N-((1R)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- (3R)-3-(((5-chloro-2-fluorophenyl)sulfonyl)amino)-N-((4R)-6-chloro-7-(1-piperidiny)methyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluorobutanamide;
- (3R)-3-(((3-chloro-2-fluorophenyl)sulfonyl)amino)-N-((4R)-6-chloro-7-(1-piperidiny)methyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluorobutanamide;
- 20 (3R)-3-(((3-chloro-2-fluorophenyl)sulfonyl)amino)-N-((4R)-7-(1-piperidiny)methyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;
- (3R)-3-((2,3-dihydro-1,4-benzodioxin-6-yl)sulfonyl)amino)-4,4,4-trifluoro-N-((1R)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 1,1-dimethylethyl-4-(((5R)-5-(((3R)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanoyl)amino)-5,6,7,8-tetrahydro-2-naphthalenyl)methyl)-1-piperazinecarboxylate;
- (3R)-4,4,4-trifluoro-N-((1R)-6-(1-piperazinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3R)-4,4,4-trifluoro-N-((1R)-6-(((2R)-2-methyl-1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3R)-4,4,4-trifluoro-N-((1R)-6-(((3S)-3-methyl-1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((3*S*)-3-hydroxy-1-pyrrolidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((3*R*)-3-hydroxy-1-pyrrolidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((3*R*)-3-(hydroxymethyl)-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((3*R*)-3-(methoxy)-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-(methylsulfonyl)-1-piperazinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 10 (3*R*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*R*)-3-(((5-chloro-2-fluorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- (3*R/S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((3-oxo-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R/S*)-3-(((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 20 (3*R/S*)-3-(((3,5-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((3-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-methyl-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3*R*)-4,4,4-trifluoro-3-((phenylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((2-bromo-5-(trifluoromethyl)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((2-bromophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 30 (3*R*)-4,4,4-trifluoro-3-(((2-nitrophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((4*R*)-6-fluoro-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*R*)-4,4,4-trifluoro-3-((1*R*)-6-(1-piperidinylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-((trifluoromethyl)oxy)phenyl)sulfonyl)amino)butanamide;
- 5 (3*R*)-3-(((5-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-methyl-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-*N*-((1*R*)-6-(((2*R*,3*S*,4*S*,5*S*,6*S*)-3,5-dihydroxy-2-(hydroxymethyl)-6-(methoxy)tetrahydro-2H-pyran-4-yl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 10 (3*R*)-4,4,4-trifluoro-3-(((2-fluorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-3-(((4-methylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-3-(((4-fluorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 15 (3*R*)-3-(((3-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-6-fluoro-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((4*R*)-6-fluoro-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-((trifluoromethyl)oxy)phenyl)sulfonyl)amino)butanamide;
- 20 (3*R*)-3-(((3-chlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((4-chlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((2-chlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3*R*)-4,4,4-trifluoro-3-(((3-fluorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-methyl-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3*R*)-3-(((2-aminophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((2-chloro-4-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

- (5*R*)-5-(((4-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-3-(((3-methylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((4-((trifluoromethyl)oxy)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-3-(((3-chloro-4-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((3-bromophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinyl-
- 10 methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-3-(((4-ethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinyl-
- methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 15 (3*R*)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-4,4,4-trifluoro-3-(((5-fluoro-2-methylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((2-chloro-6-methylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-
- 20 piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((4-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-4,4,4-trifluoro-3-(((2-fluoro-5-methylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-
- piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3*R*)-3-(((3,4-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-(((3,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinyl-
- methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-3-(((3-(methyloxy)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-
- 30 piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-(4-methyl)piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2-fluoro-3-chlorophenyl)sulfonyl)amino)butanamide;
- (3*R*)-4,4,4-trifluoro-3-(((4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)sulfonyl)-
- amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-butanamide;

(3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((1,2,3,4-tetrahydro-8-quinoliny)sulfonyl)amino)butanamide;

(3*R*)-3-(((3,5-dichloro-4-hydroxyphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

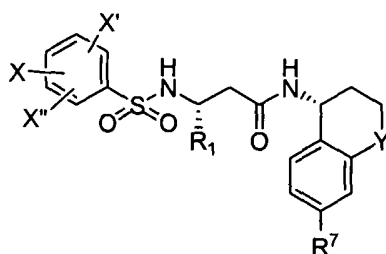
5 (3*R*)-3-(((3,4-dihydro-2*H*-1,5-benzodioxepin-7-yl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

(3*R*)-4,4,4-trifluoro-3-(((3-(1,3-oxazol-5-yl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide; and

10 (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-*tert*-butylphenyl)sulfonyl)amino)butanamide.

Unless indicated otherwise, the following compound can be prepared following the procedure described above.

Table 2



X	X'	X''	R ₁	Y	R ⁷
3-CF ₃	H	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
3-CF ₃	H	H	CH ₃	CH ₂	-CH ₂ (1-Mepiperazin-4-yl)
3-CF ₃	H	H	CH ₃	CH ₂	-CH ₂ (4-Mepiperidin-1-yl)
3-CF ₃	H	H	CH ₃	CH ₂	-CH ₂ (3-Mepiperidin-1-yl)
3-CF ₃	H	H	CH ₃	CH ₂	-CH ₂ -azepan-1-yl
3-CF ₃	H	H	CH ₃	CH ₂	-CH ₂ (3-OHpiperidin-1-yl)
3-CF ₃	H	H	CH ₃	CH ₂	-CH ₂ (3-HOCH ₂ piperidin-1-yl)
3-Cl	H	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
2-F	5-CF ₃	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Cl	5-CF ₃	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Naphthyl	H	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Cl	3-Cl	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Cl	5-Cl	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
3-Cl	4-Cl	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl

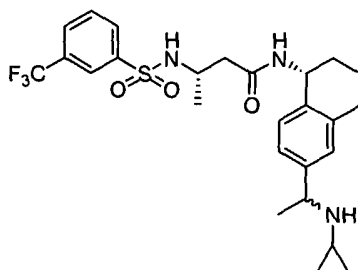
X	X'	X''	R ₁	Y	R'
2-Cl	6-Cl	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
2-F	5-Cl	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
2-F	3-Cl	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Me	5-Me	4-Cl	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
4-Bu- <i>tert</i>	H	H	CH ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Me	5-Me	4-Cl	CH ₃	O	-CH ₂ piperidin-1-yl
2-Me	5-Me	4-Cl	CH ₃	-	-CH ₂ piperidin-1-yl
2-Me	5-Me	4-Cl	CF ₃	-	-CH ₂ piperidin-1-yl
4-Cl	H	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Cl	H	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
2-OCF ₃	H	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
3-OMe	H	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
3-OCF ₃	H	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Cl	3-Cl	H	CF ₃	CH ₂	-CH ₂ azepan-1-yl
3-CF ₃	H	H	CF ₃	CH ₂	-CH ₂ azepan-1-yl
3-CF ₃	H	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
3-CF ₃	H	H	CF ₃	CH ₂	-CH ₂ (4-Mepiperidin-1-yl)
3-CF ₃	H	H	CF ₃	CH ₂	-CH ₂ (3-OHpiperidin-1-yl)
3-CF ₃	H	H	CF ₃	CH ₂	-CH ₂ (3-HOCH ₂ piperidin-1-yl)
H	H	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Cl	5-Cl	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
3-Me	H	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
3-Cl	H	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
2-F	4-Cl	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
2-F	3-Cl	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
2-F	5-Cl	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Cl	3-Cl	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Cl	6-Cl	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
3-Cl	4-Cl	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
3-Cl	5-Cl	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
2-Cl	3-CF ₃	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl
2-naphthyl	H	H	CF ₃	CH ₂	-CH ₂ piperidin-1-yl

X	X'	X''	R ₁	Y	R'
2-naphthyl	H	H	CF ₃	O	-CH ₂ piperidin-1-yl
2-Me	5-Me	4-Cl	CF ₃	O	-CH ₂ piperidin-1-yl
2-naphthyl	H	H	Et	CH ₂	-CH ₂ piperidin-1-yl
2-naphthyl	H	H	<i>i</i> -Pr	CH ₂	-CH ₂ piperidin-1-yl
2-naphthyl	H	H	<i>c</i> -Pr	CH ₂	-CH ₂ piperidin-1-yl
2-naphthyl	H	H	<i>tert</i> -Bu	CH ₂	-CH ₂ piperidin-1-yl
2-naphthyl	H	H	CN	CH ₂	-CH ₂ piperidin-1-yl
2-naphthyl	H	H	C≡CH	CH ₂	-CH ₂ piperidin-1-yl
2-naphthyl	H	H	CH ₂ C≡CH	CH ₂	-CH ₂ piperidin-1-yl
2-naphthyl	H	H	CH ₂ F	CH ₂	-CH ₂ piperidin-1-yl
2-naphthyl	H	H	CH ₂ CN	CH ₂	-CH ₂ piperidin-1-yl

Example 3

Synthesis of (*S*)-*N*-((*R*)-6-(1-(cyclopropylamino)ethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenyl)sulfonamido)butanamide

5



Step A: Synthesis of [6-(1-hydroxy-ethyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-carbamic acid tert-butyl ester

To a solution of (6-formyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-carbamic acid tert-butyl ester (2.80 g, 10.2 mmol, 1.0 eq) in THF (100 mL) at -78°C was added a solution of MeMgBr [Aldrich, 1.4M in toluene/THF (3:1), 29 mL, 40.7 mmol, 4.0 eq] slowly. The reaction mixture was stirred at -78°C for 20 min, warmed up to room temperature and stirred at room temperature for 2 h. The reaction was quenched with saturated NaHCO₃ (120 mL), and the crude product was extracted with EtOAc (100 mL x 3). The extract phase was washed with saturated NaCl, dried over Na₂SO₄, filtered and concentrated. The title compound was obtained as a white solid. MS (ESI, pos. ion) *m/z*: 292 (M+1).

Step B: Synthesis of (6-acetyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-carbamic acid tert-butyl ester

A mixture of [6-(1-hydroxy-ethyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-carbamic acid tert-butyl ester (2.63 g, 9.04 mmol, 1.0 eq) and MnO₂ (Aldrich, 10.2 g, 117.5 mmol, 13 eq) in CH₂Cl₂ (100 mL) was stirred at room temperature overnight. The reaction mixture was allowed to pass through a pad of Celite and the pad was washed with CH₂Cl₂ (100 mL x 2). The concentration of the filtrate afforded the title compound as a white sticky semi-solid (1.89 g). MS (ESI, pos. ion) m/z: 290 (M+1).

Step C: Synthesis of (S)-N-((R)-6-acetyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide

A mixture of (6-acetyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-carbamic acid tert-butyl ester (650 mg, 2.25 mmol, 1.0 eq) in HCl/EtOAc (4.7M, 20 mL) was stirred at room temperature for 3 h, 20 min. The solvent was removed with a rotary evaporator, and the resulting 1-(5-amino-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethanone hydrogen chloride was dried in vacuo. To the flask was added (S)-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid (840 mg, 2.7 mmol, 1.2 eq), EDCI (Aldrich, 776 mg, 4.05 mmol, 1.8 eq), HOBt (Aldrich, 61 mg, 0.45 mmol, 0.2 eq) and diisobutylethylamine (Aldrich, 582 mg, 4.50 mmol, 2.0 eq) in CH₂Cl₂ (20 mL) and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with H₂O (100 mL). The crude product was extracted with CH₂Cl₂ (100 mL x 3). The extract phase was washed with saturated NaCl, dried over Na₂SO₄, filtered and concentrated. Flash column chromatography (silica gel, 0-7 % MeOH-CH₂Cl₂) afforded the title compound as a white solid. MS (ESI, pos. ion) m/z: 483 (M+1). (S)-N-((R)-6-Acetyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide was converted to (S)-N-((R)-6-(1-(cyclopropylamino)ethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide by reacting it with cyclopropylamine as described Example 2, Step C above.

Similarly the following compounds were made.

(3S)-N-((1R/S)-6-((1S)-1-(cyclopentylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
(3S)-N-((1R/S)-6-((1S)-1-((2-methylpropyl)amino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
(3S)-N-((1R/S)-6-((1R)-1-(cyclobutylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

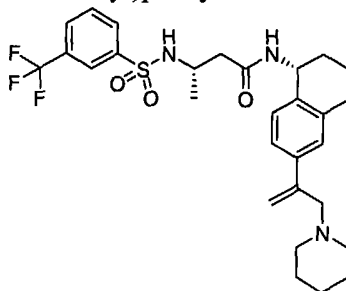
(3*S*)-*N*-((1*R/S*)-6-((1*S*)-1-((cyclopropylmethyl)amino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide; and

(3*S*)-*N*-((1*R*)-6-((1*R/S*)-1-((2-(methyloxy)ethyl)amino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide.

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Example 4

Synthesis of (*S*)-*N*-((*R*)-6-(3-(piperidin-1-yl)prop-1-en-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide



10

To a 20 mL flask equipped with stirring was added (*S*)-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid (68 mg, 0.22 mmol), 6-(1-piperidin-1-ylmethyl-vinyl)-1,2,3,4-tetrahydro-naphthalen-1-ylamine (54 mg, 0.20 mmol), EDC (Aldrich, 58 mg, 0.30 mmol), HOBt (Aldrich, 27 mg, 0.2 mmol), and CH₂Cl₂ (2 mL). The reaction mixture was stirred at room temperature overnight and diluted with CH₂Cl₂ (50 mL). The organic phase was washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude was purified by preparative TLC in 10% MeOH-CH₂Cl₂ to afford the title compound. MS (ESI): 564 (M+H)⁺.

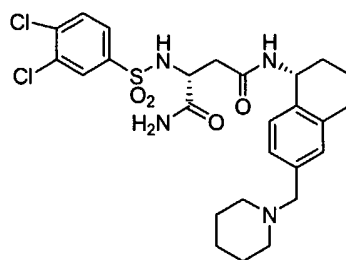
Similarly (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(3-(piperidin-1-yl)prop-1-en-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide was prepared.

20

Example 5

Synthesis of (*R*)-3-(3,4-dichlorophenylsulfonamido)-*N*1-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)succinamide

25

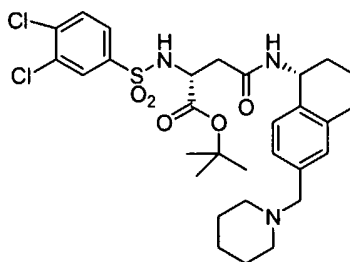


(*R*)-4-Amino-3-(3,4-dichlorophenylsulfonamido)-4-oxobutanoic acid (250 mg, 0.733 mmol) was dissolved in anhydrous DMF (7 mL). (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (259 mg, 0.953 mmol) and HOBt (Aldrich, 129 mg, 0.953 mmol) were added followed by EDCI (Aldrich, 183 mg, 0.953 mmol). The reaction mixture was stirred at RT for 2 h. EtOAc/water (2:1, 50 mL) was added and the solution was washed with saturated sodium bicarbonate/brine (1:1, 2x30 mL), then with brine (30 mL). It was concentrated and dried in vacuo to give 0.481 g of crude product. It was purified by flash column chromatography (10% MeOH/CH₂Cl₂, ISCO CombiFlash) to give (*R*)-3-(3,4-dichlorophenylsulfonamido)-*N*¹-(*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)succinamide. MS 567 (M+H).

Similarly, (*R*)-benzyl 2-(3,4-dichlorophenylsulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoate; and (*R*)-benzyl 2-(4-methylphenylsulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoate were prepared.

Example 6

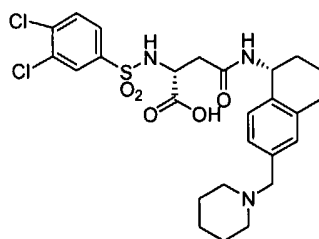
Synthesis of (*R*)-tert-butyl 2-(3,4-dichlorophenylsulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoate



The title compound was prepared according to Example 5 from (*R*)-4-tert-butoxy-3-(3,4-dichlorophenylsulfonamido)-4-oxobutanoic acid. MS: 624.4 (M+H).

Example 7

Synthesis of (*R*)-2-(3,4-dichlorophenylsulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoic acid



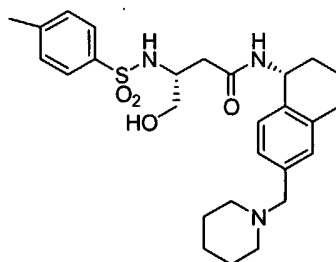
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To (*R*)-tert-butyl 2-(3,4-dichlorophenylsulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoate prepared in Example 6 (0.15 g) in DCM (2 mL) was added TFA (2 mL). The reaction mixture was stirred overnight at RT. The solvents were evaporated and dried to give the titled compound. MS: 568.2 (M+H).

10

Example 8

Synthesis of (*R*)-4-hydroxy-3-(4-methylphenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide



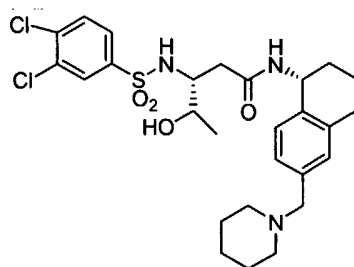
15

To (*R*)-benzyl 2-(4-methylphenylsulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoate (described in Example 5; 80 mg) in 5 mL of DCM was added DIBAL (Aldrich, 1.5M in toluene, 0.8 mL). The reaction mixture was stirred at RT overnight. EtOAc (1 mL) was added and stirred for 10 min. Sodium sulfate (about 1 g) was added and followed by 15 drops of saturated ammonium chloride. The reaction mixture was filtered after stirring for 10 min. The filtrate was evaporated. The crude product was further purified by preparative TLC (10% 2N NH₃/MeOH/DCM) to give the title compound. MS: 500.2 (M+H).

20

Example 9

25 Synthesis of (3*R*,4*R*)-3-(3,4-dichlorophenylsulfonamido)-4-hydroxy-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)pentanamide



Step A: Synthesis of 3,4-dichloro-*N*-((2*R*,3*R*)-2-methyl-5-oxo-tetrahydrofuran-3-yl)benzenesulfonamide

To a mixture of L-β-homothreonine hydrochloride (1.04 g) and sodium carbonate (1.8 g) in dioxane (10 mL) and water (10 mL) at RT was added 3,4-dichlorobenzenesulfonyl chloride (2.0 g) and the reaction mixture was stirred overnight. EtOAc (100 mL) and brine (70 mL) were added. The reaction mixture was acidified and stirred for 20 min. The organic layer was separated, washed with brine (3x 70 mL), dried and evaporated to give the crude product. Column chromatograph purification (silica gel; 10-30% ethyl acetate/hexanes) gave the title compound. MS: 322 (M+H).

Step B: Synthesis of (3*R*,4*R*)-3-(3,4-dichlorophenylsulfonamido)-4-hydroxy-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)pentanamide

To a mixture of (*R*)-(5-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (0.17 g) in DCM (10 mL) at 0 °C was added trimethylaluminum (1 mL of 2.0M in toluene, Aldrich). The reaction mixture was stirred for 30 min. The above lactone (0.36 g) was added. The reaction mixture was stirred for 4 h. HCl solution (2 mL, 0.05N) was added. The organic layer was separated and dried. The organic layer was separated and dried to give the title compound.

Step C: Synthesis of (3*R*,4*R*)-3-(3,4-dichlorophenylsulfonamido)-*N*-((*R*)-6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-4-hydroxypentanamide

(3*R*,4*R*)-3-(3,4-Dichlorophenylsulfonamido)-4-hydroxy-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)pentanamide (0.12 g) in DCM (300-400 mL) was stirred with MnO₂ at RT for 2 h. The reaction mixture was filtered through a pad of celite. The filtrate was evaporated to give the title compound. MS: 497.2 (M+H).

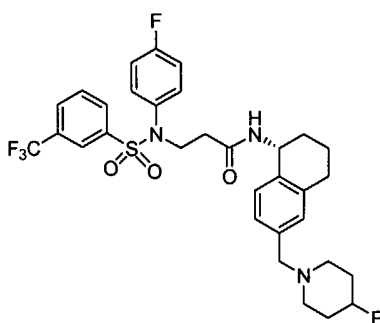
Step D: Synthesis of (3*R*,4*R*)-3-(3,4-dichlorophenylsulfonamido)-4-hydroxy-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)pentanamide

A mixture of (3*R*,4*R*)-3-(3,4-dichlorophenylsulfonamido)-*N*-((*R*)-6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-4-hydroxypentanamide (0.14 g), piperidine (0.2 g), and NaBH(OAc)₃ (0.36 g) in DCE (10 mL) was stirred at RT overnight. DCM (50 mL) and brine (15 mL) were added. The organic layer was separated, dried, and evaporated. The crude

product was purified by column chromatography (silica gel, 0-1.5% MeOH/DCM) to give the title compound. MS: 568.2 (M+H).

Example 10

- 5 Synthesis of (*R*)-3-(*N*-(4-fluorophenyl)-3-(trifluoromethyl)phenylsulfonamido)-*N*-(6-((4-fluoropiperidin-1-yl)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide



Step A: Synthesis of methyl 3-(4-fluorophenylamino)propanoate

- 10 To a 30-mL microwave vial containing methyl 3-bromopropanoate (6.2 mL, 57 mmol, Aldrich) was added 4-fluorophenylaniline (5.5 mL, 57 mmol, Aldrich). The reaction was stirred at 100 °C for 4 min in microwave. Purification with column chromatography over silica gel with hexane:EtOAc (5:1) gave the title compound. MS (ESI, pos. ion.) *m/z*: 198 (M+1).

Step B: Synthesis of methyl 3-(*N*-(4-fluorophenyl)-3-(trifluoromethyl)-

- 15 phenylsulfonamido)propanoate

- To a 50-mL round-bottomed flask containing methyl 3-(4-fluorophenylamino)-propanoate (1.4 g, 7.3 mmol, Step A) in THF (15 mL), was added 3-trifluoromethylbenzene sulfonylchloride (2.7 g, 11 mmol, Aldrich) and sat. K₂CO₃ (10 mL). The reaction was stirred at RT for 4 h. The compound was extracted with EtOAc (2×20 mL). The combined organic
- 20 phase was washed with 5% brine (2×15 mL), dried over Na₂SO₄. Purification with column chromatography over silica gel with hexane:EtOAc (5:1) gave the title compound. MS (ESI, pos. ion.) *m/z*: 406 (M+1).

Step C: Synthesis of 3-(*N*-(4-fluorophenyl)-3-(trifluoromethyl)phenylsulfonamido)propanoic acid

- 25 To a 100-mL round-bottomed flask containing methyl 3-(*N*-(4-fluorophenyl)-3-(trifluoromethyl)phenylsulfonamido) propanoate (2.0 g, 4.8 mmol, Step B) in THF (10 mL), was added LiOH·H₂O (2.0 g, 48 mmol, Aldrich) and water (10 mL). The reaction was stirred at RT for 5 h. After acidified to pH 5 with 2N HCl, the compound was extracted with EtOAc

(2×20 mL). The organic phase was washed with 5% brine (2×15 mL), dried over Na₂SO₄, filtered, and concentrated to yield the title compound. MS (ESI, pos. ion.) *m/z*: 390 (M-1).

Step D: Synthesis of (*R*)-3-(*N*-(4-fluorophenyl)-3-(trifluoromethyl)phenylsulfonamido)-*N*-(6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide

5 To a 50-mL reaction tube containing 3-(*N*-(4-fluorophenyl)-3-(trifluoromethyl)-phenylsulfonamido)propanoic acid (1.6 g, 4.1 mmol, Step C) in CH₂Cl₂ (10 mL), was slowly added oxalyl chloride (10 mL, 21 mmol, 2.0M, Aldrich). After the reaction was stirred at RT for 0.5 h, the solvent was removed in vacuo. To the residue was added (*R*)-(5-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (0.72 g) in THF (8 mL) and sat. K₂CO₃ (5 mL). The
10 reaction was stirred at RT for 2.5 h. The compound was extracted with EtOAc (2×10 mL). The organic phase was washed with 5% brine (2×5 mL), dried over Na₂SO₄, filtered, and concentrated. Purification with column chromatography over silica gel with hexane:EtOAc (1:1) gave the title compound as a white solid. MS (ESI, pos. ion.) *m/z*: 551 (M+1).

Step E: Synthesis of (*S*)-*N*-(4-fluorophenyl)-*N*-(4-(6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-oxobutyl)-3-(trifluoromethyl)benzenesulfonamide

15 To a 50-mL reaction tube containing (*R*)-3-(*N*-(4-fluorophenyl)-3-(trifluoromethyl)-phenylsulfonamido)-*N*-(6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide (0.6 g, 1.1 mmol, Step D) in CH₂Cl₂ (15 mL), was added MnO₂ (1.4 g, 16 mmol, Aldrich). The reaction was stirred at RT for 4 h, and filtration through Celite gave the title compound as
20 a yellow solid. MS (ESI, pos. ion.) *m/z*: 549 (M+1).

Step F: Synthesis of (*R*)-3-(*N*-(4-fluorophenyl)-3-(trifluoromethyl)phenylsulfonamido)-*N*-(6-((4-fluoropiperidin-1-yl)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide

To a 50-mL reaction tube containing (*S*)-*N*-(4-fluorophenyl)-*N*-(4-(6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-oxobutyl)-3-(trifluoromethyl)benzenesulfonamide (80 mg, 0.15
25 mmol, Step E) in DMF (3 mL), was added 4-fluoropiperidine hydrobromide (0.27 g, 1.5 mmol, Oakwood Products), Et₃N (0.20 mL, 1.5 mmol, Aldrich), NaBH(OAc)₃ (0.16 g, 0.7 mmol, Aldrich), and 2 drops of AcOH (J.T. Baker). The reaction was stirred at RT for 12 h. The reaction was quenched with K₂CO₃ (8 mL, 5%), and the compound was extracted with EtOAc (2×10 mL). The organic phase was washed with 5% brine (2×5 mL), dried over Na₂SO₄,
30 filtered, and concentrated. Purification with column chromatography over silica gel with hexane:EtOAc:MeOH (2M, NH₃) (10:10:1) gave the title compound as a white solid. MS (ESI, pos. ion.) *m/z*: 636 (M+1).

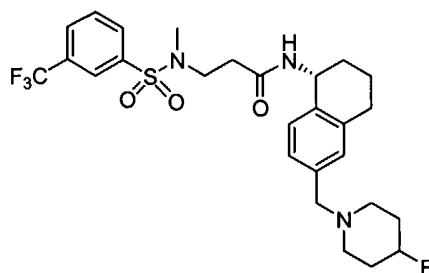
Similarly, (*R*)-3-(*N*-phenylnaphthalene-2-sulfonamido)-*N*-(6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide; (*R*)-3-(*N*-phenylnaphthalene-2-sulfonamido)-*N*-(7-

(piperidin-1-ylmethyl)chroman-4-yl)propanamide; and (*R*)-*N*-(6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(*N*-phenyl-3-(trifluoromethyl)phenylsulfonamido)propanamide were made.

5

Example 11

Synthesis of (*R*)-*N*-(6-((4-fluoropiperidin-1-yl)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)propanamide

10 Step A: Synthesis of *N*-methyl-3-(trifluoromethyl)benzenesulfonamide

To a 50-mL round-bottomed flask containing 3-trifluoromethylbenzene sulfonyl chloride (2.5 mL, 6.7 mmol, Aldrich) in THF (15 mL), was slowly added a methyl amine solution (575 μ L, 6.7 mmol, 40wt.%, Aldrich). The reaction was stirred at RT for 1 h. The reaction mixture was acidified to pH 5 with 2N HCl and the compound was extracted with EtOAc (2 $\times$ 10 mL). The combined organic phase was washed with 5% brine (2 $\times$ 8 mL), dried over Na₂SO₄. Purification with column chromatography over silica gel with hexane:EtOAc (5:1) gave the title compound. MS (ESI, pos. ion.) *m/z*: 362 (M+Na).

15 Step B: Synthesis of methyl 3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)propanoate

To a 100-mL round-bottomed flask containing *N*-methyl-3-(trifluoromethyl)benzenesulfonamide (1.5 g, 6.3 mmol, Step A) in DMF (10 mL), was added methyl 3-bromopropanoate (28 mL, 257 mmol, Aldrich) and K₂CO₃ (2.3 g, 17 mmol, Aldrich). The reaction mixture was refluxed at 140 °C for 13 h. The reaction was quenched with water (15 mL) and the compound was extracted with EtOAc (2 $\times$ 20 mL). The organic phase was washed with 5% brine (2 $\times$ 10 mL), dried over Na₂SO₄, filtered, and concentrated. Purification with column chromatography over silica gel with hexane:EtOAc (5:1) gave the title compound. MS (ESI, pos. ion.) *m/z*: 326 (M+1).

25 Step C: Synthesis of 3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)propanoic acid

To a 50-mL round-bottomed flask containing methyl 3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)propanoate (1.3 g, 4.0 mmol, Step B) in THF (8 mL), was added

30 LiOH.H₂O (1.3 mg, 8.0 mmol, Aldrich) and water (8 mL). The reaction was stirred at RT for 5

h. After acidified to pH 5 with 2N HCl, the compound was extracted with EtOAc (2×10 mL). The organic phase was washed with 5% brine (2×8 mL), dried over Na₂SO₄, filtered, and concentrated to yield the title compound. MS (ESI, pos. ion.) *m/z*: 312 (M+1).

Step D: Synthesis of (*R*)-*N*-(6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)propanamide

To a 50-mL reaction tube containing 3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)propanoic acid (0.25 g, 0.80 mmol, Step C) in DMF (3 mL), was added (*R*)-(5-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (0.14 g, 0.80 mmol), TBTU (0.36 g, 1.1 mmol, Advanced ChemTech), and *i*Pr₂EtN (0.56 mL, 3.2 mmol, Aldrich). The reaction was stirred at RT for 5 h. The reaction was quenched with 5% brine (5 mL) and the compound was extracted with EtOAc (2×10 mL). The organic phase was washed with 5% brine (2×5 mL), dried over Na₂SO₄, filtered, and concentrated. Purification with column chromatography over silica gel with hexane:EtOAc:MeOH (2M, NH₃) (5:5:1) gave the title compound as a white powder. MS (ESI, pos. ion.) *m/z*: 471 (M+1).

Step E: Synthesis of (*R*)-*N*-(6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)propanamide

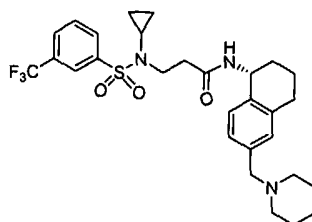
To a 50-mL reaction tube containing (*R*)-*N*-(6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)propanamide (0.12 g, 0.25 mmol, Step D) in CH₂Cl₂ (4 mL), was added MnO₂ (0.17 g, 2.0 mmol, Aldrich). The reaction was stirred at RT for 2 h, and filtration through Celite gave the title compound as a yellow solid. MS (ESI, pos. ion.) *m/z*: 469 (M+1).

Step F: Synthesis of (*R*)-*N*-(6-((4-fluoropiperidin-1-yl)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)propanamide.

To a 50-mL reaction tube containing (*R*)-*N*-(6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)propanamide (0.11 g, 0.23 mmol, Step E) in DMF (3 mL), was added 4-fluoropiperidine hydrochloride (66 mg, 0.47 mmol, Matrix), Et₃N (66 μ L, 0.73 mmol, Aldrich), NaBH(OAc)₃ (0.15 g, 0.70 mmol, Aldrich), and 2 drops of AcOH (J.T. Baker). The reaction was stirred at RT for 12 h. The reaction was quenched with K₂CO₃ (8 mL 5%), and the compound was extracted with EtOAc (2×10 mL). The organic phase was washed with 5% brine (2×5 mL), dried over Na₂SO₄, filtered, and concentrated. Purification with column chromatography over silica gel with hexane:EtOAc:MeOH (2M, NH₃) (10:10:1) gave the title compound as clear oil. MS (ESI, pos. ion.) *m/z*: 556 (M+1).

Example 12

Synthesis of (*R*)-3-(*N*-cyclopropyl-3-(trifluoromethyl)phenylsulfonamido)-*N*-(6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide



5 Step A: Synthesis of *N*-cyclopropyl-3-(trifluoromethyl) benzenesulfonamide

To a 50-mL round-bottomed flask containing 3-trifluoromethylbenzenesulfonyl chloride (4.0 mL, 25 mmol, Aldrich) in THF (15 mL), was slowly added cyclopropylamine (0.74 g, 13 mmol, Aldrich). The reaction was stirred at RT for 1 h. The reaction mixture was quenched with water (10 mL), and the compound was extracted with EtOAc (2×15 mL). The combined organic phase was washed with 5% brine (2×8 mL), dried over Na₂SO₄. Purification with column chromatography over silica gel with hexane:EtOAc (5:1) gave the title compound as a clear oil. MS (ESI, pos. ion.) *m/z*: 264 (M-1).

Step B: Synthesis of *tert*-butyl 3-(*N*-cyclopropyl-3-(trifluoromethyl)phenylsulfonamido)propanoate.

15 To a 100-mL round-bottomed flask containing *N*-cyclopropyl-3-(trifluoromethyl) benzenesulfonamide (1.7 g, 6.2 mmol, step A) in DMF (10 mL), was added *tert*-butyl acrylate (6.9 mL, 47 mmol, Aldrich) and K₂CO₃ (4.3 g, 31 mmol, Aldrich). The reaction mixture was refluxed at 100 °C for 2 h. The reaction was quenched with water (15 mL) and the compound was extracted with EtOAc (2×20 mL). The organic phase was washed with 5% brine (2×10 mL), dried over Na₂SO₄, filtered, and concentrated. Purification with column chromatography over silica gel with hexane:EtOAc (5:1) gave the title compound. MS (ESI, pos. ion.) *m/z*: 394 (M+1).

Step C: Synthesis of 3-(*N*-cyclopropyl-3-(trifluoromethyl)phenylsulfonamido)propanoic acid.

25 To a 50-mL round-bottomed flask containing *tert*-butyl 3-(*N*-cyclopropyl-3-(trifluoromethyl) phenylsulfonamido) propanoate (1.7 g, 4.2 mmol, step B), was added trifluoroacetic acid (5.0 mL, 65 mmol, Aldrich). The reaction was stirred at RT for 1.5 h. Evaporation in vacuo provided the title compound as a white solid. MS (ESI, pos. ion.) *m/z*: 338 (M+1).

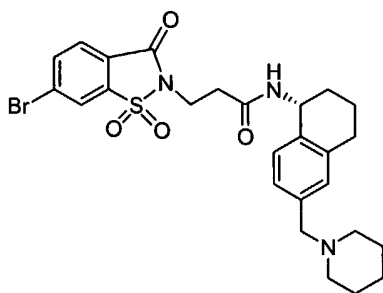
Step D: Synthesis of (*R*)-3-(*N*-cyclopropyl-3-(trifluoromethyl)phenylsulfonamido)-*N*-(6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide.

To a 50-mL reaction tube containing 3-(*N*-cyclopropyl-3-(trifluoromethyl)phenylsulfonamido)propanoic acid (0.13 g, 0.39 mmol, step C) in DMF (5 mL), was added (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (0.14 g), TBTU (0.30 g, 0.78 mmol, Advanced ChemTech), and *i*Pr₂EtN (0.27 mL, 1.6 mmol, Aldrich). The reaction was stirred at RT for 5 h. The reaction was quenched with 5% brine (10 mL) and the compound was extracted with EtOAc (2×15 mL). The organic phase was washed with 5% brine (2×8 mL), dried over Na₂SO₄, filtered, and concentrated. Purification with column chromatography over silica gel with hexane:EtOAc:MeOH (2M, NH₃) (5:5:1) gave the title compound as a white solid. MS (ESI, pos. ion.) *m/z*: 564 (M+1).

Similarly, (*R*)-3-(*N*-cyclohexyl-3-(trifluoromethyl)phenylsulfonamido)-*N*-(6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide; (*R*)-3-(*N*-isopropyl-3-(trifluoromethyl)phenylsulfonamido)-*N*-(6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide, (*R*)-*N*-(6-((*tert*-butylamino)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(*N*-cyclopropyl-3-(trifluoromethyl)phenylsulfonamido)-propanamide were synthesized.

Example 13

Synthesis of (*R*)-3-(3-bromosaccharinyl)-*N*-(6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide



Step A: Synthesis of methyl 3-(3-bromo-saccharinyl)propanoate

To a 100-mL round-bottomed flask containing 3-bromosaccharin (1.0 g, 3.8 mmol, Synthelee) in DMF (5 mL), was slowly added NaH (0.15 g, 3.8 mmol, 60% in mineral oil, Aldrich) at room temp. Methyl 3-bromo-propanoate (2.1 mL, 19 mmol, Aldrich) was added and the reaction mixture was refluxed at 130 °C for 6 h. The reaction was quenched with water (15 mL) and the compound was extracted with EtOAc (2×20 mL). The organic phase was washed with 5% brine (2×10 mL), dried over Na₂SO₄, filtered, and concentrated. Purification

with column chromatography over silica gel with hexane:EtOAc:MeOH (5:5:1) gave the title compound.

Step B: Synthesis of 3-(3-bromosaccharinyl)propanoic acid

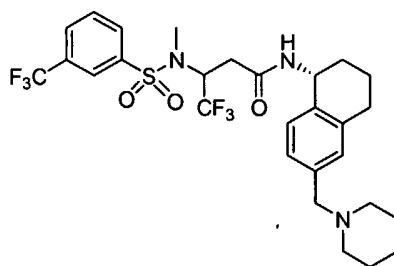
To a 50-mL round-bottomed flask containing methyl 3-(3-bromo-saccharinyl)propanoate (0.61 g, 1.8 mmol, step A) in THF (6 mL), was added LiOH.H₂O (0.37 g, 8.8 mmol, Aldrich) and water (6 mL). The reaction was stirred at RT for 6 h. The reaction mixture was acidified to pH 5, and the compound was extracted with EtOAc (15 mL). The organic phase was washed with water, dried over Na₂SO₄, filtered, and concentrated to yield the title compound.

Step C: Synthesis of (*R*)-3-(3-bromo-saccharinyl)-*N*-(6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide

To a 50-mL reaction tube containing 3-(3-bromo-saccharinyl) propanoic acid (0.11 g, 0.33 mmol, step B) in DMF (5 mL), was added (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (80 mg, 0.33 mmol), TBTU (0.25 g, 0.66 mmol, Advanced ChemTech), and *i*Pr₂EtN (0.23 mL, 1.3 mmol, Aldrich). The reaction was stirred at RT for 5 h. The reaction was quenched with 5% brine (10 mL) and the compound was extracted with EtOAc (2×15 mL). The organic phase was washed with 5% brine (2×8 mL), dried over Na₂SO₄, filtered, and concentrated. Purification with column chromatography over silica gel with hexane:EtOAc:MeOH (2M, NH₃) (5:5:1) gave the title compound as a yellow solid. MS (ESI, pos. ion.) *m/z*: 561 (M+1).

Example 14

Synthesis of 4,4,4-trifluoro-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide



Step A: Synthesis of ethyl 4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanoate

To a 50-mL round-bottomed flask containing ethyl 3-amino-4,4,4-trifluorobutanoate (0.40 g, 2.2 mmol, Lancaster) in THF (5 mL), was added 3-trifluoromethylbenzene sulfonylchloride (0.36 mL, 3.4 mmol, Aldrich) and sat. K₂CO₃ (4 mL). The reaction was stirred at RT for 1 h. The reaction mixture was acidified to pH 5 with 2N HCl and the

compound was extracted with EtOAc (2×10 mL). The combined organic phase was washed with 5% brine (2×8 mL), dried over Na₂SO₄. Purification with column chromatography over silica gel with hexane:EtOAc (3:1) gave the title compound. MS (ESI, pos. ion.) *m/z*: 394 (M+1).

5 Step B: Synthesis of 4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid

To a 50-mL round-bottomed flask containing ethyl 4,4,4-trifluoro-3-(3-(trifluoromethyl) phenylsulfonamido)butanoate (0.37 g, 0.95 mmol, step A) in THF (2 mL), was added LiOH.H₂O (0.12 g, 2.9 mmol, Aldrich) and water (2 mL). The reaction was stirred at RT for 6 h. After acidified to pH 5 with 2N HCl, the compound was extracted with EtOAc (2×5 mL).

10 The organic phase was washed with 5% brine (2×4 mL), dried over Na₂SO₄, filtered, and concentrated to yield the title compound. MS (ESI, pos. ion.) *m/z*: 364 (M-1).

Step C: Synthesis of 4,4,4-trifluoro-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide

To a 50-mL reaction tube containing 4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid (1.6 g, 4.1 mmol, step B) in DMF (10 mL), was added (*R*)-(5-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (0.72 g, 4.1 mmol), TBTU (0.25 g, 0.66 mmol, Advanced ChemTech), and *i*Pr₂EtN (0.23 mL, 1.3 mmol, Aldrich). The reaction was stirred at RT for 5 h. The reaction was quenched with 5% brine (10 mL) and the compound was extracted with EtOAc (2×15 mL). The organic phase was washed with 5% brine (2×8 mL), dried over Na₂SO₄, filtered, and concentrated. Purification with column chromatography over silica gel with hexane:EtOAc:MeOH (2M, NH₃) (10:10:1) gave the title compound. MS (ESI, pos. ion.) *m/z*: 525 (M+1).

Step D: Synthesis of 4,4,4-trifluoro-*N*-((*R*)-6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide

25 To a 50-mL reaction tube containing 4,4,4-trifluoro-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide 1.5 g, 2.9 mmol, step C) in CH₂Cl₂ (25 mL), was added MnO₂ (1.4 g, 16 mmol, Aldrich). The reaction was stirred at RT for 10 h, and filtration through Celite gave the title compound as a clear oil. MS (ESI, pos. ion.) *m/z*: 523 (M+1).

30 Step E: Synthesis of 4,4,4-trifluoro-*N*-((*R*)-6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)butanamide

To a 100-mL round-bottomed flask containing 4,4,4-trifluoro-*N*-((*R*)-6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide (0.35 g, 0.67 mmol, step D) in DMF (5 mL), was added MeI (0.13 mL, 2.0 mmol, Aldrich) and K₂CO₃ (0.17

g, 2.0 mmol, Aldrich). The reaction mixture was stirred at RT for 1 h. The reaction was quenched with water (8 mL) and the compound was extracted with EtOAc (2×10 mL). The organic phase was washed with 5% brine (2×10 mL), dried over Na₂SO₄, filtered, and concentrated to yield the title compound. MS (ESI, pos. ion.) *m/z*: 535 (M-1).

5 Step F: Synthesis of 4,4,4-trifluoro-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide

To a 50-mL reaction tube containing 4,4,4-trifluoro-*N*-((*R*)-6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(*N*-methyl-3-(trifluoromethyl)phenylsulfonamido)butanamide (0.30 g, 0.56 mmol, step E) in DMF (3 mL), was added piperidine (0.17 mL, 1.7 mmol, Aldrich), NaBH(OAc)₃ (0.37 g, 1.7 mmol, Aldrich), and 2 drops of AcOH (J.T. Baker). The reaction was stirred at RT for 12 h. The reaction was quenched with K₂CO₃ (8 mL, 5%), and the compound was extracted with EtOAc (2×10 mL). The organic phase was washed with 5% brine (2×5 mL), dried over Na₂SO₄, filtered, and concentrated. Purification with column chromatography over silica gel with hexane:EtOAc:MeOH (2M, NH₃) (5:5:1) gave the title compound as a white solid. MS (ESI, pos. ion.) *m/z*: 606 (M+1).

Similarly,

(*S*)-3-(5-chloro-2-fluoro-*N*-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;

(*S*)-3-(3-chloro-2-fluoro-*N*-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;

(*S*)-3-(2,5-dichloro-*N*-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;

(*S*)-3-(3,4-dichloro-*N*-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;

(*S*)-3-(2,3-dichloro-*N*-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;

(*S*)-3-(2,5-dichloro-*N*-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-7-(piperidin-1-ylmethyl)chroman-4-yl)butanamide;

(*S*)-3-chloro-2-fluoro-*N*-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-7-(piperidin-1-ylmethyl)chroman-4-yl)butanamide;

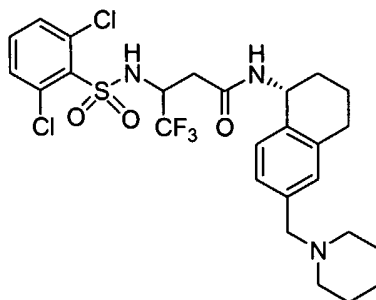
3-(2,3-dichloro-*N*-methylphenylsulfonamido)-2-methyl-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide; and

3-(2,3-dichloro-*N*-methylphenylsulfonamido)-2-hydroxy-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide were made.

Example 15

Synthesis of 3-(2,6-dichlorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide

5



Step A: Synthesis of ethyl 3-(tert-butoxycarbonyl)-4,4,4-trifluorobutanoate

To a 50-mL round-bottomed flask containing ethyl 3-amino-4,4,4-trifluorobutanoate (1.4 g, 81 mmol, Lancaster) in THF (40 mL), was added *t*BOC₂O (27 g, 120 mmol, Aldrich) and sat. K₂CO₃ (35 mL). The reaction was stirred at RT for 8 h. The compound was extracted with EtOAc (2×30 mL) and the combined organic phase was washed with 5% brine (2×20 mL), dried over Na₂SO₄. Purification with column chromatography over silica gel with hexane:EtOAc (5:1) gave the title compound. MS (ESI, pos. ion.) *m/z*: 286 (M+1).

Step B: Synthesis of 3-(tert-butoxycarbonyl)-4,4,4-trifluorobutanoic acid

To a 50-mL round-bottomed flask containing ethyl 3-(tert-butoxycarbonyl)-4,4,4-trifluorobutanoate (12 g, 42 mmol, step A) in THF (15 mL), was added LiOH·H₂O (3.5 g, 84 mmol, Aldrich) and water (10 mL). The reaction was stirred at RT for 6 h. After acidified to pH 5 with 2N HCl, the compound was extracted with EtOAc (2×50 mL). The organic phase was washed with 5% brine (2×20 mL), dried over Na₂SO₄, filtered, and concentrated to yield the title compound. MS (ESI, pos. ion.) *m/z*: 258 (M+1).

Step C: Synthesis of tert-butyl 1,1,1-trifluoro-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butan-2-ylcarbamate

To a 100-mL reaction tube containing 3-(tert-butoxycarbonyl)-4,4,4-trifluorobutanoic acid (0.46 g, 1.8 mmol, step B) in DMF (8 mL), was added (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (0.65 g, 2.7 mmol), TBTU (1.4 g, 3.6 mmol, Advanced ChemTech), and *i*Pr₂EtN (1.3 mL, 7.2 mmol, Aldrich). The reaction was stirred at RT for 5 h. The reaction was quenched with 5% brine (15 mL) and the compound was extracted with EtOAc (2×25 mL). The organic phase was washed with 5% brine (2×10 mL), dried over Na₂SO₄, filtered, and concentrated. Purification with column chromatography over silica gel

with hexane:EtOAc:MeOH (2M, NH₃) (5:5:1) gave the title compound as a light yellow solid. MS (ESI, pos. ion.) *m/z*: 484 (M+1).

Step D: Synthesis of 3-amino-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide bis-hydrochloride

5 To a 50-mL reaction tube containing tert-butyl 1,1,1-trifluoro-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butan-2-ylcarbamate (0.54 g, 1.1 mmol, step C), was added HCl (3.0 mL, 12 mmol, 4.0N in 1,4-dioxane, Aldrich). The reaction was stirred at RT for 2 h, and evaporation in vacuo gave the title compound. MS (ESI, pos. ion.) *m/z*: 384 (M+1).

10 Step E: Synthesis of 3-(2,6-dichlorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide

To a 50-mL round-bottomed flask containing 3-amino-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide bis-hydrochloride 0.12 g, 0.26 mmol, step D), was added 2,6-dichlorobenzene sulfonylchloride (0.19 g, 0.78 mmol, Aldrich) and pyridine (3 mL, Aldrich). After the reaction was stirred at 50 °C for 1.5 h, the solvent was evaporated in vacuo. The residue was taken in EtOAc (20 mL) and was washed with 5% brine (2×8 mL), dried over Na₂SO₄. Purification with column chromatography over silica gel with hexane:EtOAc:MeOH (2M, NH₃) (5:5:1) gave the title compound as a white solid. MS (ESI, pos. ion.) *m/z*: 592 (M+1).

20 Similarly,

3-(2,3-dihydrobenzo[b][1,4]dioxine-6-sulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;

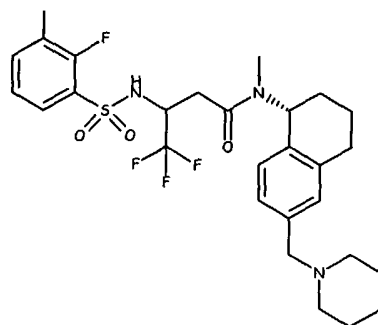
4,4,4-trifluoro-3-(3-methylphenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide; and

25 3-(benzo[c][1,2,5]oxadiazole-4-sulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide were made.

Example 16

Synthesis of 3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide

30



Step A: Synthesis of *(R)*-(5-(methylamino)-5,6,7,8-tetrahydronaphthalen-2-yl)methanol

To a solution of acetic formic anhydride (prepared by stirring 12 mL of acetic anhydride and 4.3 mL of formic acid at 60° C for 2 h then cooling to room temperature) was added 3.0 g of *(R)*-(5-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol. The reaction mixture was stirred at room temp for 3 h. The reaction was monitored by TLC (10% MeOH in EtOAc) of aliquots quenched in sat. NaHCO₃ and extracted with EtOAc. After the reaction was complete the reaction mixture was slowly quenched with sat. NaHCO₃ until the solution was slightly basic and then extracted with EtOAc (2 x 100 mL), washed with brine (1 x 100 mL), and dried with sodium sulfate. After concentration the crude material was dissolved in dry THF (20 mL) and slowly added to lithium aluminum hydride (2.4 g) in THF (75 mL). The reaction mixture was heated to 40° C for 3 h and quenched with sodium potassium tartrate solution. After filtration, the filtrate was diluted with 100 mL of EtOAc, dried with sodium sulfate, and concentrated. Purification by chromatography over silica gel with 0 to 5% MeOH (2M, NH₃) in DCM gave the title compound. MS (ESI, pos. ion) *m/z*: 192 (M+1).

Step B: Synthesis of 3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methylbutanamide

In dry DCM (10 mL), 3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluorobutanoic acid (0.5 mmol) and PyClU (1-(chloro-1-pyrrolidinylmethylene)pyrrolidinium hexafluorophosphate) (0.5 mmol) were combined. *(R)*-(5-(Methylamino)-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (0.6 mmol) and DIEA (1.5 mmol) were added and the mixture was stirred at room temperature under nitrogen for 1 h. The reaction mixture was quenched with 20 mL of saturated sodium bicarbonate, then extracted with EtOAc (2 x 30 mL), washed with brine (1 x 20 mL), dried with sodium sulfate, and concentrated. Purification by chromatography over silica gel with 20 to 60% EtOAc in hexane gave the title compound. MS (ESI, pos. ion) *m/z*: 523 (M+1).

Step C: Synthesis of 3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methylbutanamide

Manganese dioxide (2.5 mmol) was added to a solution of 3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methylbutanamide (0.25 mmol) in 15 mL of DCM. The reaction mixture was stirred at room temp for 4 h, then filtered through celite. The residue was washed repeatedly with EtOAc and MeOH, then the filtrate was concentrated to give the title compound. MS (ESI, pos. ion) *m/z*: 521 (M+1).

Step D: Synthesis of 3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide

In 1,2-dichloroethane (10 mL), 3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methylbutanamide (0.2 mmol) was dissolved. Piperidine (0.6 mmol) and sodium triacetoxyborohydride (0.4 mmol) were added. The reaction mixture was stirred at room temperature under nitrogen overnight, then quenched with saturated sodium bicarbonate. The product was extracted with ethyl acetate (2 x 20 mL), and washed with brine (1 x 20 mL), dried with sodium sulfate, and concentrated. Purification by chromatography over silica gel with 0 to 5% MeOH (2M, NH₃) in DCM gave the title compound. MS (ESI, pos. ion) *m/z*: 590 (M+1).

Similarly,

(*S*)-3-(3-chlorophenylsulfonamido)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;

(*S*)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;

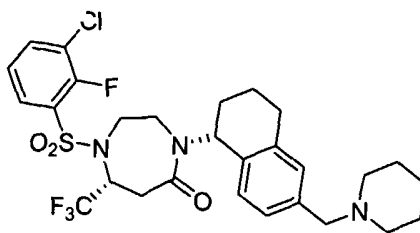
(2*R*,3*S*)-4,4,4-trifluoro-2-hydroxy-*N*-methyl-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;

(*S*)-3-(5-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide; and

(*S*)-3-(2,3-dichlorophenylsulfonamido)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide were made.

Example 17

Synthesis of 1-(3-chloro-2-fluorophenylsulfonyl)-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-7(*R*)-(trifluoromethyl)-1,4-diazepan-5-one



Step A: Synthesis of (*R*)-ethyl 3-(3-chloro-2-fluoro-*N*-(2-oxoethyl)phenylsulfonamido)-4,4,4-trifluorobutanoate:

- 5 A solution of (*R*)-ethyl 3-(*N*-allyl-3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluorobutanoate, prepared according to Reference 14, Step A (776 mg, 1.86 mmol) in *tert*-butanol (15 mL), THF (3 mL) and water (1.5 mL) was treated with osmium tetroxide (567 mg of a 2.5 mol% w/w in *tert*-butanol, 0.05 mmol, 0.03 equiv) and 4-methylmorpholine *N*-oxide (435 mg, 3.72 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 17
- 10 h. A solution of a pH 7.2 phosphate buffer (20 mL) was added, followed by sodium periodate (1.99 g, 9.3 mmol, 5.0 equiv). The white suspension was stirred for 2 h, diluted with saturated ammonium chloride solution (25 mL) and extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (30 mL), dried (MgSO₄) and purified on silica gel using 25% ethyl acetate in hexane as eluant, affording (*R*)-ethyl 3-(3-chloro-2-fluoro-*N*-(2-oxoethyl)phenylsulfonamido)-4,4,4-trifluorobutanoate. MS: 420.2 (M+H)⁺.

Step B: Synthesis of (*R*)-ethyl 3-(3-chloro-2-fluoro-*N*-(2-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)ethyl)phenylsulfonamido)-4,4,4-trifluorobutanoate

- A solution of (*R*)-ethyl 3-(3-chloro-2-fluoro-*N*-(2-oxoethyl)phenylsulfonamido)-4,4,4-trifluorobutanoate (689 mg, 1.64 mmol) in 1,2-dichloroethane (20 mL) was treated with (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (595 mg, 2.43 mmol, 1.48
- 20 equiv), sodium triacetoxyborohydride (700 mg, 3.28 mmol, 2.0 equiv) and catalytic glacial acetic acid (5 drops). After being stirred at room temperature for 16 h, the reaction was diluted with saturated sodium bicarbonate solution (30 mL) and extracted with dichloromethane (3×25 mL). The combined organic layers were dried (MgSO₄) and purified on silica gel using 5% methanol in dichloromethane as eluant, affording (*R*)-ethyl 3-(3-chloro-2-fluoro-*N*-(2-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)ethyl)phenylsulfonamido)-4,4,4-trifluorobutanoate. MS: 648.2 (M+H)⁺.

Step C: Synthesis of (*R*)-3-(3-chloro-2-fluoro-*N*-(2-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)ethyl)phenylsulfonamido)-4,4,4-trifluorobutanoic acid.

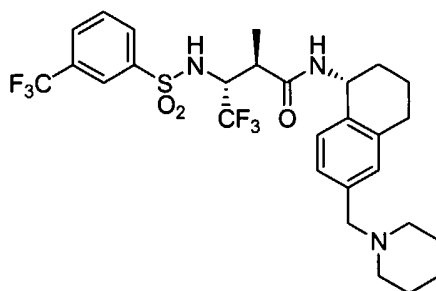
A solution of (*R*)-ethyl 3-(3-chloro-2-fluoro-*N*-(2-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)ethyl)phenylsulfonamido)-4,4,4-trifluorobutanoate (653 mg, 1.01 mmol) in 10% aqueous hydrochloric acid (20 mL) and dioxane (20 mL) was heated to reflux for 24 h. The reaction was cooled to room temperature and concentrated *in vacuo* to afford (*R*)-3-(3-chloro-2-fluoro-*N*-(2-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)ethyl)phenylsulfonamido)-4,4,4-trifluorobutanoic acid as a HCl salt. MS: 620.2 (M+H)⁺.

Step D: Synthesis of (*R*)-1-(3-chloro-2-fluorophenylsulfonyl)-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-7-(trifluoromethyl)-1,4-diazepan-5-one

(*R*)-3-(3-Chloro-2-fluoro-*N*-(2-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)ethyl)phenylsulfonamido)-4,4,4-trifluorobutanoic acid dihydrochloride salt (210 mg, 0.30 mmol) in *N,N*-dimethylformamide (30 mL) was treated triethylamine (0.1 mL, 0.60 mmol, 2.0 equiv). After stirring at room temperature for 10 min, coupling agents HOBt (62 mg, 0.45 mmol, 1.5 equiv) and EDCI (88 mg, 0.45 mmol, 1.5 equiv) were added. The reaction was stirred at room temperature for further 23 h, diluted with saturated sodium bicarbonate solution (40 mL) and extracted with EtOAc (2×40 mL). The combined organic layers were washed with water (40 mL), brine (40 mL), dried (MgSO₄) and purified on silica gel using 5% methanol in dichloromethane as eluant, affording (*R*)-1-(3-chloro-2-fluorophenylsulfonyl)-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-7-(trifluoromethyl)-1,4-diazepan-5-one. MS: 602.1 (M+H)⁺.

Example 18

Synthesis of (2*R*,3*R*)-4,4,4-trifluoro-2-methyl-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide



Step A: Synthesis of (2*R*,3*R*)-ethyl 4,4,4-trifluoro-2-methyl-3-(3-(trifluoromethyl)phenylsulfonamido)butanoate

A solution of (*R*)-ethyl 4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanoate (760 mg, 1.93 mmol) and lithium chloride (410 mg, 9.65 mmol, 5.0 equiv) in

THF (15 mL) was cooled to -78°C and treated with lithium bis(trimethylsilyl)amide (4.85 mL of a 1.0M solution in THF, 4.85 mmol, 2.5 equiv). Methyl iodide (0.24 mL, 3.86 mmol, 2.0 equiv) was added after 30 min, and the bath was allowed to warm to -35°C over 4 h. The reaction was quenched with 9:1 THF:water (5 mL), warmed to room temperature, diluted with ethyl acetate (30 mL), washed with saturated ammonium chloride solution (25 mL) and brine (30 mL), dried (MgSO_4) and purified on silica gel using 20% ethyl acetate in hexane as eluant, affording (2*R*,3*R*)-ethyl 4,4,4-trifluoro-2-methyl-3-(3-(trifluoromethyl)phenylsulfonamido)-butanoate. MS: 408.2 ($\text{M}+\text{H}$)⁺.

Step B: Synthesis of (2*R*,3*R*)-4,4,4-trifluoro-2-methyl-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid

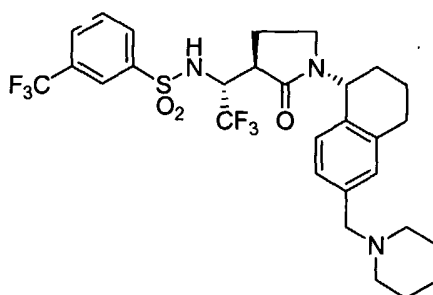
A solution of (2*R*,3*R*)-ethyl 4,4,4-trifluoro-2-methyl-3-(3-(trifluoromethyl)phenylsulfonamido)butanoate (654 mg, 1.60 mmol) in THF (8 mL) and water (2 mL) was treated with lithium hydroxide monohydrate (340 mg, 8.03 mmol, 5.0 equiv). After being stirred at room temperature for 4 days, the reaction was quenched with Dowex-50 acid ion-exchange resin (till the pH was acidic). The resin was filtered and the filtrate was concentrated and azeotroped with toluene (3×10 mL) to remove excess water, affording (2*R*,3*R*)-4,4,4-trifluoro-2-methyl-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid. MS: 380.2 ($\text{M}+\text{H}$)⁺.

Step C: (2*R*,3*R*)-4,4,4-trifluoro-2-methyl-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide.

A solution of (2*R*,3*R*)-4,4,4-trifluoro-2-methyl-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid (275 mg, 0.72 mmol) in *N,N*-dimethylformamide (5 mL) was treated with (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (180 mg, 0.72 mmol, 1.0 equiv), the coupling agent TBTU (346 mg, 1.08 mmol, 1.5 equiv) and *N,N*-diisopropylethylamine (0.31 mL, 1.80 mmol, 2.0 equiv). The reaction was stirred at room temperature for 15 h, diluted with ethyl acetate (15 mL), washed with saturated sodium bicarbonate solution (15 mL), water (15 mL), brine (15 mL) and dried (MgSO_4). The crude mixture was purified on silica gel using 5% methanol in dichloromethane as eluant, affording (2*R*,3*R*)-4,4,4-trifluoro-2-methyl-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide. MS: 606.3 ($\text{M}+\text{H}$)⁺.

Example 19

Synthesis of *N*-((*R*)-2,2,2-trifluoro-1-((*R*)-2-oxo-1-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidin-3-yl)ethyl)-3-(trifluoromethyl)benzene-sulfonamide



Step A: Synthesis of (*R*)-ethyl 2-((*R*)-2,2,2-trifluoro-1-(3-(trifluoromethyl)phenyl)sulfonamido)ethyl)pent-4-enoate

A solution of (*R*)-ethyl 4,4,4-trifluoro-3-(3-(trifluoromethyl)phenyl)sulfonamido)-butanoate (3.26 g, 8.29 mmol) and lithium chloride (1.75 mg, 41.47 mmol, 5.0 equiv) in THF (40 mL) was cooled to -78°C and treated with lithium bis(trimethylsilyl)amide (21.0 mL of a 1.0 M solution in THF, 21.0 mmol, 2.5 equiv). Allyl bromide (1.4 mL, 16.58 mmol, 2.0 equiv) was added after 30 min, and the bath was allowed to warm to 0°C over 7 h. The reaction was quenched with saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (75 mL). The organic layer was washed with brine (50 mL), dried (MgSO_4) and purified on silica gel using 15% ethyl acetate in hexane as eluant, affording (*R*)-ethyl 2-((*R*)-2,2,2-trifluoro-1-(3-(trifluoromethyl)phenyl)sulfonamido)ethyl)pent-4-enoate. MS: 432.2 ($\text{M}-\text{H}^-$).

Step B: Synthesis of (2*R*,3*R*)-ethyl 4,4,4-trifluoro-2-(2-oxoethyl)-3-(3-(trifluoromethyl)phenyl)sulfonamido)-butanoate

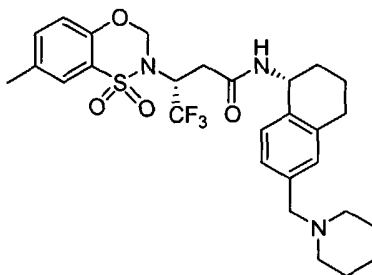
A solution of (*R*)-ethyl 2-((*R*)-2,2,2-trifluoro-1-(3-(trifluoromethyl)phenyl)sulfonamido)ethyl)pent-4-enoate (1.37 g, 3.16 mmol) in *tert*-butanol (30 mL): THF (6 mL): water (3 mL) was treated with osmium tetroxide (965 mg of a 2.5 mol % w/w in *tert*-butanol, 0.09 mmol, 0.03 equiv) and 4-methylmorpholine *N*-oxide (740 mg, 6.32 mmol, 2.0 equiv). The reaction was stirred at room temperature for 15 h. A solution of a pH 7.2 phosphate buffer (40 mL) was added, followed by sodium periodate (3.4 g, 15.8 mmol, 5.0 equiv). The white suspension was stirred for 2 h, diluted with saturated ammonium chloride solution (50 mL) and extracted with EtOAc (3 $\times$ 75 mL). The combined organic layers were washed with brine (75 mL), dried (MgSO_4) and purified on silica gel using 25% ethyl acetate in hexane as eluant, affording (2*R*,3*R*)-ethyl 4,4,4-trifluoro-2-(2-oxoethyl)-3-(3-(trifluoromethyl)phenyl)sulfonamido)butanoate. MS: 434.2 ($\text{M}-\text{H}^-$).

Step C: Synthesis of *N*-((*R*)-2,2,2-trifluoro-1-((*R*)-2-oxo-1-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidin-3-yl)ethyl)-3-(trifluoromethyl)benzene-sulfonamide

A solution of (2*R*,3*R*)-ethyl 4,4,4-trifluoro-2-(2-oxoethyl)-3-(3-(trifluoromethyl)-phenylsulfon-amido)butanoate (333 mg, 0.76 mmol) in 1,2-dichloroethane (8 mL) was treated with (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (206 mg, 0.84 mmol, 1.11 equiv), sodium triacetoxyborohydride (324 mg, 1.53 mmol, 2.0 equiv) and catalytic
 5 glacial acetic acid (5 drops). The reaction was heated at 60 °C for 15 h, diluted with saturated sodium bicarbonate solution (10 mL) and extracted with dichloromethane (3×15 mL). The combined organic layers were washed with brine (20 mL) and dried (MgSO₄). The crude mixture was purified on silica gel using 5% methanol in dichloromethane as eluant, affording
 10 *N*-((*R*)-2,2,2-trifluoro-1-((*R*)-2-oxo-1-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidin-3-yl)ethyl)-3-(trifluoromethyl)benzene-sulfonamide.
 MS: 618.3 (M+H)⁺.

Example 20

Synthesis of (*R*)-4,4,4-trifluoro-3-(1,1-dioxo-7-methylbenzo[e][1,4,3]oxathiazin-2(3*H*)-yl)-*N*-
 15 ((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide



Step A: Synthesis of (*R*)-4,4,4-trifluoro-3-(2-methoxy-5-methylphenylsulfonamido)butanoic acid.

To a 150-mL round-bottomed flask containing 2-methoxy-5-methylbenzene-1-sulfonyl
 20 chloride (0.44 g, 2.0 mmol, Trans World Chemicals) was added (*R*)-ethyl 3-amino-4,4,4-trifluorobutanoate (0.37 g, 2.0 mmol) and pyridine (3 mL). The reaction mixture was stirred at RT for 2 h. Evaporation of the solvents *in vacuo* gave an oily material, which was taken in THF (3 mL). LiOH·H₂O (0.17 g, 4.0 mmol, Aldrich) and water (2 mL) was added and the reaction mixture was stirred at RT for 8 h. The reaction mixture was acidified to pH-5 by
 25 adding 2N HCl and the product was extracted with EtOAc, and the organic phase was separated and washed with 5% brine, dried over Na₂SO₄. Filtration and evaporation *in vacuo* gave title compound (0.47 g, 69%). MS (ESI, pos. ion.) *m/z*: 342 (M+1).

Step B: Synthesis of (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(2-methoxy-5-methylphenylsulfonamido)butanamide.

To a 50-mL round-bottomed flask containing (*R*)-4,4,4-trifluoro-3-(2-methoxy-5-methylphenylsulfonamido)butanoic acid [0.60 g, 1.8 mmol, Step (a)] in DMF (5 mL), was added (*R*)-(5-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (0.31 mg, 1.8 mmol), TBTU (1.3 g, 3.5 mmol, Advanced ChemTech), and *i*Pr₂EtN (1.2 mL, 7.0 mmol, Aldrich). The reaction mixture was stirred at RT for 10 h and then the reaction mixture was quenched with 5% brine (5 mL) then acidified to pH-5 by adding 1 N HCl. The product was extracted with EtOAc (2×10 mL). The organic phase was washed with 5% brine (2×5 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was taken in a solvent mixture of EtOAc:CH₂Cl₂:MeOH (5:5:2) and the product was precipitated. Filtration gave the title compound (0.73 g, 83%) as a pale yellow solid. MS (ESI, pos. ion.) *m/z*: 501 (M+1).

Step C: Synthesis of (*R*)-*N*-((*R*)-6-(bromomethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-4,4,4-trifluoro-3-(2-hydroxy-5-methylphenylsulfonamido)butanamide

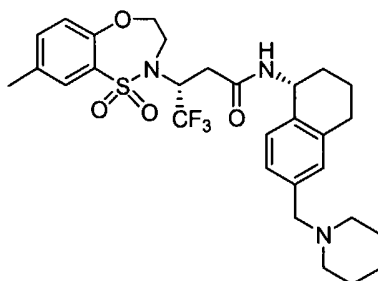
To a 100-mL round-bottomed flask containing a suspension of (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(2-methoxy-5-methylphenylsulfonamido)butanamide [0.73 g, 1.5 mmol, Step (b)] in CH₂Cl₂ (20 mL), was added BBr₃ (15 mL, 15 mmol, Aldrich) through a syringe at 0 °C under N₂. The reaction mixture was then stirred at RT for 12 h. The reaction mixture was cooled to 0 °C with an ice bath, and the reaction was quenched slowly with ice water. The product was extracted with CH₂Cl₂ (2×8 mL). The organic phase was washed with 5% brine (2×10 mL) and the product was precipitated. Filtration gave the title compound (0.68 g, 85%) as a white solid. MS (ESI, neg. ion.) *m/z*: 548 (M-1).

Step D: Synthesis of (*R*)-4,4,4-trifluoro-3-(1,1-dioxo-7-methylbenzo[*e*][1,4,3]oxathiazin-2(3*H*)-yl)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide

To a 100-mL round-bottomed flask containing a solution of (*R*)-*N*-((*R*)-6-(bromomethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-4,4,4-trifluoro-3-(2-hydroxy-5-methylphenylsulfonamido)butanamide [0.16 g, 0.47 mmol, Step (c)] and paraformaldehyde (0.18 g, 6.4 mmol, Aldrich) in 1,4-dioxane (10 mL), was bubbled HCl gas through a tubing for 5 min. The reaction mixture was then stirred at RT for 4 h. The solvent was removed *in vacuo* and the residue was taken in THF (15 mL) and piperidine (0.25 mL, 2.6 mmol, Aldrich) was added. The reaction mixture was stirred at RT for 1 h and then diluted with EtOAc (15 mL). The organic phase was washed with 5% brine (2×8 mL), dried over Na₂SO₄, filtered, and concentrated. Column chromatography over silica gel with hexane:EtOAc:MeOH (2M, NH₃) (10:10:1) gave the title compound (0.12 g, 32%). MS (ESI, pos. ion.) *m/z*: 566 (M+1).

Example 21

Synthesis of (*R*)-4,4,4-trifluoro-3-(1,1-dioxo-8-methyl-3,4-dihydrobenzo[*b*][1,4,5]-oxathiazepin-2-yl)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide



5

Step A: Synthesis of (*R*)-4,4,4-trifluoro-3-(2-methoxy-5-methylphenylsulfonamido)butanoic acid.

To a 150-mL round-bottomed flask containing 2-methoxy-5-methylbenzene-1-sulfonyl chloride (0.44 g, 2.0 mmol, Trans World Chemicals) was added (*R*)-ethyl 3-amino-4,4,4-trifluorobutanoate (0.37 g, 2.0 mmol) and pyridine (3 mL). The reaction mixture was stirred at RT for 2 h. Evaporation of the solvents *in vacuo* gave an oily material, which was taken in THF (3 mL). Then LiOH.H₂O (0.17 g, 4.0 mmol, Aldrich) and water (2 mL) was added. The reaction mixture was stirred at RT for 8 h. The reaction mixture was acidified to pH-5 by adding 2 N HCl and the product was extracted with EtOAc, and the organic phase was separated and washed with 5% brine, dried over Na₂SO₄. Filtration and evaporation *in vacuo* gave title compound (0.47 g, 69%). MS (ESI, pos. ion.) *m/z*: 342 (M+1).

Step B: Synthesis of (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(2-methoxy-5-methylphenylsulfonamido)butanamide

To a 50-mL round-bottomed flask containing (*R*)-4,4,4-trifluoro-3-(2-methoxy-5-methylphenylsulfonamido)butanoic acid [0.60 g, 1.8 mmol, Step (a)] in DMF (5 mL), was added (*R*)-(5-amino-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (0.31 mg, 1.8 mmol), TBTU (1.3 g, 3.5 mmol, Advanced ChemTech), and *i*Pr₂EtN (1.2 mL, 7.0 mmol, Aldrich). The reaction was stirred at RT for 10 h and then quenched with 5% brine (5 mL) and acidified to pH-5 by adding 1 N HCl. The product was extracted with EtOAc (2×10 mL). The organic phase was washed with 5% brine (2×5 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was taken in a solvent mixture of EtOAc:CH₂Cl₂:MeOH (5:5:2) and the product was precipitated. Filtration gave the title compound (0.73 g, 83%) as a pale yellow solid. MS (ESI, pos. ion.) *m/z*: 501 (M+1).

25

Step C: Synthesis of (*R*)-*N*-((*R*)-6-(bromomethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-4,4,4-trifluoro-3-(2-hydroxy-5-methylphenylsulfonamido)butanamide

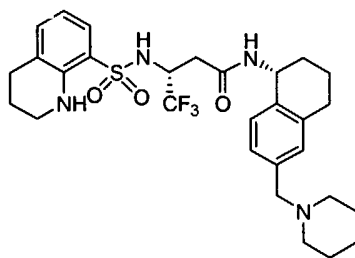
To a 100-mL round-bottomed flask containing a suspension of (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(2-methoxy-5-methylphenylsulfonamido)butanamide [0.73 g, 1.5 mmol, Step (b)] in CH₂Cl₂ (20 mL), was added BBr₃ (15 mL, 15 mmol, Aldrich) through a syringe at 0 °C under N₂. The reaction mixture was then stirred at RT for 12 h. The reaction mixture was cooled to 0 °C with an ice bath, and the reaction was quenched slowly with ice water. The product was extracted with CH₂Cl₂ (2×8 mL). The organic phase was washed with 5% brine (2×10 mL) and the product was precipitated. Filtration gave the title compound (0.68 g, 85%) as a white solid. MS (ESI, neg. ion.) *m/z*: 548 (M-1).

Step D: Synthesis of (*R*)-4,4,4-trifluoro-3-(1,1-dioxo-8-methyl-3,4-dihydrobenzo[*b*][1,4,5]-oxathiazepin-2-yl)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide

To a 100-mL round-bottomed flask containing a solution of (*R*)-*N*-((*R*)-6-(bromomethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-4,4,4-trifluoro-3-(2-hydroxy-5-methylphenylsulfonamido)butanamide [0.35 g, 0.64 mmol, step (c)] in DMF (8 mL), was added 1,2-dibromoethane (0.23 mL, 2.7 mmol, Aldrich) and Cs₂CO₃ (0.83 g, 2.5 mmol, Aldrich). The reaction mixture was then stirred at 55 °C for 3 h. The reaction mixture was diluted with EtOAc (15 mL). The organic phase was washed with 5% brine (2×8 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was taken in THF (6 mL) and piperidine (0.25 mL, 2.6 mmol, Aldrich) was added. The reaction mixture was stirred at 55 °C for 3 h then diluted with EtOAc (15 mL). The organic phase was washed with 5% brine (2×8 mL), dried over Na₂SO₄, filtered, and concentrated. Column chromatography over silica gel with EtOAc gave the title compound (0.16 g, 43%). MS (ESI, pos. ion.) *m/z*: 580 (M+1).

Example 22

Synthesis of (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(1,2,3,4-tetrahydroquinoline-8-sulfonamido)butanamide



Step A: Synthesis of (R)-ethyl 4,4,4-trifluoro-3-(quinoline-8-sulfonamido)butanoate

To a 150-mL round-bottomed flask containing quinoline-8-sulfonyl chloride (1.5 g, 6.6 mmol, Aldrich), was added (R)-ethyl 3-amino-4,4,4-trifluorobutanoate (1.0 g, 5.5 mmol) and pyridine (3 mL). The reaction mixture was stirred at RT for 2 h. Evaporation of the solvents *in vacuo* gave an oily material, which was taken in EtOAc (15 mL), and the organic phase was separated and washed with 5% brine, dried over Na₂SO₄. Filtration and evaporation *in vacuo* gave title compound (1.7 g, 82%). MS (ESI, pos. ion.) *m/z*: 377 (M+1).

Step B: Synthesis of (R)-ethyl 4,4,4-trifluoro-3-(1,2,3,4-tetrahydroquinoline-8-

sulfonamido)butanoate

To a 150-mL round-bottomed flask containing (R)-ethyl 4,4,4-trifluoro-3-(quinoline-8-sulfonamido)butanoate [3.3 g, 8.9 mmol, from the above (a)] in EtOAc:EtOH (1:1, 20 mL), was added 10% Pd/C (0.94 g, 0.89 mmol, Aldrich) and AcOH (3 mL) under N₂. The reaction mixture was purged with H₂ and then stirred at RT for 18 h under H₂ (H₂ balloon) atmosphere. After filtration through Celite, the filtrate was concentrated *in vacuo* to yield the title compound (3.3 g, 98%). MS (ESI, pos. ion.) *m/z*: 381 (M+1).

Step C: Synthesis of (R)-4,4,4-trifluoro-3-(1,2,3,4-tetrahydroquinoline-8-sulfonamido)-butanoic acid.

To a 50-mL round-bottomed flask containing (R)-ethyl 4,4,4-trifluoro-3-(1,2,3,4-tetrahydroquinoline-8-sulfonamido)butanoate [3.3 g, 8.7 mmol, step (b)] in THF (8 mL), was added LiOH.H₂O (1.4 g, 34 mmol, Aldrich) and water (8 mL). The reaction was stirred at 50 °C for 3 h. After acidification to pH 5 with 2 N HCl, the product was extracted with EtOAc (2×50 mL). The organic phase was washed with 5% brine (2×20 mL), dried over Na₂SO₄, filtered, and concentrated to yield the title compound (2.8 g, 91%). MS (ESI, pos. ion.) *m/z*: 535 (M+1).

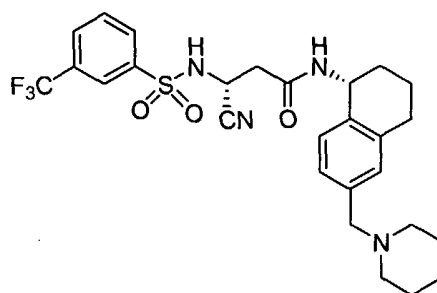
Step D: Synthesis of (R)-4,4,4-trifluoro-N-((R)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(1,2,3,4-tetrahydroquinoline-8-sulfonamido)butanamide.

To a 100-mL reaction tube containing (R)-4,4,4-trifluoro-3-(1,2,3,4-tetrahydroquinoline-8-sulfonamido)butanoic acid [0.16 g, 0.45 mmol, step (c)] in DMF (5 mL), was added (R)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (0.65 g, 2.7 mmol), TBTU (0.34

g, 0.90 mmol, Advanced ChemTech), and *i*Pr₂EtN (0.31 mL, 1.8 mmol, Aldrich). The reaction was stirred at RT for 5 h and then quenched with 5% brine (15 mL). The product was extracted with EtOAc (2×25 mL). The organic phase was washed with 5% brine (2×10 mL), dried over Na₂SO₄, filtered, and concentrated. Purification with column chromatography over silica gel with hexane:EtOAc:MeOH (2M, NH₃) (10:10:1) gave the title compound (0.18 g, 69%) as a light yellow solid. MS (ESI, pos. ion.) *m/z*: 579 (M+1).

Example 23

Synthesis of (*R*)-3-cyano-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)propanamide



Step A: Synthesis of (*R*)-4-amino-4-oxo-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid

To a 150-mL round-bottomed flask containing 3-trifluoromethylbenzenesulfonyl chloride (3.7 g, 15 mmol, Aldrich) in THF (15 mL), was added H-(D)-ASP-NH₂ (2.0 g, 15 mmol, ChemImpex) and 5% K₂CO₃ (15 mL). The reaction mixture was stirred at RT for 5 h. The reaction mixture was acidified to pH-5 by adding 2 N HCl, and the product was extracted with EtOAc (25 mL). The organic phase was separated and washed with 5% brine, dried over Na₂SO₄. Filtration and evaporation *in vacuo* gave title compound (3.8 g, 74%). MS (ESI, pos. ion.) *m/z*: 341 (M+1).

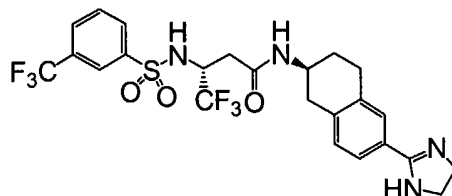
Step B: Synthesis of (*R*)-3-cyano-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)propanamide.

To a 100-mL round-bottomed flask containing (*R*)-4-amino-4-oxo-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid [3.8 g, 11 mmol, step (a)] in DMF (8 mL), was added (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine dihydrochloride (3.9 g, 12 mmol), TBTU (3.6 g, 11 mmol, Advanced ChemTech), and *i*Pr₂EtN (4.3 g, 34 mmol, Aldrich). The reaction mixture was stirred at RT for 5 h and then quenched with 5% brine (15 mL). The product was extracted with EtOAc (2×25 mL). The organic phase was washed with 5% brine (2×10 mL), dried over Na₂SO₄, filtered, and concentrated. Purification

with column chromatography over silica gel with hexane:EtOAc:MeOH (2M, NH₃) (10:10:1) gave the title compound (3.3 g, 54%). MS (ESI, pos. ion.) *m/z*: 549 (M+1).

Example 24

- 5 Synthesis of (*R*)-*N*-((*S*)-6-(4,5-dihydro-1H-imidazol-2-yl)-1,2,3,4-tetrahydro-naphthalen-2-yl)-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide



- 10 Step A: Synthesis of (*S*)-*N*-(6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroacetamide

To a solution of (*S*)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-amine hydrochloride (2.62 g, 10 mmol) in DCM (30 mL) was added trifluoroacetic anhydride (1.554 mL, 11 mmol) followed by triethylamine (4.13 mL, 30 mL). After stirring at RT overnight, the reaction solution was washed with water, dried over Na₂SO₄ and filtered through silica gel pad with

15 DCM to give the title compound (3.24 g, 100%) as a white solid.

Step B: Synthesis of (*S*)-*N*-(6-cyano-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroacetamide

A mixture of (*S*)-*N*-(6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroacetamide (0.969 g, 3 mmol), NiBr₂ (655 mg, 3 mmol) and NaCN (294 mg, 6 mmol)

20 in 3 mL of NMP was heated at 200 °C in microwave for 30 min. After cooling to RT, the reaction mixture was filtered with the help of excess of DCM. The filtrate was evaporated and was submitted to flash chromatography (SiO₂, DCM to DCM/EtOAc = 4:1) to afford the title compound (0.39 g) as a white solid and 0.45 g of recovered starting material.

Step C: Synthesis of (*S*)-6-amino-5,6,7,8-tetrahydronaphthalene-2-carbonitrile

25 To a solution of (*S*)-*N*-(6-cyano-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroacetamide (700 mg, 2.61 mmol) in a mixture of solvents THF/MeOH/H₂O = 8 mL/20 mL/4 mL was added NaOH (209 mg, 5.22 mmol). After stirring at RT for 12 h, the solvent was evaporated and the residue was submitted to flash chromatograph (SiO₂, EtOAc to EtOAc/2 M NH₃ in MeOH = 100:10 to 100:20 to 100:30) to give the title compound (320 mg)

30 as a white solid.

Step D: Synthesis of (*R*)-*N*-((*S*)-6-cyano-1,2,3,4-tetrahydronaphthalen-2-yl)-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide

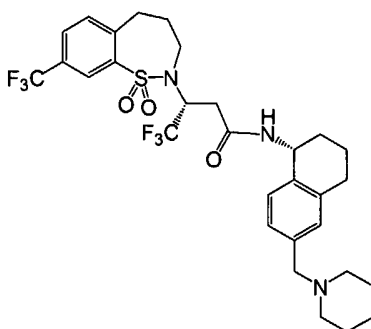
A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (70 mg, 0.364 mmol), 1-hydroxybenzotriazole (49 mg, 0.364 mmol), (*R*)-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid (132.5 mg, 0.363 mmol) and (*S*)-6-amino-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (75 mg, 0.436 mmol) in 1.0 mL of DMF was stirred overnight. The reaction was quenched with Sat. NaHCO₃, extracted with EtOAc/hexane = 3:1, washed with brine, dried over Na₂SO₄, and evaporated. Column chromatography (SiO₂, EtOAc/hexane = 1:2 to 2:3 to 1:1) gave the title compound (120 mg) as a white solid.

Step E: Synthesis of (*R*)-*N*-((*S*)-6-(4,5-dihydro-1H-imidazol-2-yl)-1,2,3,4-tetrahydronaphthalen-2-yl)-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide

(*R*)-*N*-((*S*)-6-cyano-1,2,3,4-tetrahydronaphthalen-2-yl)-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide (90 mg) was azeotroped with benzene and was dissolved in 10 mL of anhydrous EtOH. To this solution dry HCl was bubbled through for 90 min at 0 °C. The solvent was evaporated to dryness under high vacuum to give a yellow solid. This yellow solid was dissolved in 10 mL of dry EtOH. Ethylene diamine (0.4 mL) was added and the resulting solution was stirred at RT overnight. The solvent was evaporated to dryness under high vacuum. Flash chromatography (SiO₂, EtOAc/2M NH₃ in MeOH = 100:15 to 100:30) afforded the title compound (100 mg) as a white solid.

Example 25

Synthesis of (*R*)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-4,4,4-trifluoro-3-[1,1-dioxo-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-1-yl]-butanamide



Step A: Synthesis of (*R*)-ethyl 3-(2-bromo-5-(trifluoromethyl)phenylsulfonamido)-4,4,4-trifluorobutanoate

10 a solution of (*R*)-ethyl 5-amino-4,4,4-trifluorobutanoate (3.25 g, 13 mol) in pyridine (2 mL) was added 2-bromo-5-(trifluoromethyl)benzene-1-sulfonyl chloride (3.72 mL) dropwise. The resulting solution was then stirred at room temperature for 16 h, and then poured into ethyl acetate (50 mL)-ice water mixture. The layers are separated, the aqueous
5 layer is extracted with ethyl acetate (3 x 50 mL) and the combined organic layers are washed with water (3x50 mL) and dried over sodium sulfate. The crude product was purified by silica gel chromatograph to give (*R*)-ethyl 3-(2-bromo-5-(trifluoromethyl)phenylsulfonamido)-4,4,4-trifluorobutanoate (5.7 g) as oil product. LC-MS: m/z 473.9 ($M+H$)⁺.

Step B: Synthesis of (*R*)-ethyl 4,4,4-trifluoro-3-(2-(3-hydroxyprop-1-ynyl)-5-(trifluoromethyl)-phenylsulfonamido)butanoate
10

To a solution of (*R*)-ethyl 3-(2-bromo-5-(trifluoromethyl)phenylsulfonamido)-4,4,4-trifluorobutanoate (100 mg) in toluene (2 mL) was added copper (I) iodide (20 mg), tetrakis(triphenylphosphine) palladium(0) (20 mg), and propargyl alcohol (0.1 mL). The reaction mixture was heated in microwave at 80 °C for 90 min. The reaction mixture was cooled to
15 room temperature and then filtered through celite. The crude product was purified by silica gel chromatograph to give (*R*)-ethyl 4,4,4-trifluoro-3-(2-(3-hydroxyprop-1-ynyl)-5-(trifluoromethyl)phenylsulfonamido)butanoate (50 mg) as oil product. LC-MS: m/z 465.0 ($M+H_2O$)⁺.

Step C: Synthesis of (*R*)-ethyl 4,4,4-trifluoro-3-(2-(3-hydroxypropyl)-5-(trifluoromethyl)-phenylsulfonamido)butanoate
20

To a solution of (*R*)-ethyl 4,4,4-trifluoro-3-(2-(3-hydroxyprop-1-ynyl)-5-(trifluoromethyl)phenylsulfonamido)butanoate (200 mg) in Ethanol (20 mL) was added palladium (10 wt. % on carbon, 50 mg). The reaction solution was stirred under hydrogen balloon for 2 days. It was filtered through celite and concentrated under vacuum to give (*R*)-
25 ethyl 4,4,4-trifluoro-3-(2-(3-hydroxypropyl)-5-(trifluoromethyl)phenylsulfonamido)butanoate (80 mg) as oil product. LC-MS: m/z 469.1 ($M+H$)⁺.

Step D: Synthesis of (*R*)-ethyl-4,4,4-trifluoro-3-[1,1-dioxo-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-1-yl]butanoate

To a solution of (*R*)-ethyl 4,4,4-trifluoro-3-(2-(3-hydroxypropyl)-5-(trifluoromethyl)-phenylsulfonamido)butanoate (100 mg, 0.2 mol) in THF (50 mL) was added diisopropyl azodicarboxylate (60 mg, 0.3 mol) and triphenyl phosphine (75 mg, 0.3 mole) at room temperature. The reaction mixture was stirred at room temperature for 24 hours. Ethyl acetate was added to the reaction mixture and filtered through Celite. The crude product was purified
30

by silica gel preparation TLC plate to give (*R*)-ethyl-4,4,4-trifluoro-3-[1,1-dioxo-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-1-yl]butanoate (80 mg) as an oil.

LC-MS: m/z 434 ($M+H$)⁺; 451 ($M+18$)⁺.

Step E: Synthesis of (*R*)-4,4,4-trifluoro-3-[1,1-dioxo-8-(trifluoromethyl)-2,3,4,5-

5 tetrahydrobenzo[f][1,2]thiazepin-1-yl]butanoic acid

To a solution (*R*)-ethyl-4,4,4-trifluoro-3-[1,1-dioxo-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-1-yl]butanoate (80 mg, 185 μ mol) in dioxane (2 mL), and water (2 mL) was added hydrochloride solution (1 mL, 10%). The reaction mixture was heated in 80 °C oil bath for 1h. The reaction mixture was cooled to room temperature, diluted
10 with ethylacetate (10 ml), and then extracted with Na₂CO₃ solution (10%, 10 mLx2). The basic aqueous layer was acidified with hydrochloride (10%) to pH = 4. It was extracted with methylene chloride (15 mLx3), dried with Na₂SO₄ and concentrated on vacuum to give the title compound as an oil (12 mg, yield: 10%). LC-MS: m/z 403.9 ($M-H$)⁺

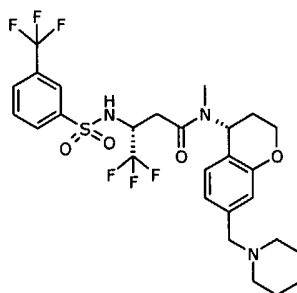
Step F: Synthesis of (*R*)-(*N*)-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-
15 4,4,4-trifluoro-3-[1,1-dioxo-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-1-yl]butanamide

To a solution of (*R*)-4,4,4-trifluoro-3-[1,1-dioxo-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-1-yl]butanoic acid (12 mg) in DMF (2mL) was added TBTU (80 mg), (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (15 mg) and
20 DIEA (0.2 mL) at room temperature. The reaction mixture was stirred at room temperature for 45 min. The reaction mixture was diluted with EtAc (15 mL) and extracted with Na₂CO₃ solution (10%, 10 mLx2). The organic layer was dried with Na₂SO₄ and concentrated on vacuum. The residue was purified by prep-TLC using 5% MeOH (NH₃)-CH₂Cl₂ to give the title compound (12 mg, yield 63%). LC-MS: m/z 632.2 ($M+H$)⁺

25

Example 26

Synthesis of (*R*)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-7-(piperidin-1-ylmethyl)chroman-4-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide



Step A: Synthesis of (*R*)-tert-butyl 7-(hydroxymethyl)chroman-4-ylcarbamate

To (*R*)-(4-aminochroman-7-yl)methanol (10 g) was added ethyl acetate (30 mL), DCM (30 mL), methanol (30 mL), and TEA (30 mL). Di-*t*-butyldicarbonate (18 g, 280 mmol) was slowly added and the mix was stirred under nitrogen overnight. The reaction mixture was then concentrated, dissolved in ethyl acetate (300 mL), and washed with saturated sodium carbonate (50 mL) twice. The ethyl acetate layer was then dried with sodium sulfate and concentrated to give the title compound (14 g).

Step B: Synthesis of (*R*)-4-aminochroman-7-carbaldehyde.

In DCM (200 mL), (*R*)-tert-butyl 7-(hydroxymethyl)chroman-4-ylcarbamate (5 g) and manganese oxide (7.5 g) were combined and the reaction mixture was stirred under nitrogen overnight. The solution was then filtered through celite and the pad was washed with methanol. The filtrate was then concentrated to give the title compound (4.65 g) which was used in the next step without further purification.

Step C: Synthesis of (*R*)-tert-butyl 7-(piperidin-1-ylmethyl)chroman-4-ylcarbamate

In 1,2-dichloroethane (100 mL), (*R*)-4-aminochroman-7-carbaldehyde (4.65 g) and piperidine (2.8 g) were combined. Sodium triacetoxy borohydride (6.9 g) was added and the reaction mixture was stirred under nitrogen overnight. The reaction mixture was then dissolved in ethyl acetate, washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and concentrated. The crude product was then purified on silica using 0 to 20% MeOH (2 M ammonia) in DCM to give the title compound (4.6 g).

Step D: Synthesis of (*R*)-7-(piperidin-1-ylmethyl)chroman-4-amine

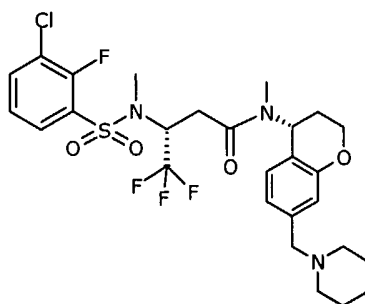
In dry toluene (200 mL), (*R*)-tert-butyl 7-(piperidin-1-ylmethyl)chroman-4-ylcarbamate (4.6 g) and lithium aluminum hydride (1.5 g, 41 mmol) were combined and gently refluxed for 24 h. The reaction mixture was quenched with 5 g of sodium sulfate decahydrate and allowed to stir for 2 h. The reaction mixture was then filtered over celite and the pad was washed with ethyl acetate several times. The filtrate was then concentrated and the crude was purified on silica using 0 to 20% MeOH (2 M ammonia) in ethyl acetate to give the title compound (1.7 g). MS (ESI, pos. ion) m/z 261.7

Step E: Synthesis of (*R*)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-7-(piperidin-1-ylmethyl)chroman-4-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide

In dry DMF (2 mL), (*R*)-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenyl-sulfonamido)-butanoic acid (0.50 mmol) and PyClU (0.60 mmol) are combined. (*R*)-7-(piperidin-1-ylmethyl)chroman-4-amine (0.57 mmol), and DIEA (1.71 mmol) were added and the reaction mixture was stirred at room temperature under nitrogen for 1 h. The reaction mixture was quenched with 20 mL saturated sodium bicarbonate, then extracted with EtOAc (2 x 30 ml), washed with brine (1 x 20 ml), dried with sodium sulfate, and concentrated. Purification by chromatography over silica gel with 20 to 60% EtOAc in hexane gave the title compound. MS (ESI, pos. ion) *m/z* 608.2

Example 27

Synthesis of (*R*)-3-(3-chloro-2-fluoro-*N*-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-7-(piperidin-1-ylmethyl)chroman-4-yl)butanamide



Step A: Synthesis of (*R*)-tert-butyl 7-(hydroxymethyl)chroman-4-ylcarbamate

To (*R*)-(4-aminochroman-7-yl)methanol (10 g) was added ethyl acetate (30 mL), DCM (30 mL), methanol (30 mL), and TEA(30 mL). Di-t-butyl dicarbonate (18 g, 280 mmol) was slowly added and the mix was stirred under nitrogen overnight. The reaction mixture was then concentrated, dissolved in 300 mL of ethyl acetate, and washed with 50 mL of saturated sodium carbonate twice. The ethyl acetate layer was then dried with sodium sulfate and concentrated to give the title compound (14 g).

Step B: Synthesis of (*R*)-4-aminochroman-7-carbaldehyde

In DCM (200 mL), (*R*)-tert-butyl 7-(hydroxymethyl)chroman-4-ylcarbamate (5 g) and manganese oxide (7.5 g) were combined and the mix was stirred under nitrogen overnight. The solution was then filtered through celite and the pad was washed with methanol. The filtrate was then concentrated to give the title compound (4.65 g).

Step C: Synthesis of (R)-tert-butyl 7-(piperidin-1-ylmethyl)chroman-4-ylcarbamate

In 1,2-dichloroethane (100 mL), ((R)-4-aminochroman-7-carbaldehyde (4.65) and piperidine (2.8 g) were combined. Sodium triacetoxo borohydride (6.9 g) was added and the reaction mixture was stirred under nitrogen overnight. The reaction mixture was then dissolved in 100 mL of ethyl acetate, washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and concentrated. The crude was then purified on silica using 0 to 20% MeOH (2 M ammonia) in DCM to give the title compound (4.6 g).

Step D: Synthesis of (R)-7-(piperidin-1-ylmethyl)chroman-4-amine

In dry toluene (200 mL), (R)-tert-butyl 7-(piperidin-1-ylmethyl)chroman-4-ylcarbamate (4.6 g) and lithium aluminum hydride (1.5 g, 41 mmol) were combined and gently refluxed for 24 h. The reaction mixture was quenched with sodium sulfate decahydrate (5 g) and allowed to stir for 2 h. The reaction mixture was then filtered over celite and the pad was washed with ethyl acetate several times. The filtrate was then concentrated and the crude was purified on silica using 0 to 20% MeOH (2 M ammonia) in ethyl acetate to give the title compound (1.7 g).

MS (ESI, pos. ion) m/z 261.7

Step E: Synthesis of (R)-3-(3-chloro-2-fluoro-N-methylphenylsulfonamido)-4,4,4-trifluoro-N-methyl-N-((R)-7-(piperidin-1-ylmethyl)chroman-4-yl)butanamide

In dry DMF (2 mL), (R)-3-(3-chloro-2-fluoro-N-methylphenylsulfonamido)-4,4,4-trifluorobutanoic acid (0.5 mmol) and PyCIU (0.6 mmol) were combined. (R)-7-(Piperidin-1-ylmethyl)chroman-4-amine (0.57 mmol), and DIEA (1.71 mmol) were added and the reaction mixture was stirred at room temperature under nitrogen for 1 h. The reaction mixture was quenched with saturated sodium bicarbonate, then extracted with EtOAc (2 x 30 ml), washed with brine (1 x 20 ml), dried with sodium sulfate, and concentrated. Purification by chromatography over silica gel with 20 to 60% EtOAc in hexane gave the title compound. MS

(ESI, pos. ion) m/z 606.1

Biological Testing

Although the pharmacological properties of the compounds of Formula (I) vary with structural change, in general, activity possessed by compounds of Formula (I) may be demonstrated *in vivo*. The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological *in vitro* assays. The exemplified pharmacological assays, which follow, have been carried out with the compounds according to the invention and their salts. Compounds of the present invention showed binding IC_{50} 's of B1 at doses less than 20 μ M.

Human Bradykinin B1 Receptor and human B2 Receptor *In Vitro* Binding Assays

Example 1

Radioligand Binding Assay for human B1 and human B2 bradykinin receptor

5 Step 1 Preparation of membranes expressing human B1 bradykinin receptor:

Membranes were prepared from CHO-d⁻AQN cells stably transfected with human bradykinin B1 receptor cDNA. For large-scale production of membranes, cells were grown in 100L suspension culture to 1.0E8 cells/mL then harvested using the Viafuge at continuous centrifugation of 1000g. For pilot studies, cells were grown in 2 L spinner culture and
10 harvested by centrifugation (1900 g, 10 min, 4 °C). The cell pellet was washed with PBS, centrifuged (1900 g, 10 min, 4 °C), then the cells resuspended in lysis buffer (25 mM HEPES, pH 7.4, 5 mM EDTA, 5 mM EGTA, 3 mM MgCl₂, 10% (w/v) sucrose, Complete Protease Inhibitor tablets (EDTA-free)) to a density of 14% w/v for passage through a microfluidizer (Microfluidics 110S, 3 passes, 6,000 psi). The resulting cell lysate was centrifuged (1900g, 10
15 min, 4 °C), and the crude particulate fraction isolated by centrifugation (142,000g, 1 h, 4 °C) of the low-speed supernatant. The resulting pellet was resuspended in 1/3 the original lysis buffer volume, homogenized, and recentrifuged as above. The membrane pellet was resuspended by homogenization in storage buffer (25 mM HEPES, pH 7.4, 3 mM MgCl₂, 10% (w/v) sucrose and Complete Protease Inhibitor tablets (EDTA-free)). Single-use aliquots were made and
20 flash-frozen in liquid N₂ prior to storage at -80 °C.

Membranes containing human bradykinin B2 receptor were purchased from Receptor Biology (now Perkin Elmer Life Sciences). They were derived from a CHO-K1 line stably expressing the human B2 receptor developed by Receptor Biology and subsequently purchased by Amgen. For some studies, membranes were prepared in-house from this same cell line
25 using the method described for human B1 receptor membranes, except cells were grown in roller bottles and harvested using Cellmate.

Step 2 Human B1 receptor binding assay was performed in 96-well polypropylene plates (Costar 3365) by adding 50 µl [³H] des-arg¹⁰ kallidin (NET1064; Perkin Elmer Life Sciences) to 10 µL test compound diluted in 90 µL assay buffer (24 mM TES, pH 6.8, 1 mM 1,10 *o*-
30 phenanthroline, 0.3% BSA, 0.5 mM Pefabloc SC, 2 µg/mL aprotinin, 5 µg/mL leupeptin, and 0.7 µg/mL pepstatin A). Membranes (50 µL) were added last. [³H] des-arg¹⁰ kallidin was diluted from stock into assay buffer to yield a final concentration of ~0.3nM in the assay but was adjusted as needed to ensure a concentration at or below the K_d determined for each batch of receptor membranes. Nonspecific binding was defined with 2 µM des-Arg¹⁰Leu⁹ kallidin.

Membranes were diluted in assay buffer to yield a final concentration of 0.068 nM hB1 receptor in the assay. Compounds were solubilized in either DMSO or ddH₂O, plated into polypropylene plates (Costar 3365), then serially diluted in either DMSO or dilution buffer (20 mM Hepes, pH 7.6, 0.1% BSA) to yield a final concentration of either 5% DMSO or no DMSO in the assay. The assay mixture was incubated with shaking for 1 h at RT and then filtered through GF/C plates presoaked in 0.5% polyethyleneimine (Unifilter; Perkin Elmer Life Sciences) using a Filtermate 96-well harvester (Perkin Elmer Life Sciences). Filter plates were rapidly washed 6 times with 200 μ L ice-cold buffer (50mM Tris, pH 7.4), dried in a vacuum oven at 55 °C for 15-20 min, backed, and 40 μ L per well of Microscint 20 was added. The plates were sealed and activity read on Topcount (Perkin Elmer Life Sciences) using a count time of 3 min per channel.

For human B2 bradykinin receptor, the same procedure was followed with the following exceptions: [³H] bradykinin (NET706; Perkin Elmer Life Sciences) was used at a final concentration of ~0.2 nM and non-specific binding was defined with 2 μ M bradykinin. Human B2 receptor concentration was 0.068 nM final in the assay.

Data analysis

Data was analyzed in *XLFit* with the four-parameter logistic $y = A + ((B - A)/(1 + ((C/x)^D)))$ and fit with the Levenburg-Marquardt algorithm. Raw cpm were converted to percent of control values prior to analysis ($POC = ((\text{compound cpm} - \text{nonspecific cpm}) / (\text{no-compound cpm} - \text{nonspecific cpm}) * 100)$). K_i values were determined from the IC_{50} using the Cheng-Prusoff equation and K_d values determined by direct saturation binding of the radioligands.

Example 2

In vitro B1-Inhibition Activity

25 *In vitro* Assay of human B1 Receptor Function using Calcium Flux

Activation of the G_q linked B1 receptor results in an increase in intracellular calcium. The calcium sensitive photoprotein aequorin can, therefore, be used as an indicator of B1 receptor activation. Aequorin is a 21-kDa photoprotein that forms a bioluminescent complex when linked to the chromophore cofactor coelenterazine. Following the binding of calcium to this complex, an oxidation reaction of coelenterazine results in the production of apoaequorin, coelenteramide, CO₂, and light that can be detected by conventional luminometry.

A stable CHO D-hB1/Aequorin cell line was established and the cells were maintained in suspension in spinner bottles containing a 1:1 ratio of DMEM and HAM F12 (Gibco 11765-047), high glucose (Gibco 11965-084), 10% Heat Inactivated Dialyzed serum (Gibco 26300-

061), 1X Non-Essential Amino Acids (Gibco 11140-050), 1X Glutamine-Pen-Strep (Gibco 10378-016), and Hygromycin, 300 µg/mL (Roche 843555). 15-24 h prior to the luminometer assay, 25,000 cells/well (2.5E6 cells/10 mL/plate) were plated in 96-well black-sided clear bottom assay plates (Costar #3904).

5 Media was removed from the wells and replaced with 60 µL of serum free HAM's F12 with 30 mM HEPES (pH 7.5) and 15µM coelenterazine (Coelenterazine h Luciferin #90608 from Assay Designs). The plates were incubated for 1.5-2 h. Ten point IC₅₀ compound plates containing 1:3 or 1:5 dilutions of antagonist compounds and an agonist activator plate (20nM des-Arg10-Kallidin final concentration, EC₈₀) were prepared using Ham's F12 with 30mM
10 HEPES, pH 7.5. Following coelenterazine incubation, an automated flash-luminometer platform was used to dispense the B1 antagonist compounds (dissolved in DMSO and diluted with buffer to the desired concentration (final DMSO concentration <1% DMSO)) to the cell plate, a CCD camera situated underneath the cell plate took 12 images of the cell plate at 5 second intervals to determine if there was any agonist activity with the compounds. The hB1
15 agonist, des-Arg₁₀-Kallidin, was added to the cell plate and another 12 images were recorded to determine the IC₅₀ of the antagonist(s).

In vitro Assay of hB2 Receptor Function using Calcium Flux

The intracellular calcium flux induced by hB2 receptor activation was analyzed using an hB2 recombinant cell line (CHO-K1) purchased from PerkinElmer (Catalog Number:
20 RBHB2C000EA) on a fluorometric imaging plate reader (FLIPR). The cells were cultured in T225 flask containing Ham's F12 Nutrient Mixture (Invitrogen Corp., Cat # 11765-047), 10% Fetal Clone II Bovine Serum (HyClone, Cat # SH3006603), 1 mM Sodium pyruvate (100 mM stock, Invitrogen Corp., Cat# 12454-013), and 0.4 mg/mL Geneticin (G418; 50 mg/mL active geneticin, Invitrogen, Cat# 10131-207). Culture medium was changed every other day. 24 h
25 prior to the FLIPR assay, the hB2/CHO cells were washed once with PBS (Invitrogen) and 10 mL of Versene (1:5000, Invitrogen, Cat# 15040-066) was added to each flask. After 5 min incubation at 37 °C, Versene was removed and cells were detached from the flask and resuspended in culture medium. Cells were counted and 25,000 cells/well were plated in 96-well black-sided clear bottom assay plates (Costar #3904). Cells were incubated in a 37 °C
30 CO₂ incubator overnight.

The media was aspirated from the cells and replaced with 65 µL of dye-loading buffer. The loading buffer was prepared by diluting a stock solution of 0.5mM Fluo-4 AM (Molecular Probes, dissolved in DMSO containing 10% [w/v] pluronic acid) to a concentration of 1µM in Clear Dulbecco's Modified Eagle Medium (DMEM) containing 0.1% BSA, 20 mM HEPES,

and 2.5 mM probenecid. The cells were dye-loaded for 1 h at RT. The excess dye was removed by washing the cells 2x with assay buffer. The assay buffer consists of Hank's Balanced Salt Solution (HBSS) containing 20 mM HEPES, 0.1% BSA, and 2.5 mM probenecid. After the wash cycles, a volume of 100 μ L was left in each well, and the plate was ready to be assayed in the FLIPR System. Single point (10 μ M final concentration) POC antagonist compound plates or ten point IC₅₀ compound plates containing 1:3 or 1:5 dilutions of antagonist compounds (dissolved in DMSO and diluted with buffer to the desired concentration (final DMSO concentration <1% DMSO)) and an agonist activator plate (0.3 nM bradykinin final concentration, EC₈₀) were prepared using assay buffer. The cell plate and the compound plates were loaded onto the FLIPR and during the assay, fluorescence readings are taken simultaneously from all 96 wells of the cell plate. Ten 1-second readings were taken to establish a stable baseline for each well, then 25 μ L from the B1 antagonist plate was rapidly (50 μ L/sec.) added. The fluorescence signal was measured in 1-second (1 min) followed by 6-second (2 min) intervals for a total of 3 min to determine if there is any agonist activity with the compounds. The B2 agonist, bradykinin, was added to the cell plate and another 3 min were recorded to determine the percent inhibition at 10 μ M (POC plates) or the IC₅₀ of the antagonist.

Example 3

Cell and Tissue based *In Vitro* Assays of hB1 Receptor Binding

These studies established the antagonist activity of several compounds at the bradykinin B1 receptors in *in vitro* cell-based and isolated organ assays.

1. Rabbit endothelial cell B1-specific PGI₂ secretion Assay
2. B1 and B2 umbilical vein Assay

In vitro B1-Inhibition Activity:

The effectiveness of the compounds as inhibitors of B1 activity (i.e., B1 "neutralization") can be evaluated by measuring the ability of each compound to block B1 stimulated CGRP and substance P release and calcium signaling in Dorsal Root Ganglion (DRG) neuronal cultures.

Dorsal Root Ganglion Neuronal Cultures:

Dorsal root ganglia are dissected one by one under aseptic conditions from all spinal segments of embryonic 19-day old (E19) rats that are surgically removed from the uterus of timed-pregnant, terminally anesthetized Sprague-Dawley rats (Charles River, Wilmington, MA). DRG are collected in ice-cold L-15 media (GibcoBRL, Grand Island, NY) containing 5% heat inactivated horse serum (GibcoBRL), and any loose connective tissue and blood

vessels are removed. The DRG are rinsed twice in Ca^{2+} - and Mg^{2+} -free Dulbecco's phosphate buffered saline (DPBS), pH 7.4 (GibcoBRL). The DRG are dissociated into single cell suspension using a papain dissociation system (Worthington Biochemical Corp., Freehold, NJ). Briefly, DRG are incubated in a digestion solution containing 20 U/mL of papain in Earle's

- 5 • Balanced Salt Solution (EBSS) at 37 °C for fifty minutes. Cells are dissociated by trituration through fire-polished Pasteur pipettes in a dissociation medium consisting of MEM/Ham's F12, 1:1, 1 mg/mL ovomucoid inhibitor and 1 mg/mL ovalbumin, and 0.005% deoxyribonuclease I (DNase). The dissociated cells are pelleted at 200 x g for 5 min and re-suspended in EBSS containing 1 mg/mL ovomucoid inhibitor, 1 mg/mL ovalbumin and
- 10 0.005% DNase. Cell suspension is 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, then filtered through a 88- μM nylon mesh (Fisher Scientific, Pittsburgh, PA) to remove any clumps. Cell number is determined with a hemocytometer, and cells are seeded into poly-ornithine 100 $\mu\text{g/mL}$ (Sigma, St. Louis, MO) and mouse laminin 1 $\mu\text{g/mL}$ (GibcoBRL)-coated
- 15 96-well plates at 10×10^3 cells/well in complete medium. The complete medium consists of minimal essential medium (MEM) and Ham's F12, 1:1, penicillin (100 U/mL), streptomycin (100 $\mu\text{g/mL}$), and 10% heat inactivated horse serum (GibcoBRL). The cultures are kept at 37 °C, 5% CO_2 and 100% humidity. For controlling the growth of non-neuronal cells, 5-fluoro-2'-deoxyuridine (75 μM) and uridine (180 μM) are included in the medium.

- 20 Two hours after plating, cells are treated with recombinant human β -b1 or recombinant rat β -b1 at a concentration of 10 mg/ml (0.38 nM). Positive controls comprising serial-diluted anti-b1 antibody (r&d systems, minneapolis, mn) are applied to each culture plate. Compounds are added at ten concentrations using 3.16-fold serial dilutions. All samples are diluted in complete medium before being added to the cultures. Incubation time is generally
- 25 around 40 h prior to measurement of vr1 expression.

Measurement of VR1 Expression in DRG Neurons:

- Cultures are fixed with 4% paraformaldehyde in Hanks' balanced salt solution for 15 min, blocked with Superblock (Pierce, Rockford, IL), and permeabilized with 0.25% Nonidet P-40 (Sigma) in Tris.HCl (Sigma)-buffered saline (TBS) for 1 h at RT. Cultures are rinsed
- 30 once with TBS containing 0.1% Tween 20 (Sigma) and incubated with rabbit anti-VR1 IgG (prepared at Amgen) for 1.5 h at RT, followed by incubation of Eu-labeled anti-rabbit second antibody (Wallac Oy, Turku, Finland) for 1 h at RT. Washes with TBS (3 x five min with slow shaking) are applied after each antibody incubation. Enhance solution (150 mL/well, Wallac Oy) is added to the cultures. The fluorescence signal is measured in a time-resolved

fluorometer (Wallac Oy). VR1 expression in samples treated with the compounds is determined by comparing to a standard curve of B1 titration from 0–1000 ng/mL. Percent inhibition (compared to maximum possible inhibition) of B1 effect on VR1 expression in DRG neurons is determined by comparing to controls that are not B1-treated.

5

Example 4

In vivo antinociceptive activity in rat and monkey pain models

Rat Neuropathic Pain Model

Male Sprague-Dawley rats (200 g) are anesthetized with isoflurane inhalant anesthesia and the left lumbar spinal nerves at the level of L5 and L6 are tightly ligated (4-0 silk suture) distal to the dorsal root ganglion and prior to entrance into the sciatic nerve, as first described by Kim and Chung (Kim, S.H.; Chung, J.M. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. *Pain* 50:355-363, (1992)). The incisions are closed and the rats are allowed to recover. This procedure results in mechanical (tactile) allodynia in the left hind paw as assessed by recording the pressure at which the affected paw (ipsilateral to the site of nerve injury) was withdrawn from graded stimuli (von Frey filaments ranging from 4.0 to 148.1 mN) applied perpendicularly to the plantar surface of the paw (between the footpads) through wire-mesh observation cages. A paw withdrawal threshold (PWT) was determined by sequentially increasing and decreasing the stimulus strength and analyzing withdrawal data using a Dixon non-parametric test, as described by Chaplan et al. (Chaplan, S.R.; Bach, F.W.; Pogrel, J.W.; Chung, J.M.; Yaksh, T.L. Quantitative assessment of tactile allodynia in the rat paw. *J. Neurosci. Meth.*, 53:55-63 (1994)).

Normal rats and sham surgery rats (nerves isolated but not ligated) withstand at least 148.1 mN (equivalent to 15 g) of pressure without responding. Spinal nerve ligated rats respond to as little as 4.0 mN (equivalent to 0.41 g) of pressure on the affected paw. Rats are included in the study only if they did not exhibit motor dysfunction (e.g., paw dragging or dropping) and their PWT was below 39.2 mN (equivalent to 4.0 g). At least seven days after surgery rats are treated with compounds (usually a screening dose of 60 mg/kg) or control diluent (PBS) once by s.c. injection and PWT was determined each day thereafter for 7 days.

30 Rat CFA Inflammatory Pain Model

Male Sprague-Dawley rats (200 g) are lightly anesthetized with isoflurane inhalant anesthesia and the left hindpaw is injected with complete Freund's adjuvant (CFA), 0.15 mL. This procedure results in mechanical (tactile) allodynia in the left hind paw as assessed by recording the pressure at which the affected paw is withdrawn from graded stimuli (von Frey

filaments ranging from 4.0 to 148.1 mN) applied perpendicularly to the plantar surface of the paw (between the footpads) through wire-mesh observation cages. PWT is determined by sequentially increasing and decreasing the stimulus strength and analyzing withdrawal data using a Dixon non-parametric test, as described by Chaplan et al. (1994). Rats are included in the study only if they do not exhibit motor dysfunction (e.g., paw dragging or dropping) or broken skin and their PWT is below 39.2 mN (equivalent to 4.0 g). At least seven days after CFA injection rats are treated with compounds (usually a screening dose of 60 mg/kg) or control solution (PBS) once by s.c. injection and PWT is determined each day thereafter for 7 days. Average paw withdrawal threshold (PWT) is converted to percent of maximum possible effect (%MPE) using the following formula: $\%MPE = 100 * (PWT \text{ of treated rats} - PWT \text{ of control rats}) / (15 - PWT \text{ of control rats})$. Thus, the cutoff value of 15 g (148.1 mN) is equivalent to 100% of the MPE and the control response is equivalent to 0% MPE.

At the screening dose of 60 mg/kg, compounds in vehicle are expected to produce an antinociceptive effect with a PD relationship.

Example 5

Green Monkey LPS Inflammation Model

The effectiveness of the compounds as inhibitors of B1 activity are evaluated in Male green monkeys (*Cercopithecus aethiops St Kitts*) challenged locally with B1 agonists essentially as described by deBlois and Horlick (British Journal of Pharmacology, 132:327-335 (2002), which is hereby incorporated by reference in its entirety).

In order to determine whether compounds of the present invention inhibit B1 induced oedema the studies described below are conducted on male green monkeys (*Cercopithecus aethiops St Kitts*) at the Caribbean Primates Ltd. experimental farm (St Kitts, West Indies). Procedures are reviewed and accepted by the Animal Care Committees of the CR-CHUM (Montreal, Canada) and of Caribbean Primates Ltd. (St Kitts, West Indies). Animals weighing 6.0 ± 0.5 kg ($n=67$) were anaesthetized ($50 \text{ mg ketamine kg}^{-1}$) and pretreated with a single intravenous injection of LPS ($90 \mu\text{g kg}^{-1}$) or saline (1 mL) *via* the saphenous vein.

Inflammation studies

Kinin-induced oedema is evaluated by the ventral skin fold assay (Sciberras *et al.*, 1987). Briefly, anaesthetized monkeys were injected with captopril (1 mg kg^{-1} 30 min before assay). A single subcutaneous injection of dKD, BK or the vehicle (2 mM amastatin in 100 μL Ringer's lactate) is given in the ventral area and the increase in thickness of skin folds is monitored for 30–45 min using a calibrated caliper. The results are expressed as the difference

between the skin fold thickness before and after the subcutaneous injection. Captopril and amastatin are used to reduce degradation of kinins at the carboxyl- and amino-terminus, respectively.

Antagonist schild analysis:

- 5 The dose-response relationship for dKD (1–100 nmol)-induced oedema is determined at 24 h post-LPS in the absence or presence of different concentrations of antagonist. BK (30 nmol) is used as a positive control.

Antagonist time course

- 10 The time course of inhibition by antagonist is determined at 4, 24 and 48 h, 72 and/or 96 h after single bolus administration. BK (30 nmol) is used as a positive control.

Drugs

Ketamine hydrochloride, LPS, amastatin and captopril are from Sigma (MO, U.S.A.). All peptides are from Phoenix Pharmaceuticals (CA, U.S.A.).

Statistics

- 15 Values are presented as mean $\pm$ standard error of the mean (s.e. mean). In edema studies, the pre-injection thickness of the skin folds was subtracted from the values after subcutaneous challenge. Curve fitting and EC₅₀ calculations were obtained using the Delta Graph 4.0 software for Apple Computers. Data were compared by two-way analysis of variance followed by unpaired, one tail Student's *t*-test with Bonferroni correction. *P* < 0.05 was
20 considered statistically significant.

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.

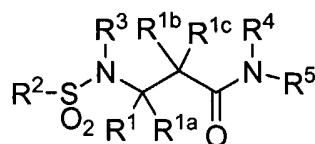
- 25 From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

- 30 No unacceptable toxological effects are expected when compounds of the present invention are administered in accordance with the present invention.

All mentioned references, patents, applications and publications, are hereby incorporated by reference in their entirety, as if here written.

WHAT IS CLAIMED IS:

1. A compound of of Formula (I):



(I)

wherein:

- R^1 is selected from H, cyano, $-C(O)OC_{1-8}alkyl$, $-C(O)OH$, $-C(=O)NR^aR^a$, or $-C_{1-8}alkyl$ substituted by 0, 1, 2, or 3 groups independently selected from R^g , cyano, oxo, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms independently selected from Br, Cl, F and I;

R^{1a} and R^{1b} are each independently, H, F, Cl, $-OCH_3$, $-C_{1-2}alkyl$ or $-CF_3$;

- R^{1c} is H, $-C_{1-8}alkyl$, $-C_{1-4}haloalkyl$, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, or $-C_{1-6}alkyl$ substituted by 0, 1, 2 or 3 substituents selected from $-C_{1-4}haloalkyl$, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

- R^2 is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic hydrocarbon ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents independently selected from R^c , R^g , $C_{1-4}haloalkyl$, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$,

- OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a,
 -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b,
 -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
 -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b,
 5 -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and the ring is additionally
 substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I;
 R³ is H, phenyl, benzyl or -C₁₋₆alkyl, the phenyl, benzyl and -C₁₋₆alkyl being
 substituted by 0, 1, 2 or 3 substituents independently selected from R^c, R^g, -C₁₋₄haloalkyl, halo,
 cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b,
 10 -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b,
 -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b,
 -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a,
 -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and
 -NR^aC₂₋₆alkylOR^a, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atom selected from Br,
 15 Cl, F and I;
 R⁴ is H, phenyl, benzyl or -C₁₋₆alkyl, the phenyl, benzyl and -C₁₋₆alkyl being substituted
 by 0, 1, 2 or 3 substituents independently selected from C₁₋₄alkyl, C₁₋₃haloalkyl, -OC₁₋₄alkyl,
 -NH₂, -NHC₁₋₄alkyl, and -N(C₁₋₄alkyl)C₁₋₄alkyl, and additionally substituted by 0, 1, 2, 3, 4, 5
 or 6 atom selected from Br, Cl, F and I;
 20 R⁵ is a saturated, partially saturated or unsaturated 8-, 9-, 10- or 11-membered bicyclic
 or 12-, 13-, 14- or 15- membered tricyclic hydrocarbon ring containing 0, 1, 2, 3 or 4 atoms
 selected from N, O and S, wherein the carbon and sulfur atoms of the ring are substituted by 0,
 1 or 2 oxo groups and the ring is substituted by R⁶, R⁷ or R⁸ independently selected from basic
 moieties, and additionally substituted by 0, 1, 2 or 3 substituents independently selected from
 25 R⁶, R⁷ and R⁸ which are selected from R^g, -C₁₋₈alkyl, -C₁₋₄haloalkyl, cyano, nitro, -C(=O)R^b,
 -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 30 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and the
 ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents selected from R⁶, R⁷, R⁸, R⁹ and
 R¹⁰ which are independently selected from Br, Cl, F and I;
 wherein, R³ and R⁴ together may additionally be C₂₋₃alkylene substituted by 0, 1 or 2
 substituents independently selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, oxo, cyano, nitro,

-C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 5 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and
 I; or

R^{1c} and R⁴ together may additionally be C₂₋₄alkylene substituted by 0, 1 or 2
 substituents selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b,
 10 -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 15 additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and
 I; or

a substituent on R² that is vicinal to the -SO₂-R² bond together with R³ may
 additionally be C₁₋₃alkylene substituted by 0, 1 or 2 substituents selected from -C₁₋₈alkyl, -
 C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,
 20 -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a,
 -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b,
 -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
 -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b,
 -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and additionally substituted
 25 by 0, 1, 2, 3 or 4 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 -C₁₋₆alkyl, the phenyl, benzyl
 and -C₁₋₆alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, -C₁₋₄alkyl, -
 C₁₋₃haloalkyl, -OC₁₋₄alkyl, -NH₂, -NHC₁₋₄alkyl, -N(C₁₋₄alkyl)C₁₋₄alkyl;

30 R^d is independently at each instance -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, cyano, nitro,
 -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,

$-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$,
 $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ or $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$;

R^c is independently at each instance $-\text{C}_{1-6}\text{alkyl}$ substituted by 0, 1, 2 or 3 substituents independently selected from R^d and additionally substituted by 0 or 1 substituents selected

5 from R^g ; and

R^g is independently at each instance a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic hydrocarbon ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents

10 independently selected from $-\text{C}_{1-8}\text{alkyl}$, $-\text{C}_{1-4}\text{haloalkyl}$, halo, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$,
 $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$,
 $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$,
 $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$,
 15 $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; or

any pharmaceutically-acceptable salt or hydrate thereof.

2. The compound of Claim 1 wherein:

20 R^1 is selected from H or $-\text{C}_{1-8}\text{alkyl}$ substituted by 0, 1, 2, or 3 groups independently selected from R^g , cyano, oxo, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$,
 $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$,
 $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$,
 $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$,
 25 $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$,
 $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I;

R^{1a} and R^{1b} are each independently, H, F, Cl, $-\text{OCH}_3$, $-\text{C}_{1-2}\text{alkyl}$ or $-\text{CF}_3$;

R^{1c} is H, $-\text{C}_{1-8}\text{alkyl}$, $-\text{C}_{1-4}\text{haloalkyl}$, halo, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$,
 30 $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$,
 $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$,
 $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$,
 $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$,
 $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, or $-\text{C}_{1-6}\text{alkyl}$

substituted by 0, 1, 2 or 3 substituents selected from C₁₋₄haloalkyl, halo, cyano, nitro,
 -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 5 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a or -NR^aC₂₋₆alkylOR^a;

R² 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 carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and
 10 the ring is substituted by 0, 1, 2 or 3 substituents selected from R^c, R^g, -C₁₋₄haloalkyl, halo,
 cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b,
 -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b,
 -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b,
 -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a,
 15 -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and
 -NR^aC₂₋₆alkylOR^a, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents
 independently selected from Br, Cl, F and I;

R³ is H, phenyl, benzyl or -C₁₋₆alkyl, the phenyl, benzyl and -C₁₋₆alkyl being
 substituted by 0, 1, 2 or 3 substituents selected from R^c, R^g, C₁₋₄haloalkyl, halo, cyano, nitro,
 20 -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 25 additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atom selected from Br, Cl, F and I;

R⁴ is H, phenyl, benzyl or -C₁₋₆alkyl, the phenyl, benzyl and -C₁₋₆alkyl being
 substituted by 0, 1, 2 or 3 substituents selected from C₁₋₄alkyl, C₁₋₃haloalkyl, -OC₁₋₄alkyl,
 -NH₂, -NHC₁₋₄alkyl, and -N(C₁₋₄alkyl)C₁₋₄alkyl, and additionally substituted by 0, 1, 2, 3, 4, 5
 or 6 atom selected from Br, Cl, F and I;

30 R⁵ is a saturated, partially saturated or unsaturated 8-, 9-, 10- or 11-membered bicyclic
 or 12-, 13-, 14- or 15- membered tricyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N,
 O and S, wherein the carbon and sulfur atoms of the ring are substituted by 0, 1 or 2 oxo
 groups and the ring is substituted by 1, 2 or 3 basic moieties, and additionally substituted by 0,
 1, 2 or 3 substituents selected from R^g, -C₁₋₈alkyl, -C₁₋₄haloalkyl, cyano, nitro, -C(=O)R^b,

-C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 5 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and the
 ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br,
 Cl, F and I;

wherein, R³ and R⁴ together may additionally be C₂₋₃alkylene substituted by 0, 1 or 2
 substituents selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b,
 10 -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 15 additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and
 I; or

R^{1c} and R⁴ together may additionally be C₂₋₄alkylene substituted by 0, 1 or 2
 substituents selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b,
 -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a,
 20 -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b,
 -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a,
 -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and
 additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and
 25 I; or

a substituent on R² that is vicinal to the -SO₂-R² bond together with R³ may
 additionally be C₁₋₃alkylene substituted by 0, 1 or 2 substituents selected from C₁₋₈alkyl,
 C₁₋₄haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a,
 -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a,
 30 -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b,
 -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b,
 -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b,
 -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and additionally substituted
 by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and I;

R^a is independently, at each instance, H or R^o;

R^b is independently, at each instance, phenyl, benzyl or -C₁₋₆alkyl, the phenyl, benzyl and -C₁₋₆alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C₁₋₄alkyl, C₁₋₃haloalkyl, -OC₁₋₄alkyl, -NH₂, -NHC₁₋₄alkyl, -N(C₁₋₄alkyl)C₁₋₄alkyl;

5 R^d is independently at each instance -C₁₋₈alkyl, C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a,
10 -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a or -NR^aC₂₋₆alkylOR^a;

R^e is independently at each instance -C₁₋₆alkyl substituted by 0, 1, 2 or 3 substituents independently selected from R^d and additionally substituted by 0 or 1 substituents selected from R^g; and

R^g is independently at each instance a saturated, partially saturated or unsaturated 5-, 6-
15 or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents selected from -C₁₋₈alkyl, -C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b,
20 -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a, and the ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br,
25 Cl, F and I.

3. The compound of Claim 1 or 2 wherein the basic moieties are independently selected from from amino, cycloalkylamino-(C₁₋₆)alkyl, cycloalkyl(C₁₋₆)alkylamino(C₁₋₆)alkyl, heterocyclylamino(C₁₋₆)alkyl, heterocyclyl(C₁₋₆)alkylamino(C₁₋₆)alkyl, arylamino(C₁₋₆)alkyl, aryl(C₁₋₆)alkylamino-(C₁₋₆)alkyl, (C₁₋₆)alkylamino(C₁₋₆)alkoxy, (C₁₋₆)alkylamino(C₁₋₆)alkoxy(C₁₋₆)-alkoxy, amino(C₁₋₆)alkoxy, amino(C₁₋₆)alkyl, (C₁₋₆)alkylamino(C₁₋₆)alkyl, (C₁₋₄)alkylamino-(C₂₋₆)alkenyl, 4-8-membered nitrogen-containing heterocyclyl(C₂₋₆)alkenyl, 5-6 membered heterocyclyloxy, 5-6 membered nitrogen-containing heterocyclyl and 5-7 membered nitrogen-containing heterocyclylalkyl wherein each basic moiety can be substituted by 0, 1, 2 or 3 groups independently selected

from halo, -NH₂, -OH, -CN, -CF₃, (C₁-C₆)alkylamino, haloalkyl, oxo, (C₁-C₆)alkoxy, (C₁-C₆)alkoxyalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, di(C₁-C₆)alkylamino, =NCN; and (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl, each of which is substituted by 0, 1, 2 or 3 groups independently selected from halo, -NH₂, -OH, -CN, -CF₃, (C₁-C₆)alkylamino, haloalkyl, oxo, (C₁-C₆)alkoxy, (C₁-C₆)alkoxyalkyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, or di(C₁-C₆)alkylamino.

4. The compound of Claim 3 wherein the basic moieties are independently selected from amino, aminomethyl, isopropylaminomethyl, *t*-butylaminomethyl, 2-*t*-butylaminoethyl, 2-tert-butylamino-1-methyl-ethyl, 1-tert-butylaminoethyl, 1-(tert-butylamino-methyl)-vinyl, 1-(piperidin-1-ylmethyl)-vinyl, N-isobutyl-aminomethyl, N-isobutyl-aminoethyl, (2,2-dimethyl)propylaminomethyl, N-isopropyl-N-ethylaminomethyl, N-isopropyl-N-methylaminomethyl, N-*t*-butyl-N-methylaminomethyl, N-*iso*-butyl-N-methylaminomethyl, N-*t*-butyl-N-ethylaminomethyl, N-isobutyl-N-methylaminomethyl, N-*t*-butyl-N-isopropylaminomethyl, N,N-di(isopropyl)aminomethyl, N,N-dimethylaminomethyl, N,N-diethylaminomethyl, N,N-di(*t*-butyl)-aminomethyl, cyclopropylaminomethyl, cyclopropylaminoethyl, cyclopropylmethylaminomethyl, cyclopropylmethylaminoethyl, cyclobutylaminomethyl, cyclobutylaminoethyl, cyclobutylmethylaminomethyl, cyclobutylmethylaminoethyl, 4,5-dihydro-imidazolyl, 1-piperidinylmethyl, 4-fluoropiperidin-1-ylmethyl, 4,4-difluoropiperidin-1-ylmethyl, 3-hydroxypiperidin-1-ylmethyl, 4-hydroxypiperidin-1-ylmethyl, 4-(dimethylamino)piperidin-1-ylmethyl, 2,6-dimethylpiperidin-1-ylmethyl, 4-morpholinylmethyl, 1-pyrrolidinylmethyl, 2-methylpyrrolidin-1-ylmethyl, 2,5-dimethylpyrrolidin-1-ylmethyl, piperazin-1-ylmethyl, azocan-1-ylmethyl, azepan-1-ylmethyl, (7-azabicyclo[2.2.1]hept-7-yl)methyl, (1,3,3-trimethyl-6-azaicyclo[3.2.1]oct-6-yl)methyl, 2-piperidinyl or 4-methylpiperazin-1-ylmethyl.

5. The compound of any of the Claims 1-4 wherein R¹ is -C₁₋₈alkyl substituted by 1, 2, 3, 4, 5 or 6 atoms selected from F, Cl, Br or I.

6. The compound of any of the Claims 1-4 wherein R¹ is trifluoromethyl and R^{1a}, R^{1b}, R^{1c} and R³ are hydrogen.

7. The compound of any of the Claims 3-6 wherein:

30 R⁴ is hydrogen and R² is phenyl or naphthyl, both of which are substituted by 1, 2 or 3 substituents selected from R^c, R^g, -C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a,

$-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$,
 $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and
 additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F
 and I.

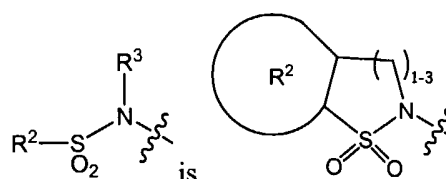
5 8. The compound of any of the Claims 3-6 wherein:

R^4 is hydrogen and R^2 is an unsaturated 5-, 6- or 7-membered monocyclic ring
 containing 1, 2 or 3 atoms selected from N, O and S, wherein the carbon atoms of the ring are
 substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents
 selected from R^c , R^g , $-C_{1-4}haloalkyl$, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$,
 10 $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$,
 $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$,
 $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$,
 $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$,
 $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and the
 15 ring is additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br,
 Cl, F and I.

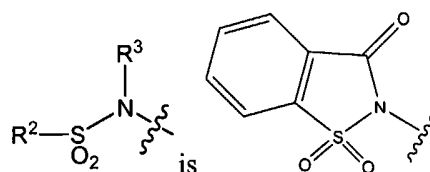
9. The compound of any of the Claims 3-6 wherein:

R^4 is hydrogen and R^2 is 2-trifluoromethylphenyl, 3-bromophenyl, 4-bromo-3-
 trifluoromethylphenyl, 3-chloro-4-fluorophenyl, 3-trifluoromethylphenyl, 4-
 20 trifluoromethoxyphenyl, 3-methylphenyl, 4-chloro-2-fluorophenyl, 2-chloro-4-fluorophenyl,
 naphthalene-2-yl, 3-*tert*-butylphenyl, 4-*tert*-butylphenyl, [1,3]-oxazol-4-ylphenyl, 3,4-dihydro-
 2H-benzo[b][1,4]dioxepin-7-yl, 1,2,3,4-tetrahydroquinolin-8-yl, 4-methyl-3,4-dihydro-2H-
 benzo[b][1,4]oxazin-7-yl, 3-chloro-2-fluorophenyl, 3-methoxyphenyl, 4-methylphenyl, 2,4-
 dimethylphenyl, 3,5-dimethylphenyl, 3,4-dimethylphenyl, 2-fluoro-5-methylphenyl, 4-
 25 trifluoromethylphenyl, 4-chlorophenyl, 2,5-dichlorophenyl, 2,3-dichlorophenyl, 3,4-
 dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 2-chloro-6-methylphenyl, 3-fluoro-6-
 methylphenyl, 5-chloro-2-methoxyphenyl, 4-chloro-3-trifluoromethylphenyl, 2-chloro-5-
 trifluoromethylphenyl, 5-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 2,6-dichloro-4-
 trifluoromethylphenyl, 4-ethylphenyl, 4-chloro-3-methylphenyl, 4-chloro-2,5-dimethylphenyl,
 30 3-chloro-4-methylphenyl, 3,4-dimethoxyphenyl, 3,5-dichloro-2-hydroxyphenyl, isoquinolin-6-
 yl, quinolin-8-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzo[b][1,4]dioxin-6-yl, 2-
 nitrophenyl, 2-aminophenyl, 2-fluoro-5-trifluoromethylphenyl, 6-chloronaphthalen-2-yl, 5-
 chloronaphthalen-1-yl, 2-nitro-4-trifluoromethylphenyl, or 4-biphenyl, 3-biphenyl.

10. The compound of any of the Claims 3-5 wherein R^1 is trifluoromethyl, R^{1a} , R^{1b} , R^{1c} and a substituent on R^2 that is vicinal to the $-\text{SO}_2-\text{R}^2$ bond together with R^3 may additionally be C_{1-3} alkylene substituted by 0, 1 or 2 substituents selected from C_{1-8} alkyl, C_{1-4} haloalkyl, halo, oxo, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and I.
11. The compound of Claim 10 wherein:



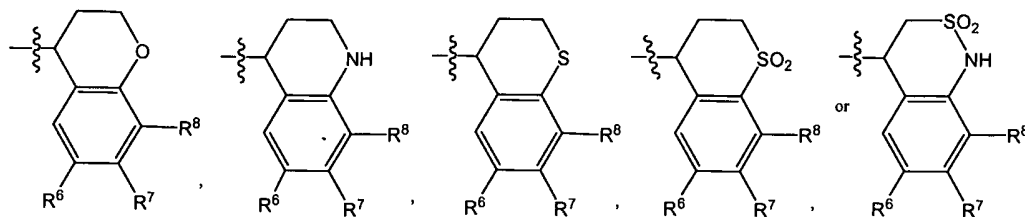
- substituted by 0, 1 or 2 substituents selected from C_{1-8} alkyl, C_{1-4} haloalkyl, halo, oxo, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and I.
12. The compound of Claim 10 wherein:



- substituted by 0, 1 or 2 substituents selected from C_{1-8} alkyl, C_{1-4} haloalkyl, halo, oxo, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and I.

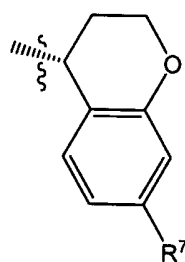
$-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and additionally substituted by 0, 1, 2, 3 or 4 substituents independently selected from Br, Cl, F and I.

13. The compound of any of the Claims 3-12 wherein R^5 is:



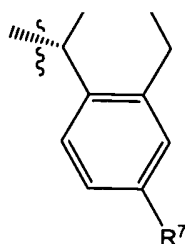
5 where the part of the above rings that is attached to the nitrogen atom in Formula (I) is substituted by 0 or 1 substituents selected from R^g , $\text{C}_{1-8}\text{alkyl}$, $\text{C}_{1-4}\text{haloalkyl}$, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylINR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylINR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, and additionally substituted by 0, 1, 2 or 3 substituents independently selected from Br, Cl, F and I and R^6 , R^7 and R^8 are independently selected from H, a basic moiety, R^g , $\text{C}_{1-8}\text{alkyl}$, $\text{C}_{1-4}\text{haloalkyl}$, cyano, nitro, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{OC}_{2-6}\text{alkylINR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{OR}^b$, $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^a$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(=\text{O})_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylINR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$, Br, Cl, F and I; provided that 1 or 2 of R^6 , R^7 and R^8 are a basic moiety.

20 14. The compound of Claim 3-12 wherein R^5 is:



where R^7 is a basic moiety.

15. The compound of any of the Claims 3-12 wherein R^5 is:



where R^7 is a basic moiety.

16. A compound selected from the group consisting of:
 - 5 (2*R*)-3-(((2,3-dichlorophenyl)sulfonyl)(methyl)amino)-2-hydroxy-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide;
 - (2*R*)-3-(((2,3-dichlorophenyl)sulfonyl)(methyl)amino)-2-methyl-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide;
 - (2*R*)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-2-methyl-*N*-((1*R*)-6-(1-piperidinyl-
 - 10 methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide;
 - (2*R*,3*R*)-4,4,4-trifluoro-2-hydroxy-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
 - (3*R*)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinyl-
 - methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
 - 15 (3*R*)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
 - (3*R*)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinyl-
 - methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
 - (3*R*)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidinyl-
 - 20 methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
 - (3*R*)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
 - (3*R*)-3-(((2,6-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinyl-
 - methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
 - 25 (3*R*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-4-fluoro-*N*-((1*R*)-6-(1-piperidinyl-
 - methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
 - (3*R*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
 - (3*R*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethyl-
 - 30 ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;

- (3*R*)-3-(((4-chlorophenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluorobutanamide;
- (3*R*)-3-(((5-chloro-2-(methyloxy)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*R*)-3-(((5-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-3-((2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-3-(((8-(methyloxy)-5-quinolinyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 10 (3*R*)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*R*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-((8-quinolinylsulfonyl)amino)butanamide;
- (3*R*)-4-hydroxy-3-(((4-methylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*R*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4-fluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 20 (3*R*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)butanamide;
- 25 (3*R*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((2,4,6-trimethylphenyl)sulfonyl)amino)butanamide;
- (3*R*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((4-methylphenyl)sulfonyl)amino)butanamide;
- (3*R*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4-fluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3*R*)-*N*-((4*R*)-7-((cyclopentylamino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*R*,4*R*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-4-hydroxy-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)pentanamide;

- (3*S*)-3-(((2,3-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((2,5-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*S*)-3-(((2,6-dichloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((2,6-dichloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-
- 10 piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((2-fluoro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 15 (3*S*)-3-(((2-nitro-4-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((3,4-bis(methyloxy)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinyl-
- 20 methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((3,4-dichlorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-(1-piperidinylmethyl)ethenyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((3,5-dichloro-2-hydroxyphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3*S*)-3-(((3-chloro-2-fluorophenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((3-chloro-4-methylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-(1,1-dimethylethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-
- 30 methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-(1,3-oxazol-5-yl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-bromo-3-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-((3-hydroxy-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-(1-pyrrolidinyl)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((4*R*)-7-((3-hydroxy-1-piperidinyl)methyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;
- 10 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 15 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((2-methylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((1-methylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 20 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((cyclopropylmethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclobutylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 25 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((3*S*)-3-hydroxy-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((1,1-dimethylethyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;
- 30 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(cyclopentylamino)methyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)butanamide;

- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((2-methylpropyl)-amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((1-methylethyl)-amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- 5 (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((cyclopropyl)-methyl)amino)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-((cyclobutylamino)-methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(((3*S*)-3-hydroxy-1-10 piperidinyl)methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-*N*-((4*R*)-7-(1-pyrrolidinyl-methyl)-3,4-dihydro-2*H*-chromen-4-yl)butanamide;
- (3*S*)-3-(((4-chloro-3-(trifluoromethyl)phenyl)sulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 15 (3*S*)-3-(((5-chloro-1-naphthalenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclopentylamino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((6-chloro-2-naphthalenyl)sulfonyl)amino)-*N*-((1*R*)-6-(((6-chloro-2-naphthalenyl)sulfonyl)(cyclopentyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-butanamide;
- 20 (3*S*)-3-(((6-chloro-2-naphthalenyl)sulfonyl)amino)-*N*-((1*R*)-6-((cyclopentylamino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(((6-chloro-2-naphthalenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-((1,1'-biphenyl-3-ylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-25 tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-((1,1'-biphenyl-4-ylsulfonyl)amino)-*N*-((1*R*)-6-(((1,1-dimethylethyl)-amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-((1,1'-biphenyl-4-ylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 30 (3*S*)-3-((2,3-dihydro-1-benzofuran-5-ylsulfonyl)amino)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-3-(methyl((3-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;

- (3*S*)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 5 (3*S*)-4,4,4-trifluoro-3-((2-naphthalenylsulfonyl)amino)-*N*-((1*R*)-6-(1-(1-piperidinylmethyl)ethenyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-4,4,4-trifluoro-3-((6-isoquinolinesulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- (3*S*)-4,4,4-trifluoro-3-(methyl((3-(trifluoromethyl)phenyl)sulfonyl)amino)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)butanamide;
- 10 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2*R*)-tetrahydro-2-furanylmethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2*S*)-tetrahydro-2-furanylmethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((1-methylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-(1-piperidinyl)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-(1-pyrrolidinyl)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 20 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-(4-morpholinyl)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-hydroxy-1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 25 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((2-methylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(((3*S*)-3-hydroxy-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-fluoro-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-hydroxy-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-methyl-1-piperazinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-((4-methyl-1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-(1-piperidiny)methyl)ethenyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2,4,6-trimethylphenyl)sulfonyl)amino)butanamide;
- 5 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2,4,6-trimethylphenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 10 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(1-pyrrolidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(4-morpholiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*S*)-4,4,4-trifluoro-*N*-((1*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((4*R*)-7-(((2-methylpropyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((4*R*)-7-(((3*R*)-3-hydroxy-1-piperidiny)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 20 (3*S*)-4,4,4-trifluoro-*N*-((4*R*)-7-((4-methyl-1-piperaziny)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4,4,4-trifluoro-*N*-((4*R*)-7-(1-piperidiny)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 25 (3*S*)-4,4,4-trifluoro-*N*-((4*R*)-7-(4-morpholiny)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-4-fluoro-*N*-((1*R*)-6-(1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)-5-hexynamide;
- 30 (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2-nitro-4-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*S*)-*N*-((1*R*)-6-(((2-(acetylamino)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((2-(diethylamino)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((2-(dimethylamino)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-
- 10 naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((2-(methyloxy)ethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((2,2-dimethylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*S*)-*N*-((1*R*)-6-(((2-methylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((2*R*,6*S*)-2,6-dimethyl-1-piperidiny)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(((cyclopropylmethyl)amino)methyl)-1,2,3,4-tetrahydro-1-
- 20 naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((1*R*)-1-((2-(methyloxy)ethyl)amino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((1*R*)-1-(cyclobutylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 25 (3*S*)-*N*-((1*R*)-6-((1*R*)-1-(cyclopropylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((1*S*)-1-((2-methylpropyl)amino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((1*S*)-1-((cyclopropylmethyl)amino)ethyl)-1,2,3,4-tetrahydro-1-
- 30 naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((1*S*)-1-(cyclopentylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((3-pyridinylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*S*)-*N*-((1*R*)-6-((cyclobutylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((cyclohexylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*S*)-*N*-((1*R*)-6-((cyclopentyl((2-fluoro-5-(trifluoromethyl)phenyl)sulfonyl)amino)-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2-fluoro-5-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 10 (3*S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((2-fluoro-5-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(methyl((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 15 (3*S*)-*N*-((1*R*)-6-(1-(1-piperidinylmethyl)ethenyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 20 (3*S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- (3*S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-chloro-4-methylphenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- (3*S*)-*N*-((1*R*)-6-(1-azepanylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3,4-bis(methoxy)phenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- 25 (3*S*)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 30 (3*S*)-*N*-((1*R*)-6-acetyl-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((1*R*)-6-formyl-1,2,3,4-tetrahydro-1-naphthalenyl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- (3*S*)-*N*-((4*R*)-6-chloro-7-(((1,1-dimethylethyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((1,1-dimethylethyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- 5 (3*S*)-*N*-((4*R*)-7-(((1,1-dimethylethyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((1-methylethyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((2-(methyloxy)ethyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-10 (((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((2,2-dimethylpropyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((2-methylpropyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-15 (((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((3*R*)-3-hydroxy-1-piperidinyl)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((cyclopropylmethyl)amino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-20 (((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-20 (((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((cyclohexylamino)methyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((cyclopentylamino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-25 (((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(((cyclopropylamino)methyl)-3,4-dihydro-2H-chromen-4-yl)-3-25 (((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(1-azepanylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((4-chloro-2,5-dimethylphenyl)sulfonyl)amino)-4,4,4-trifluorobutanamide;
- (3*S*)-*N*-((4*R*)-7-(1-azepanylmethyl)-3,4-dihydro-2H-chromen-4-yl)-4,4,4-trifluoro-3-30 (((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;
- (3*S*)-*N*-((4*R*)-7-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-chromen-4-yl)-3-(((3-(trifluoromethyl)phenyl)sulfonyl)amino)butanamide;

- 1,1-dimethylethyl *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-alpha-asparaginate;
- 1,1-dimethylethyl *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-alpha-asparaginate;
- 5 1,1-dimethylethyl *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-alpha-asparaginate;
- 1,1-dimethylethyl *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-pyrrolidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-alpha-asparaginate;
- 2-((2*R*)-2-methyl-1-((4-methylphenyl)sulfonyl)-3-oxo-2-piperazinyl)-*N*-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)acetamide;
- 10 2-(3,4-dichloro-benzenesulfonylamino)-*N*-(6-pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-succinamic acid;
- 3-(2-chloro-5-trifluoromethyl-benzenesulfonylamino)-*N*-(6-[(2-chloro-5-trifluoromethyl-benzenesulfonyl)-cyclopentyl-amino]-methyl)-1,2,3,4-tetrahydro-naphthalen-1-yl)-butyramide;
- 15 3-(6-bromo-1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)-*N*-((1*R*)-6-(1-piperidinyl-methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide;
- 3-(6-bromo-1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)-*N*-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide;
- 20 3*R*-(3,4-dichloro-benzenesulfonylamino)-4,4,4-trifluoro-*N*-(6-piperidin-1-ylmethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-butyramide;
- 3*S*-(3,4-dichloro-benzenesulfonylamino)-4,4,4-trifluoro-*N*-(6-piperidin-1-ylmethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-butyramide;
- N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-phenyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 25 *N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(3-(trifluoromethyl)phenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-fluorophenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 30 *N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-methyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-(((2,2-dimethylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-fluorophenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;

- N*-1-((1*R*)-6-((1*S*)-1-(cyclopentylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-phenyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-((1*S*)-1-(cyclopentylamino)ethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-methyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 5 *N*-1-((1*R*)-6-((4-fluoro-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-phenyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-((4-fluoro-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-methyl-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-((cyclopentylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-10 fluorophenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-((diethylamino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-fluorophenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 15 *N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-(trifluoromethyl)phenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-aspartamide;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-aspartamide;
- 20 *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-asparagine;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(((2-methylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-aspartamide;
- 25 *N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-((4-fluoro-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-aspartamide;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-aspartamide;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-30 tetrahydro-1-naphthalenyl)-*D*-asparagine;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-pyrrolidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-aspartamide;
- N*-2-((3,4-dichlorophenyl)sulfonyl)-*N*-4-((1*R*)-6-(hydroxymethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-aspartamide;

- N*-2-((4-methylphenyl)sulfonyl)-*N*-4-((1*R*)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-aspartamide;
- N*-2-((4-methylphenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-aspartamide;
- 5 *N*-2-((4-methylphenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*D*-asparagine;
- N*-3-((2-aminophenyl)sulfonyl)-*N*-1-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)-beta-alaninamide;
- N*-3-((2-nitrophenyl)sulfonyl)-*N*-1-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)-beta-alaninamide;
- 10 *N*-3-((3,4-dichlorophenyl)sulfonyl)-*N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-(4-fluorophenyl)-beta-alaninamide;
- N*-3-(1-methylethyl)-*N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 15 *N*-3-(2-amino-2-oxoethyl)-*N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-3-(2-fluoroethyl)-*N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-3-(2-naphthalenylsulfonyl)-*N*-3-(phenylmethyl)-*N*-1-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)-beta-alaninamide;
- 20 *N*-3-(2-naphthalenylsulfonyl)-*N*-3-phenyl-*N*-1-((4*R*)-7-(1-piperidinylmethyl)-3,4-dihydro-2*H*-chromen-4-yl)-beta-alaninamide;
- N*-3-(3-amino-3-oxopropyl)-*N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 25 *N*-3-(4-fluorophenyl)-*N*-1-((1*R*)-6-(((2-methylpropyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-3-(4-fluorophenyl)-*N*-1-((1*R*)-6-((4-fluoro-1-piperidinyl)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-3-cyclohexyl-*N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- 30 *N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-3-cyclopropyl-*N*-1-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-3-cyclopropyl-*N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;

- N*-3-methyl-*N*-1-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-3-((3-(trifluoromethyl)phenyl)sulfonyl)-beta-alaninamide;
- N*-4-((1*R*)-6-(((1,1-dimethylethyl)amino)methyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-*N*-2-((4-methylphenyl)sulfonyl)-D-aspartamide;
- 5 *N*-4-((4*R*)-6-chloro-7-methyl-3,4-dihydro-2H-chromen-4-yl)-*N*-2-((3,4-dichlorophenyl)sulfonyl)-D-aspartamide;
- N*-4-((4*R*)-6-chloro-7-methyl-3,4-dihydro-2H-chromen-4-yl)-*N*-2-((4-methylphenyl)sulfonyl)-D-aspartamide;
- phenylmethyl *N*-2-((4-methylphenyl)sulfonyl)-*N*-4-((1*R*)-6-(1-piperidinylmethyl)-1,2,3,4-tetrahydro-1-naphthalenyl)-D-alpha-asparaginate;
- 10 (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(2-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-3-(3-bromophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 15 (*R*)-3-(3-chloro-4-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-7-(piperidin-1-ylmethyl)chroman-4-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-(trifluoromethoxy)phenylsulfonamido)butanamide;
- 20 (*R*)-4,4,4-trifluoro-3-(3-methylphenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide
- (*R*)-3-(4-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 25 (*R*)-3-(2-chloro-4-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-tert-butyl 2-(naphthalene-3-sulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoate;
- (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-((4-methylpiperidin-1-yl)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;
- 30 (*R*)-methyl 4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)-2-(3-(trifluoromethyl)phenylsulfonamido)butanoate;
- (*R*)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)-2-(3-(trifluoromethyl)phenylsulfonamido)butanoic acid;

- (*R*)-N1-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)succinamide;
- (*R*)-3-cyano-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)propanamide;
- 5 (*R*)-2-(naphthalene-3-sulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoic acid;
- (*R*)-methyl 2-(naphthalene-3-sulfonamido)-4-oxo-4-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoate;
- (*R*)-3-(3-tert-butylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 10 (*R*)-methyl 2-(3,4-dichlorophenylsulfonamido)-4-oxo-4-((*R*)-6-(pyrrolidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-ylamino)butanoate;
- (*R*)-4,4,4-trifluoro-3-(3-(oxazol-5-yl)phenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 15 (*R*)-3-(3,4-dihydro-2H-benzo[b][1,4]dioxepine-8-sulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-*N*-((*S*)-6-(4,5-dihydro-1H-imidazol-2-yl)-1,2,3,4-tetrahydronaphthalen-2-yl)-4,4,4-trifluoro-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(1,2,3,4-tetrahydroquinoline-8-sulfonamido)butanamide;
- 20 (*R*)-4,4,4-trifluoro-3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-sulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-3-(3-chloro-2-fluorophenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-((4-methylpiperidin-1-yl)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 25 (*R*)-4,4,4-trifluoro-*N*-((*R*)-5-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(((*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-3-(3-chloro-2-fluoro-*N*-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-methyl-*N*-((*R*)-7-(piperidin-1-ylmethyl)chroman-4-yl)butanamide;
- 30 (*R*)-4,4,4-trifluoro-*N*-((*R*)-7-nitro-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(trifluoromethyl)phenylsulfonamido)butanamide;
- (*R*)-4,4,4-trifluoro-3-(3-methoxyphenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;

- (*R*)-3-(3,5-dimethylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-3-(3,4-dimethylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide
- 5 (2*R*,3*R*)-3-(3-chloro-2-fluorophenylsulfonamido)-*N*-((*R*)-6-chloro-7-(piperidin-1-ylmethyl)chroman-4-yl)-4,4,4-trifluoro-2-hydroxybutanamide;
- (*R*)-4,4,4-trifluoro-3-(2-fluoro-5-methylphenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-
- 10 3-(4-(trifluoromethyl)phenylsulfonamido)butanamide;
- (2*R*,3*R*)-3-(2,5-dichlorophenylsulfonamido)-4,4,4-trifluoro-2-hydroxy-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (2*R*,3*R*)-3-(2,3-dichlorophenylsulfonamido)-4,4,4-trifluoro-2-hydroxy-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 15 (2*R*,3*R*)-3-(3,4-dichlorophenylsulfonamido)-4,4,4-trifluoro-2-hydroxy-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-3-(2-chloro-6-methylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- (*R*)-4,4,4-trifluoro-3-(5-fluoro-2-methylphenylsulfonamido)-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 20 (2*R*,3*R*)-3-(4-ethylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide; and
- (*R*)-3-(4-ethylphenylsulfonamido)-4,4,4-trifluoro-*N*-((*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- 25 or a pharmaceutically acceptable salt thereof.
17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any of the Claims 1-16.
18. The use of a compound of any of the Claims 1-16 in the manufacture of a medicament for the treatment of a disease condition mediated by bradykinin in a mammalian subject.
- 30 19. The use of Claim 15 wherein the disease is inflammation, rheumatoid arthritis, cystitis, post-traumatic and post ischemic cerebral edema, liver cirrhosis, Alzheimer's disease, cardiovascular disease, pain, common cold, allergies, asthma, pancreatitis, burns, virus infection, head injury, multiple trauma, rhinitis, hepatorenal failure, diabetes, metastasis,

pancreatitis, neovascularization, corneal haze, glaucoma, ocular pain, ocular hypertension or angio edema.

20. The use of Claim 18 wherein the disease is osteoarthritis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/033659

A. CLASSIFICATION OF SUBJECT MATTER

C07C311/19 C07D207/48 C07D211/08 A61K31/18 A61K31/40
A61K31/445

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)

C07C C07D A61K

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

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

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/116353 A1 (FERRARI BERNARD ET AL) 17 June 2004 (2004-06-17) claims; examples; paragraphs '0001! - '0086! -----	1-20
Y	WO 93/05014 A (PHARNO-WEDROPHARM GMBH) 18 March 1993 (1993-03-18) claims, examples, Table 5, compound 25; page 1 - page 8 -----	1-20
Y	US 6 022 873 A (BECKETT ET AL) 8 February 2000 (2000-02-08) claims; examples; column 1, line 18 - column 11, line 35 ----- -/--	1-20

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

☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

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14/02/2006

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 2004/092116 A (AMGEN, INC; ARRAY BIOPHARMA, INC; GRONEBERG, ROBERT, D; ASKEW, BEN; D') 28 October 2004 (2004-10-28) examples; claims; page 1 - page 4 -----	1-20

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/033659

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004116353 A1	17-06-2004	BG 108201 A BR 0208489 A CA 2436225 A1 CN 1541211 A CZ 20032588 A3 EE 200300417 A EP 1373233 A1 FR 2822827 A1 WO 02076964 A1 HR 20030748 A2 HU 0401538 A2 JP 2004525936 T MA 26995 A1 MX PA03008756 A NO 20034267 A NZ 527429 A PL 367242 A1 SK 12042003 A3 ZA 200306037 A	30-09-2004 30-03-2004 03-10-2002 27-10-2004 17-12-2003 15-12-2003 02-01-2004 04-10-2002 03-10-2002 31-12-2004 29-11-2004 26-08-2004 20-12-2004 18-02-2004 28-11-2003 30-09-2005 21-02-2005 02-03-2004 05-08-2004
WO 9305014 A	18-03-1993	NONE	
US 6022873 A	08-02-2000	AU 713603 B2 AU 4714297 A CA 2269283 A1 EP 0934292 A1 WO 9817655 A1 GB 2324091 A JP 2001502348 T NZ 334711 A	09-12-1999 15-05-1998 30-04-1998 11-08-1999 30-04-1998 14-10-1998 20-02-2001 27-10-2000
WO 2004092116 A	28-10-2004	AU 2004231070 A1 CA 2521937 A1	28-10-2004 28-10-2004