N-SUBSTITUTED PIPERIDINYL 4-ARYLSULFONAMIDES AS MODULATORS OF THE SECRETED FRIZZLED RELATED PROTEIN-1

Compounds of formula (I): Chemical formula should be inserted here as it appears on the abstract in paper form, and pharmaceutically acceptable salt thereof, which are modulators of secreted frizzled related protein-1, are disclosed. The compounds and compositions containing the compounds, can be used to treat various diseases and disorders, including osteoporosis, arthritis, chronic obstructive pulmonary disease, cartilage defects, bone fractures, leiomyoma, acute myeloid leukemia, wound healing, prostate cancer, autoimmune inflammatory disorders, such as Graves ophthalmopathy, and combinations thereof.

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N-SUBSTITUTED PIPERIDINYL 4-ARYLSULFONAMIDES AS MODULATORS OF THE SECRETED FRIZZLED RELATED PROTEIN-1

FIELD OF THE INVENTION

[0001] The present invention relates to novel N-substituted piperidinyl 4-arylsulfonamides that act, for example, as modulators of secreted frizzled-related protein-1. The present invention also relates to processes for the preparation of N-substituted piperidinyl 4-arylsulfonamides and to their use in treating various diseases and disorders, including osteoporosis, arthritis, chronic obstructive pulmonary disease, cartilage defects, bone fractures, leiomyoma, acute myeloid leukemia, wound healing, prostate cancer, autoimmune inflammatory disorders, such as Graves ophthalmopathy, and combinations thereof.

BACKGROUND OF THE INVENTION

[0002] Bone remodeling, the process by which the adult human skeleton is continuously renewed, is carried out by osteoclasts and osteoblasts, two specialized cell types that originate from hematopoietic and mesenchymal progenitors of the bone marrow, respectively. A continuous and orderly supply of these cells is believed to be essential for skeletal homeostasis, as increased or decreased production of osteoclasts or osteoblasts and/or changes in the rate of their apoptosis are largely responsible for the imbalance between bone resorption and formation that underlies several systemic or localized bone diseases. For example, enhanced osteoclast activity has been found to play a major role in the pathogenesis of postmenopausal osteoporosis, Paget's disease, lytic bone metastases, multiple myeloma, hyperparathyroidism, rheumatoid arthritis, periodontitis, and hypercalcemia of malignancy.

[0003] Numerous genes and gene families (and the polypeptides encoded by them) that participate in the regulation of bone cell production and apoptosis have been identified. Wnt proteins have been identified as a family of growth factors consisting of more than a dozen structurally related molecules that are involved in the regulation of fundamental biological processes such as apoptosis, adipogenesis, embryogenesis, organogenesis, morphogenesis and tumorigenesis (Nusse and Varmus, Cell 1992, 69:1073-1087). Wnt polypeptides are
multipotent factors and have biological activities similar to those of other secretory proteins such as transforming growth factor (TGF)-β, fibroblast growth factors (FGFs), nerve growth factor (NGF), and bone morphogenetic proteins (BMPs).


0005] The first secreted frizzled-related protein (SFRP) was named "Frzb" (for "frizzled motif in bone development") and was purified and cloned from bovine articular cartilage extracts based on its ability to stimulate in vivo chondrogenic activity in rats (Hoang et al., J. Biol. Chem. 1996, 271:26131-26137; Jones & Jomary, Bioessays 2002, 24:811-820). The human homologue of the bovine gene has also been cloned. Unlike the frizzled proteins, however, Frzb does not contain a serpentine transmembrane domain, and appears to be a secreted receptor for Wnt. The Frzb cDNA encodes a 325 amino acid/36,000 dalton protein and is predominantly expressed in the appendicular skeleton. The highest level of expression is in developing long bones and corresponds to epiphysseal chondroblasts; expression declines and disappears toward the ossification center.

0006] Studies indicate that SFRPs participate in apoptosis. Some SFRPs have thus been identified as "SARPs" for secreted apoptosis related proteins. Additional members of the SFRP family have been identified, and have been shown to be antagonists of Wnt action. There are currently at least five known human SFRP/SARP genes: SFRP-1/FrzA/FRP-1/SARP-2, SFRP-2/SDF-5/SARP-1, SFRP-3/Frzb-1/FrzB/Fritz, SFRP-4 and SFRP-5/SARP-3 (Leimeister et al., Mechanisms of Development 1998, 75:29-42). Secreted frizzled related protein-1 (SFRP-1) is a Wnt antagonist and is expressed in osteoblasts and osteocytes as well
as fibroblasts. Although the precise role that SARPs/SFRPs play in apoptosis is not yet clear, these proteins appear to either suppress or enhance the programmed cell death process. Deletion of SFRP-I in mice has been shown to lead to decreased osteoblast/osteocyte apoptosis and to increased bone formation. (Bodine, P.V.N, et ai, Mol. Endocrinol., 2004, 18(5) 1222-1237.) Deletion of SFRP-I in mice has also been shown to lead to an acceleration of chondrocyte differentiation. (Gaur, T., et al., J. Cell. Physiol., 2006, 208(1) 87-96.) Modulation of SFRP-I with an anti-SFRP-1 antibody has been shown to enhance new connective tissue formation resulting in increases in palatal wound healing (Li, C. H. and Amar, S. J. Dent. Research, 2006, 85(4), 374-378. Overexpression of SFRP-I has also been implicated in autoimmune inflammatory disorders such as Graves Ophthalmopathy by stimulating a pathogenic process of adipogenesis (Kumar, S., et ai, J. CHn. Endocrinol. Metab., 2005, 90, 4730-4735).

[0007] A need exists in the art for the identification of modulators of SFRP-I that can be used as novel agents for the treatment of bone disorders or bone fractures, including bone resorption disorders such as osteoporosis, and for regulation of bone formation in humans or for other diseases and disorders, such as arthritis, chronic obstructive pulmonary disease, cartilage defects, leiomyoma, acute myeloid leukemia, wound healing, prostrate cancer, autoimmune inflammatory disorders such as Graves ophthalmopathy, and combinations thereof.

SUMMARY OF THE INVENTION

[0008] The present invention is directed to certain N-substituted piperidinyl 4-arylsulfonamides and to their use, for example, in medical treatment. In one aspect, the invention relates to N-substituted piperidinyl 4-arylsulfonamides that act as modulators of secreted frizzled related protein-1. The compounds can be used, for example, to treat various diseases and disorders, including osteoporosis, arthritis, chronic obstructive pulmonary disease, cartilage defects, bone fractures, leiomyoma, acute myeloid leukemia, wound healing, prostate cancer, autoimmune inflammatory disorders, such as Graves ophthalmopathy, and combinations thereof.

[0009] In certain aspects, the present invention is directed to compounds of formula I:
or a pharmaceutically acceptable salt thereof;

wherein:

- \( R_1 \) is \( H, \) halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or perfluoroalkoxy;

- \( R_2 \) is \( H, \) halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, aryloxy, arylsulfonyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or perfluoroalkoxy, wherein any aryl or heteroaryl portion of \( R_2 \) may be optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, alkoxy, hydroxyl, carboxy, alkoxyalkyl, alkylamino, dialkylamino, cyano, halo, alkylcarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonylamino, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl;

- \( R_3 \) is \( H, \) halo, alkyl, alkoxy, aryl, arylalkyl, or perfluoroalkyl;

- \( R_4 \) is halo, alkyl, cyano, cycloalkyl, arylalkyl, nitro, perfluoroalkyl, or perfluoroalkoxy;

- \( R_5 \) is \( H, \) alkyl, alkylamino, cycloalkyl, cycloalkylamino, alkoxy, alkoxyalkyl, aryl, arylalkyl, arylamino, aminocarbonyl, aminoalkyl, alkylaminocarbonylaminoalkyl, heteroaryl, heteroarylamino, heterocycloalkyl, or heterocycloalkylamino, wherein any aryl, heteroaryl, or heterocycloalkyl portion of \( R_5 \) may be optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, oxo, alkoxyalkyl, alkylamino, dialkylamino, alkylaminoalkylamino, dialkylaminoalkylamino, alkylaminodialkylamino, dialkylaminodialkylamino, cyano, carboxy, halo,
alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aminocarbonyl, alkyaminocarbonyl, alkyaminocarbonylamino, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl; and

X is carbonyl, thiocarbonyl, sulfonyl, sulfoxide, alkyl, alkenyl or absent.

[0010] In a more particular embodiment, R5 is other than alkoxy when R4 is nitro and X is carbonyl.

[0011] In other embodiments, the invention relates to compositions, comprising:

a. at least one compound of formula I; and

b. at least one pharmaceutically acceptable carrier.

[0012] In yet other embodiments, the invention is directed to methods for treating a patient suffering from osteoporosis, arthritis, chronic obstructive pulmonary disease, cartilage defects, bone fractures, leiomyoma, acute myeloid leukemia, wound healing, prostate cancer, autoimmune inflammatory disorder, such as Graves ophthalmopathy, or a combination thereof, comprising the step:

administering to said patient an effective amount of a compound of formula I or pharmaceutically acceptable salt thereof.

[0013] In other embodiments, the invention is directed to use of a compound as described herein for treating a patient suffering from osteoporosis, arthritis, chronic obstructive pulmonary disease, cartilage defects, bone fractures, leiomyoma, acute myeloid leukemia, wound healing, prostate cancer, autoimmune inflammatory disorder, such as Graves ophthalmopathy, or a combination thereof. In particular embodiments, the invention is directed to use of a compound as described herein in the preparation of a medicament for treating a patient suffering from osteoporosis, arthritis, chronic obstructive pulmonary disease, cartilage defects, bone fractures, leiomyoma, acute myeloid leukemia, wound healing, prostate cancer, autoimmune inflammatory disorder, such as Graves ophthalmopathy, or a combination thereof.
Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention is directed to certain N-substituted piperidinyl 4-arylsulfonamides and to their use, for example, in medical treatment. In one aspect, the invention relates to N-substituted piperidinyl 4-aryl sulfonamides that act as modulators of secreted frizzled related protein-1. The compounds can be used, for example, to treat various diseases and disorders, including osteoporosis, arthritis, chronic obstructive pulmonary disease, cartilage defects, bone fractures, leiomyoma, acute myeloid leukemia, wound healing, prostate cancer, autoimmune inflammatory disorders such as Graves ophthalmopathy, and combinations thereof.

The following definitions are provided for the full understanding of terms and abbreviations used in this specification.

The term "alkyl," as used herein, refers to an optionally substituted aliphatic hydrocarbon chain having 1 to 12 carbon atoms (C\textsubscript{n} alkyl), preferably 1 to 8 carbon atoms (Ci-8 alkyl), and more preferably 1 to 4 carbon atoms (C1.4 alkyl). The term "alkyl" includes straight and branched chains. In one embodiment straight chain alkyl groups have 1 to 8 carbon atoms and branched chain alkyl groups have 3 to 12 carbon atoms. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, and isohexyl groups.

The term "hydroxyalkyl," as used herein, refers to the group -alkyl-OH where alkyl is an alkyl group as previously defined.
The term "carboxyalkyl," as used herein, refers to the group -alkyl-C(O)OH where alkyl is an alkyl group as previously defined.

The term "haloalkyl," as used herein, refers to the group -alkyl-halo where halo is a halogen atom and alkyl is an alkyl group as previously defined.

The term "perfluoroalkyl," as used herein, refers to an optionally substituted straight or branched aliphatic hydrocarbon chain of 1 to 8 carbon atoms, preferably 1 to 3 carbon atoms, in which all hydrogens are replaced with fluorine.

The term "perfluoroalkylalkyl," as used herein, refers to the group -alkyl-perfluoroalkyl where alkyl and perfluoroalkyl are as previously defined.

The term "alkenyl," as used herein, refers to an optionally substituted aliphatic straight or branched hydrocarbon chain having 2 to 12 carbon atoms that contain 1 to 3 double bonds. Straight chain alkenyl groups have 2 to 8 carbon atoms and branched chain alkenyl groups have 3 to 12 carbon atoms. Examples of alkenyl groups include, but are not limited to, vinyl, prop-1-enyl, allyl, but-1-enyl, but-2-enyl, but-3-enyl, 3,3-dimethylbut-1-enyl, or 2-methylvinyl.

The term "alkynyl," as used herein, refers to an optionally substituted aliphatic straight or branched hydrocarbon chain having 2 to 8 carbon atoms that contains 1 to 3 triple bonds. Straight chain alkynyl groups have 2 to 8 carbon atoms and branched chain alkynyl groups have 5 to 12 carbon atoms.

The term "cycloalkyl," as used herein, refers to an optionally substituted hydrocarbon ring containing 3 to 12 carbon atoms (C3-12 cycloalkyl) and preferably 3 to 6 carbon atoms (C3-6 cycloalkyl). Cycloalkyl groups may be monocyclic or bicyclic, and may be saturated or partially saturated. The term "bicycloalkyl," as used herein, refers to a bicyclic cycloalkyl group of 8 to 12 ring carbon atoms (Cg-n bicyclic cycloalkyl). "Bridged" cycloalkyl groups contain at least one carbon-carbon bond between two non-adjacent carbon atoms of the cycloalkyl ring.
The term "alkylcycloalkyl," as used herein, refers to the group -cycloalkyl-(alkyl)\(_n\), in which \(n\) is 1 to 3, cycloalkyl is a cycloalkyl group as previously defined, and alkyl is an alkyl group as previously defined.

The term "cycloalkylalkyl," as used herein, refers to the group -alkyl-cycloalkyl in which alkyl is an alkyl group as previously defined and cycloalkyl is a cycloalkyl group as previously defined.

The term "spirocycloalkyl," as used herein, refers to two optionally substituted cycloalkyl groups as previously defined that are joined by a single sp\(^3\) carbon atom that is the only common member of the two joined rings.

The term "heterocycloalkyl," as used herein, refers to a 3 to 12 membered, and more preferably 5 to 7 membered optionally substituted cycloalkyl group in which one to three carbon atoms of the cycloalkyl group are replaced with a heteroatom independently selected from oxygen, nitrogen, and sulfur, including sulfoxide and sulfonyl. The heterocycloalkyl group may be saturated or partially saturated, and may be monocyclic or bicyclic. The term "heterocycloalkyl" refers to the bicyclic structure formed when a heterocycloalkyl group is fused to another heterocycloalkyl group, to a cycloalkyl group, to an aryl group, or to a heteroaryl group. Heterocycloalkyl groups also include "bridged" heterocycloalkyl groups which contain at least one carbon-carbon bond between non-adjacent carbon atoms of the heterocycloalkyl ring.

The term "alkylheterocycloalkyl," as used herein, refers to the group -heterocycloalkyl-(alkyl)\(_n\) in which \(n\) is 1 to 3, heterocycloalkyl is a heterocycloalkyl group as previously defined, and alkyl is an alkyl group as previously defined.

The term "heterocycloalkylalkyl," as used herein, refers to the group -R'-heterocycloalkyl where R' is an alkyl group as previously defined and heterocycloalkyl is a heterocycloalkyl group as previously defined.
The term "aryl," as used herein refers to an optionally substituted carbocyclic aromatic ring e.g. having 6-14 ring carbon atoms. Aryl groups may be monocyclic or bicyclic. Exemplary aryl groups include phenyl and naphthyl. Aryl groups preferably have 6 to 10 carbon atoms (Ce-io aryl).

The term "carboxyaryl," as used herein, refers to the group -aryl-C(O)OH, where aryl is an aryl group as previously defined.

The term "heteroaryl," as used herein refers to an optionally substituted 5 to 10 membered monocyclic or bicyclic carbon containing aromatic ring system having 1 to 3 of its ring members independently selected from nitrogen, sulfur and oxygen. Monocyclic rings preferably have 5 to 6 members and bicyclic rings preferably have 8 to 10 membered ring structures. Examples of heteroaryls include, but are not limited to, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, quinolyl, isoquinolyl, quinoxaliny, and quinazolinyl.

The term "alkylheteroaryl," as used herein, refers to the group -heteroaryl-alkyl wherein heteroaryl is a heteroaryl group as previously defined and alkyl is an alkyl group as previously defined.

The term "arylcarbonylalkyl," as used herein, refers to the group \( R'\)-C(O)-aryl where \( R'\) is an alkyl group as previously defined and aryl is an aryl group as previously defined.

The term, "fused cycloalkylaryl," as used herein, refers to a cycloalkyl group as previously defined fused to an aryl group of five or six carbon atoms as previously defined or fused to a heteroaryl group of five or six atoms as previously defined. The point of attachment can occur at any generally acceptable position.

The term, "fused cycloalkylarylaminocarbonyl," as used herein, refers to the group -C(O)-NH-fused cycloalkylaryl where fused cycloalkylaryl is a fused cycloalkylaryl group as previously defined.
The term, "fused hetercycloalkylaryl," as used herein, refers to a heterocycloalkyl group as previously defined fused to an aryl group of five or six carbon atoms as previously defined or fused to a heteroaryl group of five or six atoms as previously defined. The point of attachment can occur at any generally acceptable position.

The term "fused hetercycloalkylarylcarbonyl," as used herein, refers to the group -C(O)- fused hetercycloalkylaryl where fused hetercycloalkylaryl is a fused heterocycloalkylaryl group as previously defined.

The term "alkylcarbonyl," as used herein, refers to the group -C(O)R' where R' is an alkyl group as previously defined.

The term "alkylthioalkylcarbonyl," as used herein, refers to the group -(O)-R'-S-R' where R' is an alkyl group as previously defined.

The term "alkylcarbonylamino," as used herein, refers to the group -NHC(O)R' where R' is an alkyl group as previously defined.

The term "alkoxycarbonylamino," as used herein, refers to the group -NHC(O)OR where R' is an alkyl group as previously defined.

The term "alkylcarbonylalkylamino," as used herein, refers to the group -NH-R'-C(O)R' where R' is an alkyl group as previously defined.

The term "alkylsulfonylamino," as used herein, refers to the group -NH$_2$-S(O)$_2$-R' where R' is an alkyl group as previously defined.

The term "carboxyaryl sulfonylamino," as used herein, refers to the group -NH$_2$-S(O)$_2$-aryl-C(O)OH where aryl is an aryl group as previously defined.

The term "alkylcarbonyloxime," as used herein, refers to the group -C(N=0R')R' where R' is an alkyl group as previously defined.
The term "alkoxy," as used herein, refers to the group -O-R' where R' is an alkyl group as previously defined.

The term "perfluoroalkoxy," as used herein, refers to the group -O-R" where R" is a perfluoroalkyl group as previously defined.

The terms "amino," "alkylamino," "dialkylamino," and "imino," as used herein, refer to the groups -NH2, -NHR', -N(R')2, and -C=NH, respectively, where each R' is, independently, an alkyl group as previously defined. The terms alkylaminoalkylamino, dialkylaminoalkylamino, dialkylaminodialkylamino refer to groups having the structure R'HNR"-NH-, (R')N-R"-NH-, (R')HN-R"-N(R") 2-, OET)N-R"-N(R") 2-, where each R' is, independently, an alkyl group and each R" is independently a divalent alkyl group.

The term "aminoalkyl," as used herein, refers to the group -R'NH2 where R' is an alkyl group as previously defined.

The term "carboxy" or "carboxyl" as used herein, refers to the group -COOH.

The term "carbonyl," as used herein, refers to a bivalent carbon atom that is further bonded to an oxygen atom through a double bond.

The term "aminocarbonyl," as used herein, refers to an amide substituent having the formula H2N-C(O)-.

The term "thiocarbonyl," as used herein, refers to a bivalent carbon atom that is further bonded to a sulfur atom through a double bond.

The terms "halogen" or "halo," as used herein, refer to chlorine, bromine, fluorine or iodine.
The term "cyano" or "cyanoalkyl," as used herein, refers to the group -CN or -R'-CN where R' is an alkyl group as previously defined.

The term "alkoxy alkyl," as used herein, refers to the group -R'-alkoxy where R' is an alkyl group as previously defined and alkoxy is an alkoxy group as previously defined.

The term "arylalkyl," as used herein, refers to the group -R'-aryl where aryl is an aryl group as previously defined, and R' is an alkyl group as previously defined.

The term "heteroarylalkyl," as used herein, refers to the group -R'-heteroaryl where heteroaryl is a heteroaryl group as previously defined, and R' is an alkyl group as previously defined.

The term "arylalkenyl," as used herein, refers to the group -alkenyl-aryl where aryl is an aryl group as previously defined, and alkenyl is an alkenyl group as previously defined.

The term "arylalkynyl," as used herein, refers to the group -alkynyl-aryl where aryl is an aryl group as previously defined, and alkynyl is an alkynyl group as previously defined.

The term "arylkynyl," as used herein, refers to the group -alkynyl-aryl where aryl is an aryl group as previously defined, and alkenyl is an alkenyl group as previously defined.

The term "carboxyalkoxy," as used herein, refers to the group -alkoxy-C(O)OH where alkoxy is an alkoxy group as previously defined.

The term "benzoxy" refers to the group -O-Cth-phenyl.

The term "aminocarbonylalkoxy," as used herein, refers to the group -alkoxy-C(O)NH2 where alkoxy is an alkoxy group as previously defined.

The term "alkoxycarbonylalkoxy," as used herein, refers to the group -alkoxy-C(O)-alkoxy where alkoxy is an alkoxy group as previously defined.
The term "arylalkylcarbonyl," as used herein, refers to the group -alkylcarbonyl-aryl wherein alkylcarbonyl is an alkylcarbonyl group as previously defined and aryl is an aryl group as previously defined.

The term "arylcarbonyl," as used herein, refers to the group -C(O)-aryl, where aryl is an aryl group of 6 to 10 carbon atoms as previously defined.

The term "dialkylaminoarylcarbonyl," as used herein, refers to the group -arylcarbonyl-N(R')(R') where arylcarbonyl is an arylcarbonyl group as previously defined.

The term "arylthio," as used herein, refers to the group -S-aryl where aryl is an aryl group as previously defined.

The term "arylsulfonyl," as used herein, refers to the group -S(O)_2-aryl where aryl is an aryl group as previously defined.

The term "arylsulfonylarylsulfonyl," as used herein, refers to the group -S(O)_2-aryl-S(O)_2-aryl where aryl is an aryl group as previously defined.

The term "carboxyarylsulfonyl," as used herein, refers to the group -S(O)_2-aryl-C(O)OH where aryl is an aryl group as previously defined.

The term "aminosulfonyl," as used herein, refers to the group -S(O)-NH where aryl is an aryl group as previously defined.

The term "heteroarylsulfonyl," as used herein, refers to the group -S(O)_2-heteroaryl where heteroaryl is a heteroaryl group as previously defined.

The term "arylester," as used herein, refers to the group -C(O)O-aryl where aryl is an aryl group as previously defined.

The term "alkylthiocarbonyl," as used herein, refers to the group -C(S)R' where R' is an alkyl group as previously defined.
The term "alkylaminoalkylcarbonyl," as used herein, refers to the group -C(O)R'NH(R') where R' is an alkyl group as previously defined.

The term "dialkylaminoalkylcarbonyl," as used herein, refers to the group -C(O)R'N(R')(R') where R' is an alkyl group as previously defined.

The term "perfluoroalkylcarbonyl," as used herein, refers to the group -C(O)R" where R" is a perfluoroalkyl group as previously defined.

The term "carboxyalkylcarbonyl," as used herein, refers to the group -C(O)R'C(O)OH where R' is an alkyl group as previously defined.

The term "alkoxycarbonyl," as used herein, refers to the group -C(O)OR' where R' is an alkyl group as previously defined.

The term "alkoxythiocarbonyl," as used herein, refers to the group -C(S)OR' where R' is an alkyl group as previously defined.

The term "alkoxycarbonylalkyl," as used herein, refers to the group -R'C(O)OR' where R' is an alkyl group as previously defined.

The term "heteroarylcarbonyl," as used herein, refers to the group -C(O)-heteroaryl where heteroaryl is a heteroaryl group as previously defined.

The term "heteroarylalkylcarbonyl," as used herein, refers to the group -C(O)-R'-heteroaryl where heteroaryl is a heteroaryl group as previously defined and R' is an alkyl group as previously defined.

The term "heterocycloalkylalkylcarbonyl," as used herein, refers to the group -C(O)-R'-heterocycloalkyl where heterocycloalkyl is a heterocycloalkyl group as previously defined and R' is an alkyl group as previously defined.
The term "heterocycloalkylalkylaminothiocarbonyl," as used herein, refers to the group -C(O)-S-NH-R'-heterocycloalkyl where heterocycloalkyl is a heterocycloalkyl group as previously defined and R' is an alkyl group as previously defined.

The term "aryloxy" as used herein, refers to the group -O-aryl where aryl is an aryl group as previously defined.

The term "arylamino" as used herein, refers to the group -NH-aryl where aryl is an aryl group as previously defined.

The term "aryloxythiocarbonyl," as used herein, refers to the group -C(S)-O-aryl where aryl is an aryl group as previously defined.

The term "cyanoarylcarbonyl," as used herein, refers to the group -C(O)-aryl-CN where aryl is an aryl group as previously defined.

The term "arylalkylcarbonyl," as used herein, refers to the group -C(O)-R'-aryl where R' is an alkyl group as previously defined and aryl is an aryl group as previously defined.

The term "cycloalkylcarbonyl," as used herein, refers to the group -C(O)-cycloalkyl where cycloalkyl is a cycloalkyl group as previously defined.

The term "cycloalkylamino" referst to the group -(NH)-cycloalkyl where cycloalkyl is a cycloalkyl group as previously defined.

The term "heterocycloalkylcarbonyl," as used herein, refers to the group -C(O)-heterocycloalkyl where heterocycloalkyl is a heterocycloalkyl group as previously defined.

The term "heterocycloalkylthiocarbonyl," as used herein, refers to the group -C(S)-heterocycloalkyl where heterocycloalkyl is a heterocycloalkyl group as previously defined.
The term "heterocycloalkylamino" as used herein, refers to the group -NH-heterocycloalkyl where heterocycloalkyl is as previously defined.

The term "aminoalkylcarbonyl," as used herein, refers to the group -C(O)-R'-NH₂ where R' is an alkyl group as previously defined.

The term "alkoxycarbonylaminothiocarbonyl," as used herein, refers to the group -C(O)-S-NH-C(O)-O-R' where R' is an alkyl group as previously defined.

The term "alkoxycarbonylalkylaminothiocarbonyl," as used herein, refers to the group -C(O)-S-NH-R'-C(O)-O-R' where R' is an alkyl group as previously defined.

The term "alkylthiocarbonylalkylcarbonyl," as used herein, refers to the group -C(O)-R'-C(O)-S-R' where R' is an alkyl group as previously defined.

The term "cyanoalkoxycarbonyl," as used herein, refers to the group -C(O)-alkoxy-CN where alkoxy refers to an alkoxy group as previously defined.

The term "alkylaryl," as used herein, refers to the group -aryl-R' where R' is an alkyl group as previously defined, and aryl is an aryl group as previously defined.

The term "alkylester," as used herein, refers to the group -C(O)OR' wherein R' is an alkyl group as previously defined.

The term "aminocarbonyl," as used herein, refers to the group -C(O)NH₂.

The terms "alkylaminocarbonyl," and "dialkylaminocarbonyl," as used herein, refer to the groups -C(O)NHR' and -C(O)N(R')₂, respectively, where each R' is, independently, an alkyl group as previously defined.

The term "heterocycloalkylaminocarbonyl," as used herein, refers to the group -C(O)NH-heterocycloalkyl where heterocycloalkyl is a heterocycloalkyl group as previously defined.
The term "carboxyalkylcarbonylheterocycloalkylaminocarbonyl," as used herein, refers to the group -heterocycloalkylaminocarbonyl-C(0)-R'-C(0)OH where heterocycloalkylaminocarbonyl is a heterocycloalkylaminocarbonyl group as previously defined and R' is an alkyl group as previously defined.

The term "carboxyalkylaminocarbonyl," as used herein, refers to the group -alkylaminocarbonyl-carboxy where carboxy is a carboxy group as previously defined and alkylaminocarbonyl is an alkylaminocarbonyl group as previously defined.

The term "alkoxycarbonylalkylaminocarbonyl," as used herein, refers to the group -alkylaminocarbonyl-carbonyl-alkoxy where alkoxy is an alkoxy group as previously defined, carbonyl is a carbonyl group as previously defined, and alkylaminocarbonyl is an alkylaminocarbonyl group as previously defined.

The term "aminocarbonylalkyl," as used herein, refers to the group -R'C(O)NH where R' is an alkyl group as previously defined.

The terms "alkylaminocarbonylalkyl," and "dialkylaminocarbonylalkyl," as used herein, refer to the groups -R'5C(O)NHR' and -R'C(O)N(R')2, respectively, where each R' is, independently, an alkyl group as previously defined.

The terms "alkylaminothiocarbonyl," and "dialkylaminothiocarbonyl," as used herein, refer to the groups -C(S)NHR' and -C(S)N(R')2, respectively, where each R' is, independently, an alkyl group as previously defined.

The term "heterocycloalkylcarbonylalkyl," as used herein, refers to the group -R'C(0)heterocycloalkyl where R' is an alkyl group as previously defined and heterocycloalkyl is a heterocycloalkyl group as previously defined.

The term "arylaminocarbonyl," as used herein, refers to the group -C(O)NH(aryl), where aryl is an aryl group as previously defined.
The term "heteroarylaminocarbonyl," as used herein, refers to the group -C(O)NH(heteroaryl), where heteroaryl is a heteroaryl group as previously defined.

The term "heteroarylamino," as used herein, refers to the group -NH(heteroaryl), where heteroaryl is a heteroaryl group as previously defined.

The term "heteroarylaminothiocarbonyl," as used herein, refers to the group -C(S)NH(heteroaryl), where heteroaryl is a heteroaryl group as previously defined.

The term "arylaminothiocarbonyl," as used herein, refers to the group -C(S)NH(aryl), where aryl is an aryl group as previously defined.

The term "cycloalkylaminocarbonyl," as used herein, refers to an alkyaminocarbonyl or dialkyaminocarbonyl group as previously defined in which at least one alkyl group is replaced by a cycloalkyl group.

The term "alkylsulfonyl," as used herein, refers to the group -S(O)-R' where R' is an alkyl group as previously defined.

The term "alkylsulfinyl," as used herein, refers to the group -S(O)-R' where R' is an alkyl group as previously defined.

The term "alkythio," as used herein, refers to the group -S-R' where R' is an alkyl group as previously defined.

The term "perfluoroalkythio," as used herein, refers to the group -S-R" where R" is a perfluoroalkyl group as previously defined.

The term "phosphonic acid alkyl," as used herein, refers to the group -R'-P(O)(OH)₂ where R' is an alkyl group as previously defined.

The term "dimethylphosphonatealkyl," as used herein, refers to the group -R'-P(O)(OCH₃)₂ where R' is an alkyl group as previously defined.
The term "oxo" as used herein, refers to the group =O. An exemplary oxo-substituted group is pyrrolidinone.

The term "nitro" as used herein, refers to -NO₂.

The term "sulfonyl" refers to -SO₂⁻.

The term "sulfoxide" refers to -SO⁻.

As used herein, the terms "optionally substituted" or "substituted or unsubstituted" are intended to refer to the optional replacement of up to four hydrogen atoms with up to four independently selected substituent groups as defined herein. Unless otherwise specified, suitable substituent groups independently include hydroxyl, nitro, amino, imino, cyano, halo, thio, sulfonyl, aminocarbonyl, carbonylamino, carbonyl, oxo, guanidine, carboxyl, formyl, alkyl, perfluroalkyl, alkymino, dialkylamino, alkoxy, alkoxyalkyl, alky carbonyl, aryl carbonyl, aralkyl carbonyl, heteroarylcarbonyl, heteroaralkyl carbonyl, alkylthio, cyanoalkyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, alkyaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, alkoxy carbonyl, dialkylaminothiocarbonyl, hydroxyalkyl, carboxy alkyl, halo alkyl, perfluroalkylalkyl, alkenyl, alkynyl, alkylicycloalkyl, cycloalkylalkyl, spirocycloalkyl, alkylheterocycloalkyl, carboxyaryl, alkylheteroaryl, arylcarbonylalkyl, alkylthioalkylcarbonyl, alkylcarbonylamino, alkoxy car bonylamino, alky carbonylalkylamino, alkylaminocarbonyl, carboxyaryl sulfon ylam ino, alkylaminocarbonyloxime, perfluoroalkoxy, arylalkyl, aryloxy, heteroaryloxy, heteroarylalkyl, arylalkenyl, arylalkoxy, aminocarbonylalkoxy, alkoxy carbonylalkoxy, carboxyalkoxy, arylalkylcarbonyl, dialkylaminoarylcarbonyl, ary lthio, arylsulfonyl, carbon ylsulfonyl, arylaminocarbonyl, aminosulfon yl, heteroaryl sulfonyl, al kythiocarbonyl, heteroarylcarbonyl, aryl oxycarbonyl, heteroaryloxycarbonyl, alkylaryl, alkyl ester, perfluoroalkylthio and the like. Substituent groups that have one or more available hydrogen atoms can in turn optionally bear further independently selected substituents, to a maximum of three levels of substitutions. For example, the term "optionally substituted aryl" is intended to mean an aryl group that can optionally have up to four of its hydrogen atoms replaced with substituent groups as defined above (i.e., a first level of
substitution), wherein each of the substituent groups attached to the aryl group can optionally have up to four of its hydrogen atoms replaced by substituent groups as defined above (i.e., a second level of substitution), and each of the substituent groups of the second level of substitution can optionally have up to four of its hydrogen atoms replaced by substituent groups as defined above (i.e., a third level of substitution).

[0134] Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "arylalkoxycabonyl" refers to the group (aryl)-(alkyl)-O-C(O)-.

[0135] It is understood that the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluoro groups). Such impermissible substitution patterns are well known to the skilled artisan.

[0136] The term "protecting group" with respect to amine groups, hydroxyl groups and sulfhydryl groups refers to forms of these functionalities which are protected from undesirable reaction with a protecting group known to those skilled in the art, such as those set forth in Protective Groups in Organic Synthesis, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999) which can be added or removed using the procedures set forth therein. Examples of protected hydroxyl groups include, but are not limited to, silyl ethers such as those obtained by reaction of a hydroxyl group with a reagent such as, but not limited to, t-butyldimethyl-chlorosilane, trimethylchlorosilane, triisopropylchlorosilane, triethylchlorosilane; substituted methyl and ethyl ethers such as, but not limited to methoxymethyl ether, methyliothiomethyl ether, benzylloxymethyl ether, t-butoxymethyl ether, 2-methoxyethoxymethyl ether, tetrahydropranyl ethers, 1-ethoxyethyl ether, allyl ether, benzyl ether; esters such as, but not limited to, benzoyleformate, formate, acetate, trichloroacetate, and trifluoracetate. Examples of protected amine groups include, but are not limited to, amides such as, formamide, acetamide, trifluoroacetamide, and benzamide; carbamates; e.g. BOC; imides, such as phthalimide, Fmoc, Cbz, PMB, benzyl, and dithiosuccinimide; and others. Examples of protected or capped sulfhydryl groups include, but are not limited to, thioethers such as S-benzyl thioether, and S-4-picolyil
thioether; substituted S-methyl derivatives such as hemithio, dithio and aminothio acetals; and others.

[0137] Reference to "activated" or "an activating group" or "$G_A$" as used herein indicates having an electrophilic moiety bound to a substituent, capable of being displaced by a nucleophile. Examples of preferred activating groups are halogens, such as Cl, Br or I, and F; triflate; mesylate, or tosylate; esters; aldehydes; ketones; epoxides; and the like. An example of an activated group is acetyl chloride, which is readily attacked by a nucleophile, such as piperidine group to form a N-acetylpiperidine functionality.

[0138] The term "deprotecting" refers to removal of a protecting group, such as removal of a benzyl or BOC group bound to an amine. Deprotecting may be preformed by heating and/or addition of reagents capable of removing protecting groups. One preferred method of removing BOC groups from amino groups is to add HCl in ethyl acetate. Many deprotecting reactions are well known in the art and are described in Protective Groups in Organic Synthesis, Greene, T.W., John Wiley & Sons, New York, NY, (1st Edition, 1981).

[0139] The term "partially saturated," as used herein, refers to a nonaromatic cycloalkyl or heterocycloalkyl group containing at least one double bond and preferably one or two double bonds.

[0140] The term "therapeutically effective amount," as used herein, refers to the amount of a compound of formula 1 that, when administered to a patient, is effective to at least partially treat a condition from which the patient is suffering or is suspected to suffer. Such conditions include, but are not limited to, osteoporosis, arthritis, chronic obstructive pulmonary disease, cartilage defects, bone fractures, leiomyoma, acute myeloid leukemia, wound healing, prostate cancer, autoimmune inflammatory disorders, such as Graves ophthalmopathy, and combinations thereof.

[0141] The term "pharmaceutically acceptable salts" or "pharmaceutically acceptable salt" includes acid addition salts, namely salts derived from treating a compound of formula 1 with an organic or inorganic acids or bases. Where the compound having formula 1 has an acidic
function, the term "pharmaceutically acceptable salts" or "pharmaceutically acceptable salt" includes salts derived from bases, for instance, sodium salts.

[0142] The term "patient," as used herein, refers to a mammal, preferably a human.

[0143] The terms "administer," "administering," or "administration," as used herein, refer to either directly administering a compound or composition to a patient, or administering a prodrug derivative or analog of the compound to the patient, which will form an equivalent amount of the active compound or substance within the patient's body.

[0144] The terms "treat" and "treating," as used herein, refer to partially or completely alleviating, inhibiting, preventing, ameliorating and/or relieving a condition from which a patient is suspected to suffer.

[0145] The terms "suffer" and "suffering," as used herein, refer to one or more conditions with which a patient has been diagnosed, or is suspected to have.

[0146] Certain embodiments of the invention are directed to compounds of formula I:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof;

wherein:

- $R_1$ is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or perfluoroalkoxy;

- $R_2$ is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, arythio, arylsulfonyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or perfluoroalkoxy, wherein any aryl or heteroaryl portion of $R_2$ may be optionally
substituted with 1 to 5 substituents, selected independently at each occurrence from
the group consisting of alkyl, aryl, arloxy, alkoxy, hydroxy, carboxy, alkoxyalkyl,
alkylamino, dialkylamino, cyano, halo, alkylcarbonyl, aminocarbonyl,
alkylaminocarbonyl, alkylcarnbonylamino, dialkylaminocarbonyl, arylaminocarbonyl,
alkylaminothioicarbonyl, dialkylaminothioicarbonyl, arylaminothioicarbonyl,
cycloalkylcarbonyl, heteroarlylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl,
perfluoroalkoxy, and perfluoroalkylcarbonyl;

R₁ is H, halo, alkyl, alkoxy, aryl, arylalkyl, or perfluoroalkyl;
R₄ is halo, alkyl, cyano, cycloalkyl, arylalkyl, nitro, perfluoroalkyl, or perfluoroalkoxy;
R₅ is H, alkyl, alkylamino, cycloalkyl, cycloalkylamino, alkoxy, alkoxyalkyl,
aryl, arylalkyl, alkylox, aminocarbonyl, aminoalkyl,
alkylaminocarbonylaminoalkyl, heteroaryl, heteroarylamino, heterocycloalkyl, or
heterocycloalkylamino, wherein any aryl, heteroaryl, or heterocycloalkyl portion of
Rs may be optionally substituted with 1 to 5 substituents, selected independently at
each occurrence from the group consisting of alkyl, aryl, alkoxy, oxo, alkoxyalkyl,
alkylamino, dialkylamino, alkyloxaminoalkyl, dialkylaminocarbonyl,
alkylaminodialkylamino, dialkylaminodialkylamino, cyano, carboxy, halo,
alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, alkoxy carbonylamino,
alkoxy carbonylaminoalkyl, aminocarbonyl, alkylaminocarbonyl,
alkylaminocarbonylamino, dialkylaminocarbonyl, arylaminocarbonyl,
alkylaminothioicarbonyl, dialkylaminothioicarbonyl, arylaminothioicarbonyl,
cycloalkylcarbonyl, heteroarlylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl,
perfluoroalkoxy, and perfluoroalkylcarbonyl; and
X is carbonyl, thiocarbonyl, sulfonyl, sulfoxide, alkyl, alkenyl or absent.

[0147] In a more particular embodiment, R⁵ is other than alkoxy when R⁴ is nitro and X is
carbonyl.

[0148] In certain embodiments of the compounds of formula I, R₁ is H, fluoro, chloro,
bromo, methyl, ethyl, propyl, butyl, methoxy, ethoxy, butoxy, phenyl, naphthyl, benzyl,
carboxyl, cyano, thiencyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl,
thiazolyl, isothiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl,
benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, or trifluoromethyl. In certain preferred embodiments, R1 is H.

[0149] In certain embodiments of the compounds of formula I, R2 is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, arylthio, arylsulfonyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or perfluoroalkoxy, wherein any aryl or heteroaryl portion of R2 may be optionally substituted with 1 or 2 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, halo, hydroxy, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl.

[0150] In certain preferred embodiments of the compounds of formula I, wherein the aryl portion of R2 is optionally substituted with 1 or 2 substituents and wherein at least one said substituents is in the ortho position. In certain especially preferred embodiments of the compounds of formula I, R2 is phenyl, o-aminocarbonyl-phenyl, o-chloro-phenyl, o-fluoro-phenyl, o-cyano-phenyl, o-fluoro-p-fluoro-phenyl, o-perfluoromethoxy-phenyl, or o-perfluoromethoxy-o-fluoro-phenyl

[0151] In certain embodiments of the compounds of formula I, R2 is halo, alkyl, aryl, or arylsulfonyl, wherein any aryl portion of R2 may be optionally substituted with 1 to 5 substituents selected, independently at each occurrence, from the group consisting of alkyl, aryl, alkoxyalkyl, alkylamino, dialkylamino, cyano, halo, alkylcarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl.

[0152] In certain preferred embodiments of the compounds of formula I, R2 is aryl optionally substituted with 1 to 5 substituents selected, independently at each occurrence, from the group consisting of alkyl, aryl, alkoxyalkyl, alkylamino, dialkylamino, cyano, halo, alkylcarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl.
arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl.

[0153] In certain other embodiments of the compounds of formula I, R₂ is bromo, isopropyl, phenyl, or phenylsulfonyl.

[0154] In certain embodiments of the compounds of formula I, R₃ is H, fluoro, chloro, bromo, methyl, ethyl, propyl, butyl, methoxy, ethoxy, butoxy, phenyl, naphthyl, benzyl, or trifluoromethyl. In certain preferred embodiments, R₃ is H.

[0155] In certain embodiments of the compounds of formula I, R₄ is perfluoroalkyl. In certain preferred embodiments, R₄ is trifluoromethyl.

[0156] In certain embodiments of the compounds of formula I, R₅ is H, aryl, heteroaryl, or heterocycloalkyl.

[0157] In certain embodiments of the compounds of formula I, X is absent (a direct bond). In certain other embodiments of the compounds of formula I, X is carbonyl. In certain embodiments of the compounds of formula I, X is sulfonyle.

[0158] In certain embodiments of the compounds of formula I,

- R₂ is aryl optionally substituted with 1 to 2 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, halo, hydroxy, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl;
- R₅ is H; and
- X is absent.

[0159] In certain embodiments of the compounds of formula I,

- R₅ is heteroaryl or heterocycloalkyl, wherein any heteroaryl or heterocycloalkyl portion of R₅ may be optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, alkoxyalkyl, alkylamino, dialkylamino, cyano, halo, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl,
alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, 
dialkylaminothiocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, 
heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl; and 
X is carbonyl.

[0160] In certain embodiments of the compounds of formula I, R5 is 6-chloropyridiny-3-yl, 
6-trifluoromethylpyridin-3-yl, or (5S)-N-tert-butyl-2-oxo-pyrrolidin-5-yl-l-carboxamide.

[0161] In certain embodiments of the compounds of formula I, 
R5 is aryl optionally substituted with 1 to 5 substituents, selected independently at 
each occurrence from the group consisting of alkyl, aryl, alkoxyalkyl, alkylamino, 
dialkylamino, cyano, carboxy, halo, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, 
aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, 
alakylaminothiocarbonyl, dialkylaminothiocarbonyl, arylaminothiocarbonyl, 
cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, 
perfluoroalkoxy, and perfluoroalkylcarbonyl; and 
X is sulfonyl.

[0162] In certain preferred embodiments of the compounds of formula I, R5 is benzoic acid. 
In certain preferred embodiments, R5 is benzoic acid and X is sulfonyl.

[0163] In certain embodiments of the compounds of formula I, 
R5 is heteroaryl or heterocycloalkyl, optionally substituted with 1 to 5 substituents, 
selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, 
alkoxyalkyl, alkylamino, dialkylamino, cyano, halo, alkylcarbonyl, arylcarbonyl, 
aloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, 
arlyaminocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, 
heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl; and 
X is carbonyl.

[0164] Preferred compounds of the invention include: 
\textit{tert-buty}4-\textit{([2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate;
tert-butyl 4-([5-bromo-2-(trifluoromethoxy)phenyl]sulfonyl)amino)piperidine-1-carboxylate;
N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;
3-4-([2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl)sulfonyl]benzoic acid;
\textit{tert}-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate;
\textit{tert}-butyl 4-([4-bromo-2-(trifluoromethoxy)phenyl]sulfonyl)amino)piperidine-1-carboxylate;
\textit{tert}-butyl 4-([2,5-bis(trifluoromethyl)phenyl]sulfonyl)arnino)piperidine-1-carboxylate;
\textit{tert}-butyl 4-([2-chloro-4-(trifluoromethyl)phenyl]sulfonyl)arnino)piperidine-1-carboxylate;
\textit{tert}-butyl 4-([2-chloro-5-(trifluoromethyl)phenyl]sulfonyl)arnino)piperidine-l-carboxylate;
\textit{tert}-butyl 4-([-2,3-dichlorophenyl)sulfonyl]arnino}piperidine-l-carboxylate;
\textit{tert}-butyl 4-([-2,4-dichlorophenyl)sulfonyl]arnino}piperidine-l-carboxylate;
\textit{tert}-butyl 4-([-2-methylphenyl)sulfonyl]arnino}piperidine-l-carboxylate;
\textit{tert}-butyl 4-([-2-cyanophenyl)sulfonyl]arnino}piperidine-l-carboxylate;
\textit{tert}-butyl 4-([-2-nitrophenyl)sulfonyl]arnino}piperidine-l-carboxylate;
4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-piperidin-4-yl-2-(trifluoromethoxy)benzenesulfonamide;
N-piperidin-4-yl-2,5-bis(trifluoromethyl)benzenesulfonamide;
2-chloro-N-piperidin-4-yl-4-(trifluoromethyl)benzenesulfonamide;
2-chloro-N-piperidin-4-yl-5-(trifluoromethyl)benzenesulfonamide;
2,3-dichloro-N-piperidin-4-ylbenzenesulfonamide;
2,4-dichloro-N-piperidin-4-ylbenzenesulfonamide;
2-methyl-N-piperidin-4-ylbenzenesulfonamide;
2-cyano-N-piperidin-4-ylbenzenesulfonamide;
2-nitro-N-piperidin-4-ylbenzenesulfonamide;
2-4-([2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl]acetamide;
3-4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl)sulfonyl]benzoic acid
3-{[4-({[4-bromo-2-(trifluoromethoxy)phenyl]sulfonyl}amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-({[2,5-bis(trifluoromethyl)phenyl]sulfonyl}amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-({[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}amino)piperidin-1-yl]sulfonyl}benzoic acid
\[\uparrow \{\uparrow \text{chloro-S-C trifluoromethylopheny}sulfonyljaminoJpiperidin-l-yl]sulfonyl\}benzoic acid
3-[(4-{{[2-nitrophenyl]sulfonyl}amino}piperidin-1-yl)sulfonyl]benzoic acid
3-[(4-{{[2-nitrophenyl]sulfonyl}amino}piperidin-1-yl)sulfonyl]benzoic acid
4-bromo-N-[1-(3-cyanophenyl)sulfonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[l-(3-cyanobenzoyl)]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[l-(2-furoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[l-(2,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[l-(3,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
N-\{l-(3-cyanophenyl)sulfonyl]piperidin-4-yl\}]-2-(trifluoromethyl)benzenesulfonamide;
N-[l-(3-cyanobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
N-[l-(2-furoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
N-[l-(2,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
N-[l-(3,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[l-(pyridin-2-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[l-(pyridin-3-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[l-(pyridin-3-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
N-[1-(isonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
\textit{tert}-butyl (2S)-2-{{[4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate;
tert-butyl (2S)-2-[(4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]carbonyl]-5-oxopyrrolidine-1-carboxylate;

tert-butyl (2S)-2-[[4-[[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;

 tert-butyl (5S)-2-oxo-5-[[4-[[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;

4-bromo-N{[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

4-bromo-N-[1-(2-chloroisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

N-[1-[(2-chloroisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

 tert-butyl 4-[[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidine-1-carboxylate;

N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;

 tert-butyl 4-[[4-(phenylsulfonyl)]-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidine-1-carboxylate;

4-(phenylsulfonyl)-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;

 tert-butyl 4-[[4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]carbonyl]piperidine-1-carboxylate;


4-bromo-N-[1-(piperidin-4-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide; N-[1-(L-3prolylpiperidin-4-yl)]-2-(trifluoromethyl)benzenesulfonamide; 4-bromo-N-{1[(5-oxo-L-prolyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

4-[[4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-\{4-((3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl\}sulfonyl\)benzoic acid

\(N\)-[1-(6-chloropyridin-4-yl)carbonyl\(\text{piperidin}^\text{4-y1}\)]\text{carbonyl}piperidin\-yl\}sulfonyl\)benzene-1-carboxylate;

\(N\)-[1-(L-prolylpiperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide;

\(N\)-[1-(5-oxo-L-prolylpiperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide;

\(t\text{ert}\)(\text{-butyl}) \(4-\{(4-cyano-2-(trifluoromethyl)phenyl)sulfonyl\}amino)piperidine-1-carboxylate;

\(4\)-cyano- \(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;

3-\{4-((4-(phenylsulfonyl)-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl\}sulfonyl\)benzoic acid

\(N\)-ll-\(o\)-chloropyridin-5-yOcarbonyl\(\text{piperidin}^\text{4-y1}\)}\(\text{phenylsulfonyl}\)benzene-1-carboxylate;

\(2\)-\{4-((4-(phenylsulfonyl)-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl\}acetamide;

\(t\text{ert}\)(\text{-butyl}) (2\text{S})-\{4-((4-(phenylsulfonyl)-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl\}carbonyl\)pyrrolidine-1-carboxylate;

\(t\text{ert}\)(\text{-butyl}) \(4-\{(4-fluoro-2-(trifluoromethyl)phenyl)sulfonyl\}amino)piperidine-1-carboxylate;

\(t\text{et/-butyl} \ 4-(\{(4-(dimethylamino)-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate;

4-(dimethylamino)- \(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;

\(t\text{ert}\)(\text{-butyl}) \(4-\{(4-isopropyl-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate;

4-isopropyl- \(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;

\(N\)-[1-\{(6-chloropyridin-5-yOcarbonyl\(\text{piperidin}^\text{4-y1}\)}\(\text{phenylsulfonyl}\}\)benzene-1-carboxylate;

\(t\text{et/-butyl} (2\text{S})-\{4-(\{(4-fluoro-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl\}carbonyl\)pyrrolidine-1-carboxylate;

\(4\)-(phenylsulfonyl)- \(N\)-[\(l\)-L-prolylpiperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

\(4\)-fluoro- \(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;
3-{{4-({4-cyano-2-(trifluoromethyl)phenyl}sulfonyl)amino}piperidin-1-yl}sulfonyl}benzoic acid

N-\{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}-4-cyano-2-(trifluoromethyl)benzenesulfonamide;

\textit{tert-buty}l (2S)-2-{{4-({4-cyano-2-(trifluoromethyl)phenyl}sulfonyl)amino}piperidin-1-yl}carbonyl pyrrolidine-1-carboxylate;

4-cyano-N-\{1-(L-prolylpiperidin-4-yl)\}-2-(trifluoromethyl)benzenesulfonamide;

4-\{\{1-[\{3-carboxyphenyl\}sulfonyl]piperidin-4-yl\}amino\}sulfonyl\}-3-(trifluoromethyl)benzoic acid

N-\{1-\{4-\{2-(dimethylamino)ethyl\}amino\}-2-fluorobenzoyl\}piperidin-4-yl\}-2-(trifluoromethyl)benzenesulfonamide;

N-\{1-\{4-\{2-(dimethylamino)ethyl\}(methyl)amino\}-3-fluorobenzoyl\}piperidin-4-yl\}-2-(trifluoromethyl)benzenesulfonamide;

N-\{1-(4-fluorobenzoyl)piperidin-4-yl\}-2-(trifluoromethyl)benzenesulfonamide;

N-\{1-(4-bromobenzoyl)piperidin-4-yl\}-2-(trifluoromethyl)benzenesulfonamide;

4-(dimethylamino)-N-\{1-(L-prolylpiperidin-4-yl)\}-2-(trifluoromethyl)benzenesulfonamide;

3-{{4-\{4-isopropyl-2-(trifluoromethyl)phenyl}sulfonyl\}amino}piperidin-1-yl}sulfonyl}benzoic acid

\textit{tert-buty}l (2S)-2-{{4-\{4-isopropyl\}-2-(trifluoromethyl)phenyl}sulfonyl\}amino}piperidin-1-yl}carbonyl pyrrolidine-1-carboxylate;

4-isopropyl-N-\{1-(L-prolylpiperidin-4-yl)\}-2-(trifluoromethyl)benzenesulfonamide;

2-\{4-\{4-bromo-2-(trifluoromethyl)phenyl\}sulfonyl\}amino}piperidin-1-yl}acetamide;

\textit{tert-buty}l 4-\{4-[\{4-chloro-2-(trifluoromethyl)phenyl\}sulfonyl\}amino\}piperidine-1-carboxylate;

3-{{4-\{4-fluoro-2-(trifluoromethyl)phenyl\}sulfonyl\}amino}piperidin-1-yl}sulfonyl}benzoic acid

4-fluoro-N-\{1-(L-prolylpiperidin-4-yl)\}-2-(trifluoromethyl)benzenesulfonamide;

4-\{\{1-[\{\textit{t}-butoxycarbonyl]-(L-prolylpiperidin-4-yl)\}amino\}sulfonyl\}-3-(trifluoromethyl)benzoic acid

N-[[6-chloropyridin-3-yl]carbonyl]piperidin-4-yl]-4-(dimethylamino)-2-(trifluoromethyl)benzenesulfonamide;


4-chloro-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;


N-(1-[[3-(2H-tetrazol-5-yl)phenyl]sulfonyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;

4-bromo-N-(1-[[3-(2H-tetrazol-5-yl)phenyl]sulfonyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;

(N-3-[[3-(2H-tetrazol-5-yl)benzoyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

tert-butyl 4-[[4-methoxy-2-(trifluoromethyl)phenyl]sulfonyl]amino]piperidine-1-carboxylate;

4-methoxy-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;


4-chloro-N-[[6-chloropyridin-3-yl]carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;


4-chloro-N-(1-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;


N-[[6-chloropyridin-3-yl]carbonyl]piperidin-4-yl]-4-methoxy-2-(trifluoromethyl)benzenesulfonamide;

4-methoxy-N-(L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[L-(pyridin-3-ylmethyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[L-(pyridin-4-ylmethyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[L-(3-cyanobenzyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[L-(pyridin-3-ylmethyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[L-(pyridin-4-ylmethyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
2-tert-butyl-N-piperidin-4-ylbenzenesulfonamide;
2,4-di-tert-butyl-N-piperidin-4-ylbenzenesulfonamide;
4-phenoxy-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[1-{(6-ethoxypyridin-3-yl)carbonyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[1-{(6-ethoxypyridin-3-yl)carbonyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[1-{(6-ethoxypyridin-3-yl)carbonyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
N-[1-{(6-ethoxypyridin-3-yl)carbonyl}piperidin-4-yl]-4-isopropyl-2-(trifluoromethyl)benzenesulfonamide;
(2S)-2-{[4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate;
3-[(4-((4-phenoxy-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl)sulfonyl]benzoic acid
3-[(4-((2-isopropylphenyl)sulfonyl)amino)piperidin-1-yl)sulfonyl]benzoic acid
3-[(4-((2,4-di-tert-butylphenyl)sulfonyl)amino)piperidin-1-yl)sulfonyl]benzoic acid
3-[(4-((3'-chloro-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl)sulfonyl]benzoic acid
3-[(4-((3'-chloro-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl)sulfonyl]benzoic acid
3-{[4-((2'-chloro-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((4'-methoxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((3'-methoxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((2'-methoxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((4'-cyano-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((3'-cyano-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((2'-carbamoyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((4'-/ε/-butyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((4-(l-naphthyl)-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((4-(2-naphthyl)-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((3-(trifluoromethyl)-l,r,4',l"-terphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((3-(trifluoromethyl)-l,r,3',l"-terphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((3',5'-dichloro-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((4-pyridin-3-yl-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
3-{[4-((2',3'-dichloro-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl}benzoic acid
4-bromo-N-1-{[(6-chloropyridin-3-yl)methyl]piperidin-4-yl}-2-(trifluoromethyl)benzenesulfonamide;
4-bromo- \( N \) -{\((6\text{-methoxypyridin-3-yl})\text{methyl}\)piperidin-4-yl} \(-2\) - (trifluoromethyl)benzenesulfonamide; 

3-\{4-\{[(4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino\}piperidin-1-yl\}methyl]benzoic acid 

\( N \) -{\((6\text{-chloropyridin-3-yl})\text{carbonyl}\)piperidin-4-yl} \(-2\) - isopropylbenzenesulfonamide; 

2-/er/-butyl- \( N \) -{\((6\text{-chloropyridin-3-yl})\text{carbonyl}\)piperidin-4-yl} \(-2\) - benzenesulfonamide; 

2,4-di-/er/-butyl- \( N \) -{\((6\text{-chloropyridin-3-yl})\text{carbonyl}\)piperidin-4-yl} \(-2\) - benzenesulfonamide; 

5-bromo-4-isopropyl- \( N \) -piperidin-4-yl \(-2\) - (trifluoromethyl)benzenesulfonamide; 

3-bromo-4-isopropyl- \( N \) -piperidin-4-yl \(-2\) - (trifluoromethyl)benzenesulfonamide; 

3-\{4-\{[(5\text{-bromo-4-isopropyl-2-(trifluoromethyl)phenyl})\text{sulfonyl}]amino\}piperidin-1-yl\}benzoic acid; 

te/7-butyl 4-(\{2'-methyl-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl]amino)piperidine-1-carboxylate; 

ter \-butyl 4-(\{2'-ethyl-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl]amino)piperidine-1-carboxylate; 

tert-buty1 4-(\{2'-isopropyl-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl]amino)piperidine-1-carboxylate; 
	e/r/-butyl 4-(\{2'-fluoro-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl]amino)piperidine-1-carboxylate; 
	e/r/-butyl 4-(\{2'-acetyl-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl]amino)piperidine-1-carboxylate; 

tert-buty1 4-(\{2'-ethoxy-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl]amino)piperidine-1-carboxylate; 
	erf-butyl 4-(\{2'-propoxy-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl]amino)piperidine-1-carboxylate; 
	e/r/-butyl 4-(\{2'-methoxymethyl)-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl]amino)piperidine-1-carboxylate; 
	e/r/-butyl 4-(\{2',6'-dimethyl-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl]amino)piperidine-1-carboxylate;
/e/-/-butyl 4-({[2',5'-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl} amino)piperidine-1-carboxylate;
4-bromo-N-l{(4-chlorobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-chlorophenyl)sulfonyl}piperidin-4-yl)l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-fluorobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-2-(trifluoromethyl)-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-2-(trifluoromethyl)-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-(trifluoromethyl)benzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-cyanobenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l{(4-ter/-butylbenzoyl)piperidin-4-yl}l-2-(trifluoromethyl)benzenesulfonamide;
2’-(methoxymethyl)-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2’,6’-dimethyl- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2’,5’-dichloro-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2’-methyl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2’-ethyl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2’-fluoro-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2’-acetyl-N-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2’-ethoxy-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2’-propoxy-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2’-(methoxymethyl)-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2’-carbamoyl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2’-carbamoyl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
/er/-butyl 4-({2’-carbamoyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl}amino)piperidine-1-carboxylate;
(5S)-N-er/-butyl-2-oxo-5-{{4-([3-(trifluoromethyl)biphenyl-4-yl)sulfonyl}amino)piperidine-1-carboxylate;
3-{{4-([2’-methyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl}amino)piperidin-1-yl}sulfonyl]benzoic acid;
3-{{4-([2’-ethyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl}amino)piperidin-1-yl}sulfonyl]benzoic acid;
3-{{4-([2’-isopropyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl}amino)piperidin-1-yl}sulfonyl]benzoic acid;
3-[(4-[(2'-fluoro-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid;
3-[(4-[(2'-acetyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid;
3-[(4-[(2'-ethoxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid;
3-[(4-[(2'-propoxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid;
3-[(4-[(2'-(methoxymethyl)-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid;
3-[(4-[(2',6'-dimethyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid;
3-[(4-[(2',5'-dichloro-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid;
4'-[(piperidin-4-ylamino)sulfonyl]-3'-(trifluoromethyl)biphenyl-2-carboxamide;
4'-[(1-(N-(6-chloropyridin-3-yl)carbonyl)piperidin-4-yl)amino)sulfonyl]-3'-(trifluoromethyl)biphenyl-2-carboxamide;
4-bromo-\(N\)-\{1-[3-(dimethylamino)benzoyl]piperidin-4-yl\}-2-(trifluoromethyl)benzenesulfonamide,
\(N\)-\{1-[3-(dimethylamino)benzoyl]piperidin-4-yl\}-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2'-chloro-\(N\)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2'-methoxy-\(N\)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2'-fluoro-6'-methoxy-\(N\)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
\(N\)'-piperidin-4-yl-2'-(trifluoromethoxy)-3-(trifluoromethyl)biphenyl-4-sulfonamide;
\(N\)-piperidin-4-yl-3-(trifluoromethyl)-1',2',1'-terphenyl-4-sulfonamide;
2'-phenoxy-\(N\)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
\(N\)-\{4'-[(piperidin-4-ylamino)sulfonyl]-3'-(trifluoromethyl)biphenyl-2-yl\}acetamide;
2'-hydroxy-\(N\)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
4'-(\{piperidin-4-ylamino)sulfonyl\}-3'-\{trifluoromethyl\}biphenyl-2-carboxylic acid
\(N\)-piperidin-4-yl-3-(2-thienyl)-2-(trifluoromethyl)benzenesulfonamide;
tert-butyl 4-(\{2'-chloro-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl)amino)piperidine-1-carboxylate;
\(\textit{tert-butyl}\) 4-(\{2'-methoxy-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl)amino)piperidine-1-carboxylate;
\(\textit{tert-butyl}\) 4-(\{2'-fluoro-6'-methoxy-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl)amino)piperidine-1-carboxylate;
\(\textit{tert-butyl}\) 4-(\{2'-(trifluoromethoxy)-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl)amino)piperidine-1-carboxylate;
\(\textit{le/-butyl}\) 4-(\{3-(trifluoromethyl)-1',1'-te \(\phi\) neryl-4-yl\}sulfonyl \{amino)piperidine-1 -carboxylate;
\(\textit{tert-butyl}\) 4-(\{2'-phenoxy-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl)amino)piperidine-1-carboxylate;
\(\textit{tert-butyl}\) 4-(\{2'-acetamido-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl)amino)piperidine-1-carboxylate;
tert-butyl 4-(\{2'-hydroxy-3-(trifluoromethyl)biphenyl-4-yl\}sulfonyl)amino)piperidine-1-carboxylate;
4'-(\{1-\(\textit{tert-butoxycarbonyl}\)piperidin-4-yl\}amino)sulfonyl)-3'-(trifluoromethyl)biphenyl-2-carboxylic acid
tert-butyl 4-((4-(2-thienyl)-2-(trifluoromethyl)phenyl) sulfonfonyl) amino)piperidine-1-carboxylate;
f/f7-butyl 4-((4-((4-bromo-2-(trifluoromethyl)phenyl) sulfonfonyl) amino)piperidin-1-yl)carbonyl)phenyl) carbamate
tert-butyl methyl(4-((3-(trifluoromethyl)biphenyl-4-yl)sulfonfonyl) amino)piperidin-1-yl) carbonyl)phenyl) carbamate
4-bromo-\(N\)-(1-[4-(methylamino)benzoyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
\(N\)-(1-[4-(methylamino)benzoyl]piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide;
tert-butyl (2R)-2-{4-((4-bromo-2-(trifluoromethyl)phenyl) sulfonfonyl) amino)piperidin-1-yl)carbonyl)pyrrolidine-1-carboxylate;
4-bromo-\(N\)-(1-D-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
(2R)-2-{4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonfonyl) amino)piperidin-1-yl)carbonyl-)\(N\)/- tert-butylpyrrolidine-1-carboxamide;
tert-butyl (2-{4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonfonyl) amino)piperidin-1-yl)carbonyl)phenyl) carbamate
tert-butyl (3-{4-((4-bromo-2-(trifluoromethyl)phenyl) sulfonfonyl) amino)piperidin-1-yl)carbonyl)phenyl) carbamate
tert-butyl (4-{4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonfonyl) amino)piperidin-1-yl)carbonyl)phenyl) carbamate
e/f7-butyl (2-{4-((3-(trifluoromethyl)biphenyl-4-yl) sulfonfonyl) amino)piperidin-1-yl)carbonyl) phenyl) carbamate
tert-butyl (3-{4-((3-(trifluoromethyl)biphenyl-4-yl) sulfonfonyl) amino)piperidin-1-yl)carbonyl) phenyl) carbamate
e/f7-butyl (4-{4-((3-(trifluoromethyl)biphenyl-4-yl) sulfonfonyl) amino)piperidin-1-yl)carbonyl)phenyl) carbamate
\(e/-/-\)-butyl 4-((4-[1-(tert-butoxycarbonyl)]-I-H-pyr toluyl)-2-yl)-2-(trifluoromethyl)phenyl)sulfonfonyl) amino)piperidine-1-carboxylate;
\(N\)-piperidin-4-yl-4-(I-H-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide;
\(N\)-[1-(2-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide;
\(N\)-[1-(3-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide;
\(N\)-[1-(4-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-\(N\)-[1-{2-{[(tert-butylcarbamoyl)amino]benzoyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-\(N\)-[1-{3-{[(tert-butylcarbamoyl)amino]benzoyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-\(N\)-[1-{4-{[(tert-butylcarbamoyl)amino]benzoyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
\(N\)-[1-{2-[(tert-butylcarbamoyl)amino]benzoyl}piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;
\(N\)-[1-{3-[(tert-butylcarbamoyl)amino]benzoyl}piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;
\(N\)-[1-{4-[(tert-butylcarbamoyl)amino]benzoyl}piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;
\(N\)-[1-{6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-4-(lH-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide;
\(N\)-[1-acetyl]piperidin-4-yl]-4-(lH-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide;
2'-chloro-\(N\)-[1-{6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-3-(trifluoromethyl)benzenesulfonamide;
\(^{\wedge}\)\{1-{(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}\}·2'-methoxy-3-(trifluoromethyl)benzenesulfonamide;
\(N\)-[1-{((6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}\}·2'-methoxy-3-(trifluoromethyl)benzenesulfonamide;
\(N\)-[1-\{((6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]\}·2'-methoxy-3-(trifluoromethyl)benzenesulfonamide;
\(N\)-[1-{((6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]\}·2'-methoxy-3-(trifluoromethyl)benzenesulfonamide;
\(N\)-fl\(^{\wedge}\)o-chloropyridin-S-yOcarbonyl]piperidin-4-yl]-3-(trifluoromethyl)benzenesulfonamide;
\[ N-O-\{(6\text{-}chloropyridin-3-yl)carbonyl\text{-}piperidin-4-yl\}^{\\wedge}\text{-}\text{phenoxy-S-}(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide}; \]
\[ N\{-4'-\{(1-[\{(6\text{-}chloropyridin-3-yl)carbonyl\text{-}piperidin-4-yl\}amino)sulfonyl]}-3'-(\text{trifluoromethyl})\text{biphenyl-2-yl}\}\text{acetamide}; \]
\[ N\{-1\-[\{(6\text{-}chloropyridin-3-yl)carbonyl\text{-}piperidin-4-yl\}]-2'-\text{hydroxy}-3-(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide}; \]
\[ 4'\-[\{(1-[\{(6\text{-}chloropyridin-3-yl)carbonyl\text{-}piperidin-4-yl\}amino)sulfonyl]}-3'-(\text{trifluoromethyl})\text{biphenyl-2-carboxylic acid} \]
\[ N\{-1\-[\{(6\text{-}chloropyridin-3-yl)carbonyl\text{-}piperidin-4-yl\}]-4\text{-}(2\text{-}thienyl)-2-(\text{trifluoromethyl})\text{benzenesulfonamide}; \]
\[ \text{tert\text{-}butyl}-\text{4-}([2'\text{-}cyano-3-(\text{trifluoromethyl})\text{biphenyl-4-yl}]{\text{sulfonamide}}]\text{-piperidine-1-carboxylate;} \]
\[ 2'\text{-}cyano-\text{N-}piperidin-4-yl\text{-}3-(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide}; \]
\[ N\{-1\-[\{(6\text{-}chloropyridin-3-yl)carbonyl\text{-}piperidin-4-yl\}]-2'-\text{cyano-3-(trifluoromethyl)}\text{biphenyl-4-sulfonamide}; \]
\[ 4\text{-}(1\text{-}acetyl-1H-pyrrol-2-yl)-\text{N-}1\-[\{(6\text{-}chloropyridin-3-yl)carbonyl\text{-}piperidin-4-yl\}]-2-(\text{trifluoromethyl})\text{benzenesulfonamide}; \]
\[ \text{tert\text{-}butyl}\text{-}4\text{-}\{[4\text{-}(\text{2\text{-}oxo-2\text{-}(\text{trifluoromethyl})\text{benzenesulfonamide}})\text{-piperidin-1-yl}\}]-2\text{-}(\text{trifluoromethyl})\text{benzenesulfonamide}; \]
\[ \text{tert\text{-}butyl}\text{-}2\text{-}(\text{4\text{-}(\text{3\text{-}(\text{trifluoromethyl})\text{biphenyl-4-yl}]{\text{sulfonamide}})\text{-piperidin-1-yl}}]-2\text{-}\text{o xoethy l}l\text{carbamate;} \]
\[ 4\text{-}[(1\text{-}glycly piperidin-4-yl)-2-(\text{trifluoronie thyl})\text{benzenesulfonamide}; \]
\[ N\{(1\text{-}acetyl\text{-}piperidin-4-yl)}]-4\text{-}(1\text{-}acetyl-1H-pyrrol-2-yl)-2-(\text{trifluoromethyl})\text{benzenesulfonamide}; \]
\[ \text{tert\text{-}butyl}\text{-}2\text{-}(\text{4\text{-}(\text{3\text{-}(\text{trifluoromethyl})\text{biphenyl-4-yl}]{\text{sulfonamide}})\text{-piperidin-1-yl}}]-2\text{-}\text{o xoethy l}l\text{carbamate;} \]
\[ 4\text{-}(1\text{-glycly piperidin-4-yl)\text{-}3-(trifluoromethyl)benphenyl-4-sulfonamide}; \]
\[ 4\text{-}\{1\text{-}[\{N\{(\text{ferM})\text{butylcarbamoyl})\text{glycly piperidin-4-yl}\})\text{-}2-(\text{trifluoromethyl})\text{benzenesulfonamide}; \]
\[ N\{-1\-[\{N\{(\text{ferM})\text{butylcarbamoyl})\text{glycly piperidin-4-yl}\})\text{-}3-(trifluoromethyl)\text{biphenyl-4-sulfonamide}; \]
\[ 4\text{-}\{[4\text{-}(\text{4-bromo-2-(trifluoromethyl)phenyl}sulfonamide\text{-}piperidin-1-yl)\text{carbonyl}]\text{-}N\{(\text{ferM})\text{butylpiperidine-1-carboxamide;}} \]
\[ 4\text{-}\{[4\text{-}(\text{4-bromo-2-(trifluoromethyl)phenyl}sulfonamide\text{-}piperidin-1-yl)\text{carbonyl}]\text{-}N\{(\text{ferM})\text{butylpiperidine-1-carboxamide;}} \]
(2S)-N-fer/-butyl-2-[4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino]piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;

4-bromo-N-{l-[N-(/er-butylcarbamoyl)-2-methylalanyl]piperidin-4-yl}-2-(trifluoromethyl)benzenesulfonamide;

N-{l-[N-(/er-butylcarbamoyl)-2-methylalanyl]piperidin-4-yl}-3-(trifluoromethyl)benzenesulfonamide;

(2S)-N-/e/-butyl-2-[4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino]piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;

4-bromo-N-{l-[3S]-pyrrolidin-3-ylcarbonyl]piperidin-4-yl}-2-(trifluoromethyl)benzenesulfonamide;

4-bromo-N-{l-[3R]-pyrrolidin-3-ylcarbonyl]piperidin-4-yl}-2-(trifluoromethyl)benzenesulfonamide;

/er/-butyl (3S)-3-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;

(2S)-N-/e/-butyl-2-[4-([2'-cyano-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino]piperidin-1-yl]carbonyl]5-oxopyrrolidine-1-carboxamide;
(2S)-N/-/e/-/-butyl-2-[[4-([4'-fluoro-3-(trifluoromethyl)biphenyl-4-y]sulfonyl)amino)piperidin-1-y]carbonyl]-5-oxopyrrolidine-1-carboxamide,
(2S)-N/-/butyl-2-[[4-([2',4'-difluoro-3-(trifluoromethyl)biphenyl-4-y]sulfonyl)amino)piperidin-1-y]carbonyl]-5-oxopyrrolidine-1-carboxamide;
(2S)-2-[[4-([2',3-bis(trifluoromethyl)biphenyl-4-y]sulfonyl)amino)piperidin-1-y]carbonyl]-N/-/ert-butyl-5-oxopyrrolidine-1-carboxamide;
2'-cyano-3-(trifluoromethyl)-N-(l-[[6-(trifluoromethyl)pyridin-3-y]carbonyl]piperidin-4-y]biphenyl-4-sulfonamide;
(35)-3-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-y]carbonyl]-N-ter/-/butylpyrrolidine-1-carboxamide;
(3/?)-3-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-y]carbonyl]-N-te/-/butylpyrrolidine-1-carboxamide;
(3R)-N-(-/ert-butyl)-3-[[4-([3-(trifluoromethyl)biphenyl-4-y]sulfonyl)amino)piperidin-1-y]carbonyl]pyrrolidine-1-carboxamide;
N-l-(pyrimidin-5-y]carbonyl]piperidin-4-y]l-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-l-(pyridazin-4-y]carbonyl]piperidin-4-y]l-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-l-(pyrazin-2-y]carbonyl]piperidin-4-y]l-3-(trifluoromethyl)biphenyl-4-sulfonamide;
4-bromo-N-l-[[(35)-l-(2,2-dimethylpropanoyl)pyrrolidin-3-y]carbonyl]piperidin-4-y]l-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-l-[[(3R)-l-(2,2-dimethylpropanoyl)pyrrolidin-3-y]carbonyl]piperidin-4-y]l-2-(trifluoromethyl)benzenesulfonamide;
N-l-[[35]-l-(2,2-dimethylpropanoyl)pyrrolidin-3-y]carbonyl]piperidin-4-y]l-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-l-[[3 R]-l-(2,2-dimethylpropanoyl)pyrrolidin-3-y]carbonyl]piperidin-4-y]l-3-(trifluoromethyl)biphenyl-4-sulfonamide; and
pharmaceutically acceptable salts thereof.
[0165] In certain embodiments of the compounds of formula I, the pharmaceutically acceptable salt is a hydrochloride salt.

[0166] Compounds of formula I may be used to modulate the activity of secreted frizzled related protein-1. Such compounds are of interest for the treatment of bone fractures as well as bone disorders, including osteoporosis, and for the treatment of arthritis, chronic obstructive pulmonary disease, cartilage defects, leiomyoma, acute myeloid leukemia, wound healing, prostate cancer, autoimmune inflammatory disorders, such as Graves ophthalmopathy, and combinations thereof.

[0167] In certain embodiments, the present invention therefore provides methods of treating, preventing, inhibiting, or alleviating each of the maladies listed above in a mammal, preferably in a human, comprising administering a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof to a patient suspected to suffer from such a malady.

[0168] In other embodiments, the invention relates to compositions comprising at least one compound of formula I, or a stereoisomer or pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents. Such compositions include pharmaceutical compositions for treating or controlling disease states or conditions of the bone. In certain embodiments, the compositions comprise mixtures of one or more compounds of formula I.

[0169] Another aspect of the invention provides a process for the preparation of a compound of formula I:

\[ \text{[Diagram]} \]

or a pharmaceutically acceptable salt thereof;

wherein:
$R_i$ is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or perfluoroalkoxy;

$R_2$ is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, arythio, arylsulfonyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or perfluoroalkoxy, wherein any aryl or heteroaryl portion of $R_2$ may be optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, hydroxy, carboxy, alkoxyalkyl, alkylaminocarbonyl, dialkylaminocarbonyl, aryaminocarbonyl, alkyaminothiocarbonyl, dialkyaminothiocarbonyl, aryaminothiocarbonyl, cycloalkylcarbonyl, heteroaryl carbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl;

$R_3$ is H, halo, alkyl, alkoxy, aryalkyl, or perfluoroalkyl;

$R_4$ is halo, alkyl, cyano, cycloalkyl, aryalkyl, nitro, perfluoroalkyl, or perfluoroalkoxy;

$R_5$ is H, alkyl, alkylamino, cycloalkylamino, dialkylamino, alkoxy, alkoxyalkyl, aryl, arylalkyl, arylamino, aminocarbonyl, aminalkyl, alkylaminocarbonylaminoalkyl, heteroaryl, heteroarylamino, heterocycloalkyl, or heterocycloalkylamino, wherein any aryl, heteroaryl, or heterocycloalkyl portion of $R_5$ may be optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, oxo, alkoxyalkyl, alkylamino, dialkylamino, alkylaminoalkylamino, dialkylaminoalkylamino, alkylaminodialkylamino, dialkylaminodialkylamino, cyano, carboxy, halo, alkoxyalkyl, arylcarbonyl, alkoxycarbonyl, alkoxyalkylamino, alkoxyalkylaminocarbonyl, aminoalkyl, alkylaminocarbonyl, alkylaminocarbonyl, alkylaminocarbonylamino, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, aryaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl; and

X is carbonyl, thiocarbonyl, sulfonyl, sulfoxide, alkyl, alkenyl or absent;

the process comprising:
reacting a compound of formula \( IA \):

\[
\begin{array}{c}
\text{IA;}
\end{array}
\]

with a compound of formula \( IB \):

\[
\begin{array}{c}
\text{IB;}
\end{array}
\]

wherein,

if \( W \) is \( X-R.5 \), the compound of formula \( I \) is formed; or

if \( W \) is a protecting group, the compound of formula \( IC \) is formed and the process further comprises the steps of:

deprotecting the compound of formula \( IC \):

\[
\begin{array}{c}
\text{IC;}
\end{array}
\]

to form a compound of formula \( BD \):

\[
\begin{array}{c}
\text{BD;}
\end{array}
\]

reacting the compound of formula \( ID \) with \( RS-X-GA \);

wherein \( G_A \) is an activating group,

thereby forming the compound of formula \( I \).

[0170] In a more particular embodiment, the activating group is selected from the group consisting of halo, tosylate, mesylate, triflate, an ester, epoxide or aldehyde. In another more particular embodiment, the protecting group is selected from the group consisting of BOC, benzyl, acetyl, PMB, alkyl, Fmoc, Cbz, or trifluoroacetyl, tosyl and triphenylmethyl.
Certain of the compounds of formula I contain stereogenic carbon atoms or other chiral elements and thus give rise to stereoisomers, including enantiomers and diastereomers. The invention generally relates to all stereoisomers of the compounds of formula I, as well as to mixtures of the stereoisomers. Throughout this application, the name of a compound without indication as to the absolute configuration of an asymmetric center is intended to embrace the individual stereoisomers as well as mixtures of stereoisomers. Reference to optical rotation [(+), (-) and (±)] is utilized to distinguish the enantiomers from one another and from the racemate. Furthermore, throughout this application, the designations R* and S* are used to indicate relative stereochemistry, employing the Chemical Abstracts convention which automatically assigns R* to the lowest numbered asymmetric center.

An enantiomer can, in some embodiments of the invention, be provided substantially free of the corresponding enantiomer. Thus, reference to an enantiomer as being substantially free of the corresponding enantiomer indicates that it is isolated or separated via separation techniques or prepared so as to be substantially free of the corresponding enantiomer. "Substantially free," as used herein, means that a significantly lesser proportion of the corresponding enantiomer is present. In preferred embodiments, less than about 90 % by weight of the corresponding enantiomer is present relative to desired enantiomer, more preferably less than about 1 % by weight. Preferred enantiomers can be isolated from racemic mixtures by any method known to those skilled in the art, including high performance liquid chromatography (HPLC), and the formation and crystallization of chiral salts, or preferred enantiomers, can be prepared by methods described herein. Methods for the preparation of enantiomers are described, for example, in Jacques, et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen, S.H., et al., Tetrahedron33:2725 (1977); EHel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S.H. Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliei, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972), each of which is hereby incorporated by reference in its entirety.

The following synthetic schemes are designed to illustrate, but not limit, general procedures for the preparation of compounds of formula I. The reagents used can be either commercially obtained or can be prepared by standard procedures described in the literature. It is intended that the scope of this invention will cover all isomers (enantiomeric and
diastereomeric) and all mixtures, including but not limited to racemic mixtures. The isomeric forms of the compounds of this invention may be separated or resolved using methods known to those skilled in the art or by synthetic methods that are stereospecific or asymmetric.

Scheme 1

As illustrated in Scheme 1, compounds of formula I can be prepared from intermediates Ia and Ib starting from suitably substituted aryl sulfonyl chlorides (II) and 4-amino piperidines (IIia). The sulfonyl chlorides can be obtained commercially, known in the literature, or prepared according to methods known and established for the preparation of sulfonyl chlorides, including procedures exemplified in the experimental section of this document, wherein R1 - R4 are as previously defined. EQa, wherein W is an acceptable protecting group known to one skilled in the art such as tert-butoxy carbonyl, t-Boc, or Boc, can be obtained commercially, known in the literature, or prepared according to methods known and established for the preparation of protected 4-amino piperidines. Compounds of formula Ia can be treated with acid, or by an appropriate reagent system for alternative protecting groups, for several hours or longer where necessary to provide the intermediates Ib. The intermediates of formula Ib can be treated with an electrophilic source such as, but not limited to, R5Z wherein Z is sulfonyl halide, activated acid, isocyanate, isothiocyanate, or
halide in the presence of an acid scavenger when appropriate to yield a compound of formula I.

Scheme 2

![Chemical Reaction Diagram]

Alternatively as illustrated in Scheme 2, compounds of formula I can be prepared from intermediates II, as previously described, and HiJe. Treatment of HIlb with R5Z, as previously defined, followed by removal of the protecting group W, using acceptable procedures, such as acid treatment to remove a Boc protecting group, yields intermediates πic. Intermediate IIIb, wherein W is an acceptable protecting group known to one skilled in the art such as tertiarybutoxy carbonyl or tBOC, can be obtained commercially, known in the literature, or prepared according to methods known and established.
In Scheme 3, intermediate Ic can be converted to compounds or intermediates of formula Id, as defined herein, by treatment with a palladium catalyst in the presence of an aryl boronic acid, or any other suitable aryl boronate species. Intermediates Ic can also be treated with a cyanide source such as zinc cyanide in the presence of a palladium catalyst to provide compounds or intermediates of formula Ie. In addition, intermediates Ic can be undergo a metal halogen exchange with a reagent such as butyl lithium to form an aryl lithium complex that can be quenched with an electrophilic source such as an aryl sulfonyl fluoride to provide compounds or intermediates of formula If. Compounds of formula Ic-f represent compounds of formula Ia and can be elaborated to compounds of formula Ib and I by methods previously described.
Scheme 4 is representative of, but not limited to, the further elaboration of compounds of formula Ig to arrive at compounds of formula Ih. The activation of an acid, such as intermediate IV, can be conducted with an activating reagent such as EDC, or according to methods known and established for the preparation of activated acids, including procedures exemplified in the experimental section of this document, followed by reaction with intermediate Ib provides compounds Ig. The protecting group, W, of compound Ig, can be removed as previously described affording Ih. Reaction of Ih with electrophilic reagents such as ReZ (where Re is alkyl, alkoxy, aryl, aryalkyl, alkylaminio, arylamino, heteroaryl, or heteroarylamino and Z is sulfonyl halide, activated acid, isocyanate, isothiocyanate, or halide in the presence of an acid scavenger when appropriate), in a suitable solvent such as DCM or THF provides compounds of formula Ii. Compounds of formula Ig, Ih, and Ii represent compounds of formula I, wherein X is carbonyl and R5 is an appropriately substituted heterocycloalkyl group.

In certain embodiments, the invention relates to compositions comprising at least one compound of formula I, or a stereoisomer or pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents. Such compositions are prepared in accordance with general pharmaceutical formulation procedures, such as, for example, those described in Remington's Pharmaceutical Sciences, 17th edition, ed. Alfonoso R. Gennaro, Mack Publishing Company, Easton, PA (1985),
which is incorporated herein by reference in its entirety. Pharmaceutically acceptable carriers are those carriers that are compatible with the other ingredients in the formulation and are biologically acceptable.

[0179] The compounds of formula I can be administered orally or parenterally, neat, or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances that can also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders, tablet-disintegrating agents, or encapsulating materials. In powders, the carrier is a finely divided solid that is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

[0180] Liquid carriers can be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both, or a pharmaceutically acceptable oil or fat. The liquid carrier can contain other suitable pharmaceutical additives such as, for example, solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.
[0181] Liquid pharmaceutical compositions that are sterile solutions or suspensions can be administered by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Compositions for oral administration can be in either liquid or solid form.

[0182] The compounds of formula I can be administered rectally or vaginally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of formula I can be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of formula I can also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier can take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments can be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorbent powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient can also be suitable. A variety of occlusive devices can be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

[0183] Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or suppositories. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

[0184] The amount provided to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, and the state of the patient, the manner of administration, and the like. In therapeutic applications, compounds of formula I are provided to a patient already suffering from a disease in an
amount sufficient to cure or at least partially ameliorate the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as a "therapeutically effective amount." The dosage to be used in the treatment of a specific case must be subjectively determined by the attending physician. The variables involved include the specific condition and the size, age, and response pattern of the patient. The compounds can be administered orally, rectally, parenterally, or topically to the skin and mucosa. The usual daily dose depends on the specific compound, method of treatment and condition treated. The usual daily dose is 0.01 - 1000 mg/kg for oral application, preferably 0.5 - 500 mg/kg, and 0.1 - 100 mg/kg for parenteral application, preferably 0.5 - 50 mg/kg.


EXAMPLES

[0186] The following examples are illustrative of certain embodiments of the invention and should not be considered to limit the scope of the invention. The reagents used can be either commercially obtained or can be prepared by standard procedures described in the literature. ACD NamePro software was employed to generate IUPAC names for the following examples. The IUPAC names of the following examples are indicative of the neutral or free base forms. Compounds were either isolated as a free base or the corresponding hydrochloride salt as indicated in the experimental procedure. The purity of compounds where indicated was determined by analytical HPLC using the following conditions: Waters Xterra RP18 HPLC column (3.5 m, 150 mm L x 4.6 mm ID), 40°C column temperature, 1.2
mL/min flow rate, photodiode array detection (210-400 nm), linear mobile phase gradient of 15 to 95% B over 10 minutes, holding 5 minutes at 95% B (mobile phase A: 10mM ammonium formate in water, pH 3.5 / mobile phase B: 1:1 methanol/acetonitrile). It is intended that the scope of this invention will cover all isomers (enantiomeric and diastereomeric) and all mixtures, including but not limited to racemic mixtures. The isomeric forms of the compounds of this invention may be separated or resolved using methods known to those skilled in the art or by synthetic methods that are stereospecific or asymmetric.

Example 1, tert-butyl 4-\{[2-(trifluoromethyl)phenylsulfonyl]amino\}piperidine-1-carboxylate

[0187] 2- Trifluoromethylbenzenesulfonyl chloride (735 mg, 3 mmol) was added to a stirred solution of 4-aminopiperidine-1-carboxylic acid tert-butyl ester (601 mg, 3 mmol) and triethylamine (0.83 mL, 6 mmol) in dichloromethane (10 mL). The reaction mixture was allowed to stir at room temperature for 16 hours. The organic phase was washed with water (2 x 10 mL) and the aqueous phase was discarded. The dichloromethane was removed in vacuo and the resulting residue was purified by flash column chromatography using a gradient of ethyl acetate and hexane (20 - 50%) resulting in the isolation of tert-butyl 4-\{[2-(trifluoromethyl)phenylsulfonyl]amino\}piperidine-1-carboxylate (1.25 g, 99%).

[0188] MS (ES-) m/z 407. i; HPLC purity 100%, Rₜ 9.3 minutes
HRMS: calculated for C₁₇H₂₃F₃N₂O₄S + H⁺, 409.14034; found (ESI, [M+H-C₄H₈]⁺), 353.0737;

Example 2, tert-butyl 4-\{[5-bromo-2-(trifluoromethoxy)phenylsulfonyl]amino\}piperidine-1-carboxylate

[0189] In an analogous manner to example 1, 5-bromo-2-trifluoromethoxy-benzenesulfonyl chloride was used to prepare tert-butyl 4-\{[5-bromo-2-(trifluoromethoxy)phenylsulfonyl]amino\}piperidine-1-carboxylate (1.6 g, 99%).

[0190] MS (ES-) m/z 500.9;
HPLC purity 100%, Rₜ 0.3 min
HRMS: calculated for C_{12}H_{22}BrF_{3}N_{2}O_{5}S + H+, 503.04576; found (ESI, [M+H-C4H8]+), 446.981.

Example 3, tert-buty1 4-((2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate

[0191] tert-butyl 4-((2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate (1.0 g, 2.5 mmol) was dissolved in ethylacetate and a saturated solution of HCl in ethyl acetate was added with stirring. A white solid precipitated and after 16 hours the solid was collected by suction filtration resulting in the isolation of N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide as an hydrochloride salt (0.78 g, 90%).

MS (ES+) m/z 308.8;
HPLC purity 100%, R\text{t} 4.7 min.;
HRMS: calculated for C_{12}H_{19}F_{3}N_{2}O_{5}S + H+, 309.08791; found (ESI, [M+H]+), 309.0869;

Example 4, 3-[[4-((2-trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl] benzoic acid

[0192] To a stirred slurry of N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride salt (0.11 rag, 0.32 mmol) in dichloromethane (10 mL) was added triethylamine (0.1 mL, 0.72 mmol) followed by 3-(chlorosulfonyl)benzoic acid (79 mg, 0.36 mmol). The reaction was allowed to stir at room temperature for 16 h. The organic phase was washed with 2N aqueous HCl solution (2 x), then brine, dried over anhydrous MgSO_{4}, filtered and concentrated. The resulting solid was suspended in dichloromethane and filtered affording 3-[[4-((2-trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl] benzoic acid (90 mg, 50%).

[0193] MS (ES+) m/z 492.7;
HPLC purity 100%, R\text{t} 8.4 minutes;
HRMS: calculated for C_{10}H_{19}F_{3}N_{2}O_{6}S_{2} + H+, 493.07094; found (ESI, [M+H]+), 493.0698;

Example 5, tert-butyl 4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate
In an analogous manner to example 1, 4-bromo-2-((trifluoromethyl)benzenesulfonyl) chloride was used to prepare tert-butyl 4-(((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate (412 mg, 84%).

MS (ES-) m/z 484.9;
HPLC purity 100.0%, Rₜ 11.3 min.;
HRMS: calculated for C₁₇H₂₂BrF₃N₂O₄S + H⁺, 487.05085; found (ESI, [M+H-C₄H₈]⁺), 430.9865;

Example 6; tert-butyl 4-(((4-bromo-2-(trifluoromethoxy)phenyl)sulfonyl)amino)piperidine-1-carboxylate

In an analogous manner to example 1, 4-bromo-2-((trifluoromethoxy)benzenesulfonyl) chloride was used to prepare tert-butyl 4-(((4-bromo-2-(trifluoromethoxy)phenyl)sulfonyl)amino)piperidine-1-carboxylate (422 mg, 84%).

MS (ES-) m/z 500.9;
HPLC purity 100.0%, Rₜ 12.1 minutes
HRMS: calculated for C₁₇H₂₂BrF₃N₂O₅S + H⁺, 503.04576; found (ESI, [M+H-C₄H₈]⁺), 446.9788

Example 7; tert-butyl 4-(((2,5-bis(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate

In an analogous manner to example 1, 2,5-bis(trifluoromethyl)benzenesulfonyl chloride was used to prepare tert-butyl 4-(((2,5-bis(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate (422 mg, 84%).

MS (ES-) m/z 475.0;
HPLC purity 100.0%, Rₜ 10.1 minutes;
HRMS: calculated for C₁₈H₂₂F₆N₂O₄S + H⁺, 477.12772; found (ESI, [M+H-C₄H₈]⁺), 421.0635
Example 8; tert-butyl 4-((2-chloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate

[0200] In an analogous manner to example 1, 2-chloro-4-(trifluoromethyl)benzenesulfonyl chloride was used to prepare tert-butyl 4-((2-chloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate (400 mg, 90%).

[0201] MS (ES-) m/z 441.0;
HPLC purity 100.0%, τ 10.0 minutes;
HRMS: calculated for C_{17}H_{22}ClF_{3}N_{2}O_{4}S + H+, 443.10136; found (ESI, [M+H-C4H8]+), 387.0366

Example 9; tert-butyl 4-((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate

[0202] In an analogous manner to example 1, 2-chloro-5-(trifluoromethyl)benzenesulfonyl chloride was used to prepare tert-butyl 4-((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate (355 mg, 80%).

[0203] MS (ES-) m/z 441.0;
HPLC purity 100.0%, τ 10.0 minutes;
HRMS: calculated for C_{17}H_{22}ClF_{3}N_{2}O_{4}S + H+, 443.10136; found (ESI, [M+H-C4H8]+), 387.0368;

Example 10; tert-butyl 4-((2,3-dichlorophenyl)sulfonyl)amino)piperidine-1-carboxylate

[0204] In an analogous manner to example 1, 2,3-dichlorobenzenesulfonyl chloride was used to prepare tert-butyl 4-((2,3-dichlorophenyl)sulfonyl)amino)piperidine-1-carboxylate (330 mg, 80%).

[0205] MS (ES-) m/z 406.9;
HPLC purity 100.0%, τ 9.7 minutes;
HRMS: calculated for C_{16}H_{22}Cl_{2}N_{2}O_{4}S + H+, 409.07501; found (ESI, [M+H-C4H8]+),
Example 11; tert-butyl 4-[[2,4-dichlorophenyl)sulfonyl]amino]piperidine-l-carboxylate

[0206] In an analogous manner to example 1, 2,4-dichlorobenzenesulfonyl chloride was used to prepare tert-butyl 4-[[2,4-dichlorophenyl)sulfonyl]amino]piperidine-l-carboxylate (328 mg, 80%).

[0207] MS (ES-) m/z 406.9;
HPLC purity 100.0%, R<sub>t</sub> 11.4 minutes;
HRMS: calculated for C<sub>16</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S +H+, 409.07501; found (ESI, [M+H-C4H8]<sup>+</sup>), 353.0087

Example 12; tert-butyl 4-[(2-ethylphenyl)sulfonyl]amino]piperidine-l-carboxylate

[0208] In an analogous manner to example 1, 2-ethylbenzenesulfonyl chloride was used to prepare tert-butyl 4-[(2-ethylphenyl)sulfonyl]amino]piperidine-l-carboxylate (272 mg, 77%).

[0209] MS (ES-) m/z 353.0;
HPLC purity 100.0%, R<sub>t</sub> 10.6 minutes;
HRMS: calculated for C<sub>17</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S +H+, 355.16860; found (ESI, [M+H]<sup>+</sup>), 355.1697;

Example 13; tert-butyl 4-[(2-cyanophenyl)sulfonyl]amino]piperidine-l-carboxylate

[0210] In an analogous manner to example 1, 2-cyanobenzenesulfonyl chloride was used to prepare tert-butyl 4-[(2-cyanophenyl)sulfonyl]amino]piperidine-l-carboxylate (117 mg, 32%).

[0211] MS (ES-) m/z 364.0;
HPLC purity 75.3%, 9.6 minutes;
HRMS: calculated for C<sub>19</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>S +H+, 366.14820; found (ESI, [M+H]<sup>+</sup>), 366.1493;
Example 14: tert-butyl 4-\{[(2-nitrophenyl)sulfonyl]amino\}piperidine-1-carboxylate

[0212] In an analogous manner to example 1, 2-nitrobenzenesulfonyl chloride was used to prepare tert-butyl 4-\{[(2-nitrophenyl)sulfonyl]amino\}piperidine-1-carboxylate (317 mg, 82%).

[0213] MS (ES-) m/z 384.0;
HPLC purity 100.0%, R<sub>t</sub> 8.8 minutes;
HRMS: calculated for C<sub>17</sub>H<sub>23</sub>N<sub>3</sub>O<sub>6</sub>S + H+, 386.13803; found (ESI, [M+H-C4H8]+), 330.0731;

Example 15: 4-bromo-\textit{N}-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide

[0214] In an analogous manner to example 3, example 5 was treated with a saturated solution of HCl in ethyl acetate to provide 4-bromo-\textit{N}-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide as a hydrochloride salt (310 mg, 93%).

[0215] MS (ES+) m/z 386.9;
HPLC purity 99.1%, R<sub>t</sub> 6.2 minutes;
HRMS: calculated for C<sub>12</sub>H<sub>14</sub>BrF<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S + H+, 386.99842; found (ESI, [M+H]⁺), 387.0002;

Example 16: 4-bromo-\textit{N}-piperidin-4-yl-2-(trifluoromethoxy)benzenesulfonamide

[0216] In an analogous manner to example 3, example 6 was treated with a saturated solution of HCl in ethyl acetate to provide 4-bromo-\textit{N}-piperidin-4-yl-2-(trifluoromethoxy)benzenesulfonamide as a hydrochloride salt (335 mg, 99%).

[0217] MS (ES+) m/z 402.9;
HPLC purity 99.1%, R<sub>t</sub> 6.4 minutes;
HRMS: calculated for C<sub>21</sub>H<sub>14</sub>BrF<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S + H+, 402.99333; found (ESI, [M+H]⁺), 402.9929;

Example 17: 4\textit{V}-piperidin-4-yl-2,5-bis(trifluoromethyl)benzenesulfonamide
In an analogous manner to example 3, example 7 was treated with a saturated solution of HCl in ethyl acetate to provide 4-piperidin-4-yl-2,5-bis(trifluoromethyl)benzenesulfonamide as a hydrochloride salt (210 mg, 85%).

MS (ES+) m/z 377.1;
HPLC purity 100.0%, Rₜ 6.3 minutes;
HRMS: calculated for C₁₃H₁₄F₆N₂O₂S + H⁺, 377.07529; found (ESI, [M+H]⁺), 377.0791;

Example 18; 2-chloro-4'-piperidin-4-yl-4-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 3, example 8 was treated with a saturated solution of HCl in ethyl acetate to provide 2-chloro-N-piperidin-4-yl-4-(trifluoromethyl)benzenesulfonamide as a hydrochloride salt (270 mg, 99%).

MS (ES+) m/z 343.0;
HPLC purity 100.0%, Rₜ 6.0 minutes;
HRMS: calculated for C₁₂H₁₄ClF₃N₂O₂S + H⁺, 343.04893; found (ESI, [M+H]⁺), 343.0505;

Example 19; 2-chloro-N-piperidin-4-yl-5-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 3, example 9 was treated with a saturated solution of HCl in ethyl acetate to provide 2-chloro-4'-piperidin-4-yl-5-(trifluoromethyl)benzenesulfonamide as a hydrochloride salt (252 mg, 92%).

MS (ES+) m/z 343.0;
HPLC purity 100.0%, Rₜ 5.9 minutes;
HRMS: calculated for C₁₂H₁₄ClF₃N₂O₂S + H⁺, 343.04893; found (ESI, [M+H]⁺), 343.0479;

Example 20; 2,3-dichloro-4'-piperidinylbenzenesulfonamide

In an analogous manner to example 3, example 10 was treated with a saturated solution of HCl in ethyl acetate to provide 2,3-dichloro-N-piperidin-4-ylbenzenesulfonamide as a hydrochloride salt (250 mg, 99%).
Example 21; 2,4-dichloro-Λ-piperidin-4-ylbenzenesulfonamide

In an analogous manner to example 3, example 11 was treated with a saturated solution of HCl in ethyl acetate to provide 2,4-dichloro-Λ-piperidin-4-ylbenzenesulfonamide as a hydrochloride salt (236 mg, 99%).

Example 22; 2-methyl-Λ-piperidin-4-ylbenzenesulfonamide

In an analogous manner to example 3, example 12 was treated with a saturated solution of HCl in ethyl acetate to provide 2-methyl-Λ-piperidin-4-ylbenzenesulfonamide as a hydrochloride salt (171 mg, 89%).

Example 23; 2-cyano-Λ-piperidin-4-ylbenzenesulfonamide

In an analogous manner to example 3, example 13 was treated with a saturated solution of HCl in ethyl acetate to provide 2-cyano-Λ-piperidin-4-ylbenzenesulfonamide as a hydrochloride salt (58 mg, 92%).
Example 24; 2-nitro-\(\text{\textalpha{}}\)-piperidin-4-ylbenzenesulfonamide

[0232] In an analogous manner to example 3, example 14 was treated with a saturated solution of HCl in ethyl acetate to provide 2-nitro-\(\text{\textalpha{}}\)-piperidin-4-ylbenzenesulfonamide as a hydrochloride salt (219 mg, 94%).

[0233] MS (ESI+) \(m/z\) 286;
HPLC purity 99.6%, \(R_t\) 3.7 minutes;
HRMS: calculated for \(\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_4\text{S} + \text{H}^+\), 286.08560; found (ESI, \([\text{M+H}]^+\)), 286.0829;

Example 25; 2-\([\text{4-}((\text{2-(trifluoromethyl)}\text{phenyl)sulfonyl})\text{amino})\text{piperidin-1-yl}]\text{acetamide}

[0234] To a suspension of \(\text{\textalpha{}}\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride salt, example 3, (74 mg, 0.21 mmol) in acetone was added potassium iodide (catalytic amount) and bromoacetamide (33 mg, 0.23 mmol). The reaction mixture was heated (50 °C, 16 h) and monitored by LCMS. The solvent was removed \textit{in vacuo} and water was added. The product was extracted with ethyl acetate and concentrated to dryness. The crude residue was purified by flash chromatography using a solvent system comprised of dichloromethane and 10% methanolic dichloromethane (0 to 80%). The isolated free base was dissolved in ethyl acetate and treated with HCl gas to afford the hydrochloride salt of 2-\([\text{4-}((\text{2-(trifluoromethyl)}\text{phenyl)sulfonyl})\text{amino})\text{piperidin-1-yl}]\text{acetamide} (72 mg, 85%).

[0235] MS (ESI+) \(m/z\) 366;
HPLC purity 100.0%, \(R_t\) 4.6 minutes;
HRMS: calculated for \(\text{C}_{4}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_3\text{S} + \text{H}^+\), 366.10937; found (ESI, \([\text{MH-H}]^+\)), 366.1075;

Example 26; 3-\([\text{4-}((\text{4-bromo-2-(trifluoromethyl)}\text{phenyl)sulfonyl})\text{amino})\text{piperidin-1-yl}]\text{sulfonyl} \text{benzoic acid}
In an analogous manner to example 4, example 15 was treated with 3-(chlorosulfonyl)benzoic acid to provide 3-\{\text{4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl}sulfonyl\}benzoic acid (145 mg, 83%).

MS (ES+) \text{m/z} 570.9; 
HPLC purity 96.9%, \(R_T\) 9.4 minutes; 
HRMS: calculated for \(\text{C}_{19}\text{H}_{18}\text{BrF}_3\text{N}_2\text{O}_6\text{S}_2 + \text{H}^+\), 570.98145; found (ESI, [M+H]+), 571.0051; 

Example 27; 3-\{\text{4-((4-bromo-2-(trifluoromethoxy)phenyl)sulfonyl)amino)piperidin-1-yl}sulfonyl\}benzoic acid

In an analogous manner to example 4, example 16 was treated with 3-(chlorosulfonyl)benzoic acid to provide 3-\{\text{4-((4-bromo-2-(trifluoromethoxy)phenyl)sulfonyl)amino)piperidin-1-yl}sulfonyl\}benzoic acid (152 mg, 88%).

MS (ES+) \text{m/z} 586.9; 
HPLC purity 95.8%, \(R_T\) 9.5 minutes; 
HRMS: calculated for \(\text{C}_{19}\text{H}_{18}\text{BrF}_3\text{N}_2\text{O}_7\text{S}_2 + \text{H}^+\), 586.97636; found (ESI, [M+Hf]), 586.976;

Example 28; 3-\{\text{4-((2,5-bis(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl}sulfonyl\}benzoic acid

In an analogous manner to example 4, example 17 was treated with 3-(chlorosulfonyl)benzoic acid to provide 3-\{\text{4-((2,5-bis(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl}sulfonyl\}benzoic acid (166 mg, 85%).

MS (ES+) \text{m/z} 560.8; 
HPLC purity 95.6%, \(R_T\) 9.3 minutes; 

Example 29; 3-\{\text{4-((2-chloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl}sulfonyl\}benzoic acid
yljsulfonyl} benzoic acid

[0242] In an analogous manner to example 4, example 18 was treated with 3-(chlorosulfonyl)benzoic acid to provide 3-[[4-([2-chloro-4-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl]benzoic acid (130 mg, 70%).

[0243] MS (ES+) m/z 526.8; HPLC purity 93.9%, R_τ 9.2 minutes;

Example 30; 3-[[4-([2-chloro-5-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl] benzoic acid

[0244] In an analogous manner to example 4, example 19 was treated with 3-(chlorosulfonyl)benzoic acid to provide 3-[[4-([2-chloro-5-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl]benzoic acid (110 mg, 60%).

[0245] MS (ES+) m/z 524.8; HPLC purity 94.0%, R_τ 9.1 minutes;

Example 31; 3-[[4-([2-nitrophenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl]benzoic acid

[0246] In an analogous manner to example 4, example 24 was treated with 3-(chlorosulfonyl)benzoic acid to provide 3-[[4-([2-nitrophenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl]benzoic acid (73 mg, 44%).

[0247] MS (ES-) m/z 467.9; HPLC purity 99.8%, R_τ 7.9 minutes; HRMS: calculated for C_{18}H_{19}N_{3}O_{8}S_{2} + H+, 470.06863; found (ESI, [M+H]), 470.0748;

Example 32, 4-bromo-[N-1-[(3-cyanophenyl)sulfonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide
Step 1: tert-butyl 4-({[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-l-carboxylate

A solution of 4-amino-l-Boc-piperidine (3.2 g, 15 mmol) and triethylamine (d 0.726, 3.0 mL, 22 mmol) in dichloromethane (150 mL) was treated with 4-bromo-2-(trifluoromethyl)benzenesulfonyl chloride (5.0 g, 15 mmol) at 23 °C. After 1 hour, the reaction solution was washed with 1N aqueous sodium hydroxide (15 mL), water (150 mL) and saturated brine (150 mL). The organic solution was dried (MgSO₄) and concentrated under vacuum to provide a clear oil. Flash column chromatography on silica gel (75 g) eluting 20 %-, then 50 % ethyl acetate-hexanes provided tert-butyl 4-({[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-l-carboxylate (6.4 g, 88 %) as a white solid. MS (ES) m/z 484.7 ([M-H]-).

Step 2: 4-bromo- N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride

[0248] A solution of tert-butyl 4-({[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-l-carboxylate (6.4 g, 13 mmol) in ethyl acetate (125 mL) was treated with hydrogen chloride gas (passed through Drierite) during several minutes at 23 °C. The flask was sealed and after 1 hour the resulting white solid was vacuum-filtered, washed with ethyl acetate and air-dried to provide 4-bromo- N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (5.1 g, 93 %) as a white solid. MS (ES) m/z 386.7 ([M+H]+).

Step 3: 4-bromo- N-1-[3-cyanophenyl)sulfonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride

[0249J 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (106 mg, 0.25 mmol), 3-cyanobenzenesulfonyl chloride (50 mg, 0.25 mmol) and triethylamine (d 0.726, 0.105 mL, 0.75 mmol) were combined in dichloromethane (2.5 mL) at 23 °C. After 2 hours, the reaction solution was washed with saturated aqueous sodium bicarbonate (2.5 mL), water (2.5 mL) and saturated brine (2.5 mL). The organic solution was dried (MgSO₄) and concentrated under vacuum. The residue was dissolved in a small
volume of dichloromethane, loaded directly onto a 4 g ISCO column (silica gel) and eluted with ethyl acetate-hexanes (30-75% solution @ 18 mL/min) to provide 4-bromo-\(N\)-[1-[(3-cyanophenyl)sulfonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (94 mg, 68%) as a white solid. MS (ES) \(m/z\) 551.5 ([M+H]⁺).

Example 33, 4-bromo-\(N\)-[1-(3-cyanobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0250] Starting from 4-bromo-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (Example 1, Step 2) and 3-cyanobenzoyl chloride in place of 3-cyanobenzenesulfonyl chloride, 4-bromo-\(N\)-[1-(3-cyanobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) \(m/z\) 515.6 ([M+H]⁺).

Example 34, 4-bromo-\(N\)-[1-(2-furoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0251] Starting from 4-bromo-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (Example 1, Step 2) and 2-furoyl chloride in place of 3-cyanobenzenesulfonyl chloride, 4-bromo-\(N\)-[1-(2-furoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) \(m/z\) 480.6 ([M+H]⁺).

Example 35, 4-bromo-\(N\)-[1-(2,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoronethyl)benzenesulfonamide

[0252] Starting from 4-bromo-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (Example 1, Step 2) and 2,4-difluorobenzoyl chloride in place of 3-cyanobenzenesulfonyl chloride, 4-bromo-\(N\)-[1-(2,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) \(m/z\) 526.6 ([M+H]⁺).

Example 36, 4-bromo-\(N\)-[1-(3,4-difluorobenzoyl)piperidin-4-yl]-2-
(trifluoromethyl)benzenesulfonamide

[0253] Starting from 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (Example 1, Step 2) and 3,4-difluorobenzoyl chloride in place of 3-cyanobenzenesulfonyl chloride, 4-bromo-N-[1-(3,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) m/z 526.6 ([M+H]+).

Example 37, \( \text{yV-}{\left[1-(3-\text{cyanophenyl})\text{sulfonyl}\right]}\text{piperidin-4-yl}\)-2-(trifluoromethyl)benzenesulfonamide

Step 1: \( \text{tert-butyl} \ 4-\left(\left[2-(\text{trifluoromethyl})\text{phenyl}\right]\text{sulfonyl}\right)\text{amino}\) piperidine-1-carboxylate

[0254] Starting from 2-(trifluoromethyl)benzenesulfonfyl chloride in place of 4-bromo-2-(trifluoromethyl)benzenesulfonfyl chloride, \( \text{tert-butyl} \ 4-\left(\left[2-(\text{trifluoromethyl})\text{phenyl}\right]\text{sulfonyl}\right)\text{amino}\) piperidine-1-carboxylate was synthesized in the same manner as described in Example 32, Step 1. MS (ES) m/z 406.8 ([M-H]−).

Step 2: \( \text{yV-piperidin-4-yl}-2-(\text{trifluoromethyl})\text{benzenesulfonamide} \) hydrochloride

[0255] Starting from \( \text{tert-butyl} \ 4-\left(\left[2-(\text{trifluoromethyl})\text{phenyl}\right]\text{sulfonyl}\right)\text{amino}\) piperidine-1-carboxylate in place of \( \text{tert-butyl} \ 4-\left(\left[4\text{-bromo-2-(trifluoromethyl})\text{phenyl}\right]\text{sulfonyl}\right)\text{amino}\) piperidine-1-carboxylate, \( \text{N-piperidin-4-yl}-2-(\text{trifluoromethyl})\text{benzenesulfonamide} \) hydrochloride was synthesized in essentially the same manner as described in Example 32, Step 2. MS (ES) m/z 308.9 ([M+H]+).

Step 3: \( \text{iV-}{\left[1-(3-\text{cyanophenyl})\text{sulfonyl}\right]}\text{piperidin-4-yl}\)-2-(trifluoromethyl)benzenesulfonamidide

[0256] Starting from \( \text{N-piperidin-4-yl}-2-(\text{trifluoromethyl})\text{benzenesulfonamide} \) hydrochloride in place of 4-bromo-\( \text{N-piperidin-4-yl}-2-(\text{trifluoromethyl})\text{benzenesulfonamide} \)
hydrochloride, N-(I-[(3-cyanophenyl)sulfonyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) m/z 473.7 ([M+H]+).

Example 38, iV-[l-(3-cyanobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0257] Starting from N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (Example 37, Step 2) in place of 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride and 3-cyanobenzoyl chloride in place of 3-cyanobenzenesulfonyl chloride, N-[I-(3-cyanobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide was synthesized in essentially the same manner as described in Example 1, Step 3. MS (ES) m/z 437.8 ([M+H]+).

Example 39, N-[l-(2-furoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0258] Starting from N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (Example 37, Step 2) in place of 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride and 2-furoyl chloride in place of 3-cyanobenzenesulfonyl chloride, N-[I-(2-furoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) m/z 402.8 ([M+H]+).

Example 40, N-[l-(2,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0259] Starting from N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (Example 37, Step 2) in place of 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride and 2,4-difluorobenzoyl chloride in place of 3-cyanobenzenesulfonyl chloride, N-[I-(2,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) m/z 448.8 ([M+H]+).
Example 41, \(N\)-[(3,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0260] Starting from \(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (Example 37, Step 2) in place of 4-bromo-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride and 3,4-difluorobenzoyl chloride in place of 3-cyanobenzenesulfonyl chloride, \(N\)-[(3,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) m/z 448.8 ([M+H]+).

Example 42, 4-bromo-\(N\)-[(pyridin-2-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0261] To a stirred solution of 4-bromo-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide (0.08 g, 0.19 mmol) and diisopropylethylamine (0.15 mL, 0.86 mmol) in dichloromethane (2 mL) was added picolinoyl chloride HCl (0.034 g, 0.19 mmol) and the resulting solution was stirred at room temperature for 30 minutes. The reaction was washed with ammonium chloride solution (sat.) and concentrated. Flash column separation using 50%-100% ethyl acetate/hexane gradient gave 4-bromo-\(N\)-[(pyridin-2-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide. (0.031 g, 33%).

[0262] MS (ES-) m/z 491.6; HPLC purity 100.0% at 210-370 nm, 8.7 minutes
HRMS: calculated for C\(_{17}\)H\(_{17}\)BrF\(_3\)N\(_3\)O\(_3\)S + H+, 492.01988; found (ESI, [M+H]+), 492.0213;

Example 43, 4-bromo-\(N\)-[(pyridin-3-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0263] In an analogous manner to example 42, 4-bromo-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and nicotinyl chloride HCl were used to prepare 4-bromo-\(N\)-[(pyridin-3-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.
Example 44, 4-bromo-\(N\)-(1-isonicotinoylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

Example 45, tert-butyl (2S)-2-\{4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl\}carbonyl}pyrrolidine-1-carboxylate

Example 46, tert-butyl (2S)-2-\{4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl\}carbonyl}pyrrolidine-1-carboxylate
(trifluoromethyl)phenyl[sulfonyl]amino)piperidin-l-yl]carbonyl]-5-oxopyrrolidine-l-carboxylate

[0269] In an analogous manner to example 45, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and BOC-L-pyroglutamic acid were used to prepare tert-butyl (2S)-2-{[4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-l-yl]carbonyl}-5-oxopyrrolidine-l-carboxylate.

[0270] MS (ES-) m/z 595.7;
HPLC purity 100.0% at 210-370 nm, 9.2 minutes

Example 47, tert-butyl (25)-2-[[4-((3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-l-yl]carbonyl]pyrrolidine-l-carboxylate

[0271] In an analogous manner to example 45, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and BOC-L-proline were used to prepare tert-butyl (25)-2-{[4-((3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-l-yl]carbonyl]pyrrolidine-l-carboxylate.

[0272] MS (ES-) m/z 579.8;
HPLC purity 100.0% at 210-370 nm, 10.4 minutes
HRMS: calculated for C_{28}H_{34}F_{3}N_{3}O_{5}S + H+, 582.22440; found (ESI, [M+H]^+), 582.2239;

Example 48, tert-butyl (5S)-2-oxo-5-{[4-((3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-l-yl]carbonyl]pyrrolidine-l-carboxylate

[0273] In an analogous manner to example 45, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and BOC-L-pyroglutamic acid were used to prepare /er-butyl (5,S^-)-2-oxo-5-{[4-((3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-l-yl]carbonyl]pyrrolidine-l-carboxylate.

[0274] MS (ES-) m/z 593.8;
HPLC purity 100.0% at 210-370 nm, 9.9 minutes
Example 49, 4-bromo-\(N\)-\{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}-2-(trifluoromethyl)benzenesulfonamide

[0275] Step 1: In an analogous manner to example 42, piperidin-4-yl-carbamic acid tert-butyl ester and 2-chloropyridine-5-carbonyl chloride were used to prepare 1-[(6-chloropyridine-3-carbonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.

[0276] Step 2: In an analogous manner to example 54, 1-[(6-chloro-pyridine-3-carbonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester was used to prepare 1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-amine.

[0277] Step 3: In an analogous manner to example 42, 1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-amine and 4-bromo-2-trifluoromethylbenzene sulfonyl chloride were used to prepare 4-bromo-iV-\{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}-2-(trifluoromethyl)benzenesulfonamide.

[0278] MS (ES-) m/z 525.5;
HPLC purity 100.0% at 210-370 nm, 9.4 minutes
HRMS: calculated for \(C_{18}H_{16}BrClF_3N_3O_3S + H^+\), 525.98091; found (ESI, [M+H]\(^{+}\)), 525.9821;

Example 50, 4-bromo-\(N\)-\{1-(2-chloroisonicotinoyl)piperidin-4-yl\}-2-(trifluoromethyl)benzenesulfonamide

[0279] Step 1: In an analogous manner to example 42, piperidin-4-yl-carbamic acid tert-butyl ester and 2-chloropyridine-4-carbonyl chloride were used to prepare tert-butyl [1-(2-chloroisonicotinoyl)piperidin-4-yl]carbamate.

[0280] Step 2: In an analogous manner to example 54, tert-butyl [1-(2-chloroisonicotinoyl)piperidin-4-yl]carbamate was used to prepare 1-(2-chloroisonicotinoyl)piperidin-4-amine.
Step 3: In an analogous manner to example 42, 1-(2-chloroisonicotinoyl)piperidin-4-amine and 4-bromo-2-trifluoromethylbenzene sulfonyle chloride were used to prepare 4-bromo-N-[1-(2-chloroisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

MS (ES-) m/z 525.6;
HPLC purity 100.0% at 210-370 nm, 9.3 minutes
HRMS: calculated for C_{i8}H_{16}BrClF_{3}N_{3}O_{3}S + H+, 525.98091; found (ESI, [M+H]-), 525.9817;

Example 51. N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

Step 1: In an analogous manner to example 42, piperidin-4-yl-carbamic acid tert-butyl ester and 2-chloropyridine-5-carbonyl chloride were used to prepare [1-(6-Chloropyridine-3-carbonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.

Step 2: In an analogous manner to example 54, [1-(6-Chloropyridine-3-carbonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester was used to prepare 1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-amine.

Step 3: In an analogous manner to example 42, 1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-amine and 2-trifluoromethylbenzene sulfonyle chloride were used to prepare JV-(1-[[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) m/z 447.7;
HPLC purity 100.0% at 210-370 nm, 8.2 minutes
HRMS: calculated for C_{i8}H_{17}ClF_{3}N_{3}O_{3}S + H+, 448.07040; found (ESI, [M+H]+), 448.0688;

Example 52, N-[1-(2-chloroisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide
Step 1: In an analogous manner to example 42, piperidin-4-yl-carbamic acid tert-butyl ester and 2-chloropyridine-4-carbonyl chloride were used to prepare tert-butyl [l-(2-chloroisonicotinoyl)piperidin-4-yl]carbamate.

Step 2: In an analogous manner to example 54, tert-butyl [l-(2-chloroisonicotinoyl)piperidin-4-yl]carbamate was used to prepare l-(2-chloroisonicotinoyl)piperidin-4-amine.

Step 3: In an analogous manner to example 42, l-(2-chloroisonicotinoyl)piperidin-4-amine and 2-trifluoromethylbenzene sulfonyl chloride were used to prepare N-[l-(2-chloroisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) m/z 447.7; 
HPLC purity 100.0% at 210-370 nm, 8.1 minutes
HRMS: calculated for C_{15}H_{17}ClF_{3}N_{3}O_{3}S + H+, 448.07040; found (ESI, [M+H]^+), 448.0718;

Example 53, tert-butyl 4-({3-(trifluoromethyl)biphenyl-4-yl}sulfonyl)amino)piperidine-1-carboxylate

To a stirred solution of tert-butyl 4-({[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate (1.0 g, 2.0 mmol) and phenyl boronic acid (0.37 g, 3.0 mmol) in glyme (18 mL) was added sodium carbonate (0.65 g, 6.1 mmol) dissolved in water (3 mL) and tetrakis(triphenylphosphine) palladium (0) (0.11 g, 0.10 mmol) and the resulting solution was heated to reflux for 3 hours, then allowed to cool to room temperature. The mixture was partitioned between ammonium chloride solution (sat) and ethyl acetate. The organic layer concentrated and flash column separation using 0%-30% ethyl acetate/hexane gradient gave tert-butyl 4-({[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate. (0.95 g, 95%).

MS (ES-) m/z 482.9; 
HPLC purity 100.0% at 210-370 nm, 10.9 minutes

Example 54, 7V-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide
To a stirred solution of tert-butyl 4-([(3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidine-1-carboxylate (0.90 g, 1.86 mmol) in ethyl acetate (30 mL) was bubbled in hydrogen chloride gas over several minutes. The resulting solution was stirred room temperature overnight and concentrated to give N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide. (0.76 g, 97%).

Example 55, tert-butyl 4-([(4-(phenylsulfonyl)-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate

To a stirred solution of tert-butyl 4-([(4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate (1.0 g, 2.05 mmol) in THF (12 mL) at 0°C was added methyl magnesium bromide 1.4 M in 75% toluene/THF (1.9 ttiL, 2.7 mmol). The reaction was stirred 15 minutes, then cooled to -78°C and n-butyl lithium 2.5 M in hexane (1.0 mL, 2.5 mmol) was added dropwise. The reaction was stirred an additional 10 minutes. The reaction was warmed to 0°C and benzene sulfonyl fluoride (0.25 mL, 2.10 mmol) was added. The reaction was stirred overnight at room temperature, partitioned between ammonium chloride solution and ethyl acetate. Flash column separation using 0%-40% ethyl acetate/hexane gradient gave tert-butyl 4-([(4-(phenylsulfonyl)-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate. (0.74 g, 66%).

Example 56, 4-(phenylsulfonyl)-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 54, tert-butyl 4-([(4-(phenylsulfonyl)-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate was used to prepare 4-(phenylsulfonyl)-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide.
Example 57, tert-butyl 4-\{4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl\}carbonyl)piperidine-1-carboxylate

Example 58, tert-butyl 4-\{4-([2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl\}carbonyl)piperidine-1-carboxylate

Example 58, tert-butyl 4-\{4-([2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl\}carbonyl)piperidine-1-carboxylate

Starting from N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonylamine hydrochloride (Example 37, Step 2) in place of 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonylamine hydrochloride, tert-butyl 4-\{4-([2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl\}carbonyl)piperidine-1-carboxylate was synthesized in essentially the same manner as described in Example 57. MS (ES) m/z 519.8 ([M+H]+).
Example 59, 4-bromo- $N$-[l-(piperidin-4-ylcarbonyl)piperidin-4-yl]-2-(trifluoroniethyl)benzenesulfonamide hydrochloride

[0301] Starting from tert-/butyl 4-[[4-([[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-l-yl]carbonyl]piperidine-l-carboxylate in place of tert-butyl 4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidine-l-carboxylate, 4-bromo- $N$-[l-(piperidin-4-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride was synthesized in essentially the same manner as described in Example 32, Step 2. $\text{MS (ES) } m/z \ 491.1 \ ([M+H]^+)$.

Example 60, $N$-[l-(piperidin-4-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride

[0302] Starting from tert-butyl 4-[[4-[[2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-l-yl]carbonyl]piperidine-l-carboxylate in place of tert-/butyl 4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidine-l-carboxylate, $N$-[l-(piperidin-4-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride was synthesized in essentially the same manner as described in Example 32, Step 2. $\text{MS (ES) } m/z \ 419.9 \ ([M+H]^+)$.

Example 61, 4-bromo-$N$-[(L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

[0303] In an analogous manner to example 54, tert-butyl (25)-2-[[4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-l-yl]carbonyl]pyrrolidine-l-carboxylate was used to prepare 4-bromo-$N$-(l-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

$\text{MS (ES-) } m/z \ 483.6$;

HPLC purity 100.0% at 210-370 nm, 7.1 minutes

HRMS: calculated for $\text{C}_{48}\text{H}_{27}\text{BrF}_{3}\text{N}_{3}\text{O}_{3}\text{S} + \text{H}^+$, 484.051 18; found (EST, $[M+H]^+$), 484.0526;
Example 62, 4-bromo-\(\text{\text{\(N\)}}\)-[l-(5-oxo-L-prolyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfoiiainide

[0304] In an analogous manner to example 54, \(\text{\text{\(L\)}}\)-butyl (25)-2-[[4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino]piperidin-1-yl]carbonyl]-5-oxopyrrolidine-1-carboxylate was used to prepare 4-bromo-\(\text{\text{\(N\)}}\)-[l-(5-oxo-L-prolyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

[0305] MS (ES-) m/z 497.6;  
HPLC purity 98.4% at 210-370 nm, 7.7 minutes  
HRMS: calculated for C\(_{17}\)H\(_{19}\)BrF\(_3\)N\(_3\)O\(_4\)S + H+, 498.03045; found (ESI, [M+H]+), 498.0301;

Example 63, 4-[[4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino]piperidin-1-yl]sulfonyl]benzoic acid

[0306] In an analogous manner to example 42, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 4-(chlorosulfonyl)benzoic acid were used to prepare 4-[[4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino]piperidin-1-yl]sulfonyl]benzoic acid.

[0307] MS (ES-) m/z 570.5;  
HPLC purity 100.0% at 210-370 nm, 9.3 minutes

Example 64, 3-[[4-[[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino]piperidin-1-yl]sulfonyl] benzoic acid

[0308] In an analogous manner to example 42, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-[[4-[[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino]piperidin-1-yl]sulfonyl]benzoic acid.

[0309] MS (ES+) m/z 568.6;  
HPLC purity 100.0% at 210-370 nm, 9.9 minutes
HRMS: calculated for C_{25}H_{23}F_3N_2O_6S_2 + H+, 569.10224; found (ESI, [M+H]^+), 569.1024;

Example 65, _N_-(1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0310] In an analogous manner to example 42, _N_-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare _N_-1-[(6-chloropyridin-4-yl)carbonyl]piperidin-4-yl]-S-(trifluoromethyl)biphenyl-4-sulfonamide.

[0311] MS (ES+) m/z 523.7;
HPLC purity 100.0% at 210-370 nm, 10.1 minutes
HRMS: calculated for C_{25}H_{24}ClF_3N_3O_3S + H+, 524.10170; found (ESI, [M+H]^+), 524.1011;

Example 66, _N_-(1-L-prolylpiperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0312] In an analogous manner to example 54, tert-butyl (25)-2-[(4-([3-(trifluoromethyl)biphenyl-4-sulfonyl]amino)piperidin-1-yl)carbonyl]pyrrolidine-1-carboxylate was used to prepare _N_-(1-L-prolylpiperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide.

[0313] MS (ES+) m/z 481.8;
HPLC purity 99.1% at 210-370 nm, 8.3 minutes
HRMS: calculated for C_{25}H_{26}F_3N_3O_3S + H+, 482.17197; found (ESI, [M+H]^+), 482.1709;

Example 67, _N_-(1-(5-oxo-L-prolyl)piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0314] In an analogous manner to example 54, tert-butyl (56>2-oxo-5-[(4-([3-(trifluoromethyl)biphenyl-4-sulfonyl]amino)piperidin-1-yl)carbonyl]pyrrolidine-1-carboxylate was used to prepare _N_-(1-(5-oxo-L-prolyl)piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide.
[0315] MS (ES+) m/z 495.8;  
HPLC purity 98.9% at 210-370 nm, 8.8 minutes  
HRMS: calculated for C_{23}H_{24}F_3N_3O_4S + H+, 496.15124; found (ESI, [M+H]^+), 496.1519;

Example 68, **tert-butyl** 4-({[4-cyano-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate

[0316] To a stirred solution of tert-butyl 4-({[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate (0.8 g, 1.64 mmol) in DMF (8 mL) was added zinc cyanide (0.12 g, 0.98 mmol), tris(dibenzylideneacetone)dipalladium(O) (0.07 g, 0.08 mmol), and 1,1’-bis(diphenylphosphino)-ferrocene (0.09 g, 0.16 mmol). The resulting solution was heated to reflux for 3 hours. The solution was filtered through celite, washed with ammonium chloride solution (sat.) and extracted with ethyl acetate. The organic layer was washed several times with brine. Flash column separation with 0%-40% ethyl acetate/ hexane gave *tert*-butyl 4-({[4-cyano-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate. (0.49 g, 69%).

[0317] MS (ES-) m/z 431.8;  
HPLC purity 100.0% at 210-370 nm, 9.5 minutes

Example 69, 4-cyano-jV-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide

[0318] In an analogous manner to example 54, *tert*-butyl 4-({[4-cyano-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate was used to prepare 4-cyano-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide.

[0319] MS (ES+) m/z 333.8;  
HPLC purity 100.0% at 210-370 nm, 5.2 minutes  
HRMS: calculated for C_{13}H_{14}F_3N_3O_2S + H+, 334.08316; found (ESI, [M+H]^+), 334.0826;

Example 70, 3-[[4-({[4-(phenylsulfonyl)-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidin-1-yl)sulfonyl]benzoic acid
In an analogous manner to example 42, 4-(phenylsulfonyl)-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-[[4-[[4-(phenylsulfonyl)-2-(trifluoromethyl)phenyl]sulfonyl]amino]piperidin-1-yl]sulfonyl]benzoic acid.

MS (ES+) m/z 632.6;
HPLC purity 99.0% at 210-370 nm, 9.3 minutes

Example 71, \( V-\{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}-4-(phenylsulfonyl)-2-(trifluoromethyl)benzenesulfonamide \)

In an analogous manner to example 42, 4-(phenylsulfonyl)-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare \( N-\{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}-4-(phenylsulfonyl)-2-(trifluoromethyl)benzenesulfonamide \).

MS (ES-) m/z 587.6;
HPLC purity 96.2% at 210-370 nm, 9.3 minutes
HRMS: calculated for \( C_{24}H_{21}ClF_3\text{N}_3\text{O}_5\text{S}_2^+ + \text{H}^+ \), 588.06360; found (ESI, [M+H]^+), 588.0637;

Example 72, \( 2-\[4-[[4-(phenylsulfonyl)]-2-(trifluoromethyl)phenyl]sulfonyl]amino\]piperidin-1-yl]acetamide \)

To stirred solution of 4-(phenylsulfonyl)-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide (0.10 g, 0.20 mmol), bromoacetamide (0.03 g, 0.20 mmol) and triethylamine (0.1 mL, 0.7 mmol) in acetone (2 mL) was added catalytic potassium iodide and the resulting solution was heated overnight at 50°C. The solution was concentrated and ethyl acetate trituration gave 2-[[4-((phenylsulfonyl))-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]acetamide. (0.068 g, 65%).

MS (ES+) m/z 505.8;
HPLC purity 100.0% at 210-370 nm, 7.1 minutes
HRMS: calculated for C_{20}H_{22}F_{3}N_{3}O_{5}S_{2} + H+, 506.10257; found (ESI, [M+H]^+), 506.1042;


[0326] In an analogous manner to example 45, 4-(phenylsulfonyl)-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and BOC-L-proline were used to prepare tert-butyl (2S)-2-[[4-((phenylsulfonyl)-2-(trifluoromethyl)phenyl)sulfonyl]amino]piperidin-l-yl]carbonyl]pyrrolidine-l-carboxylate.

[0327] MS (ES-) m/z 643.8;
HPLC purity 97.6% at 210-370 nm, 9.7 minutes
HRMS: calculated for C_{28}H_{34}F_{3}N_{3}O_{7}S_{2} + H+, 646.18630; found (ESI, [M+H]^+), 646.1876;

Example 74, tert-butyl 4-((4-fluoro-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-l-carboxylate

[0328] Step 1: To a stirred solution of 4-fluoro-2-trifluoromethylaniline (2.0 g, 11.16 mmol) in acetonitrile (80 mL) at 0°C was added concentrated acetic acid (8 mL) and concentrated hydrochloric acid (8 mL). To this solution was added sodium nitrite (0.92 g, 13.39 mmol) dissolved in water (1.25 mL) in a dropwise fashion. The resulting solution was stirred for 20 minutes, followed by bubbling in sulfur dioxide over 10 minutes. Immediately upon completion of sulfur dioxide addition, copper (II) chloride dihydrate (1.9 g, 11.2 mmol) dissolved in water (2 mL) was added all at once. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was diluted with water and extracted with ethyl acetate several times. The combined organic layer was washed with ammonium chloride solution (sat.) and water. The organic phase was dried over magnesium sulfate, and concentrated. Flash column separation using 0%-30% ethyl acetate/hexane gradient gave 4-fluoro-2-trifluoromethylbenzene sulfonyl chloride. (1.97 g, 67%).
Step 2: In an analogous manner to example 42, 4-fluoro-2-trifluoromethylbenzene sulfonyl chloride and 4-amino-piperidine-1-carboxylic acid tert-butyl ester were used to prepare tert-butyl 4-({4-fluoro-2-(trifluoromethyl)phenyl}sulfonyl)amino)piperidine-1-carboxylate.

MS (ES-) m/z 424.8;
HPLC purity 100.0% at 210-370 nm, 9.8 minutes

Example 75, tert-butyl 4-({4-(dimethylamino)-2-(trifluoromethyl)phenyl}sulfonyl)amino)piperidine-1-carboxylate

A stirred solution of tert-butyl 4-({4-fluoro-2-(trifluoromethyl)phenyl}sulfonyl)amino)piperidine-1-carboxylate (0.60 g, 1.4 mmol) in 2M dimethylamine in THF (6 mL) was microwave irradiated for 20 minutes at 180°C. The resulting solution was washed with ammonium chloride solution (sat.) and extracted with ethyl acetate. The organic layer was concentrated and flash column separation using 0%-40% ethyl acetate/hexane gradient gave tert-butyl 4-({4-(dimethylamino)-2-(trifluoromethyl)phenyl}sulfonyl)amino)piperidine-1-carboxylate. (0.35 g, 60%).

MS (ES-) m/z 449.9;
HPLC purity 100.0% at 210-370 nm, 9.9 minutes

Example 76, 4-(dimethylamino)-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 54, tert-butyl 4-({4-(dimethylamino)-2-(trifluoromethyl)phenyl}sulfonyl)amino)piperidine-1-carboxylate was used to prepare 4-(dimethylamino)-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) m/z 351.9;
HPLC purity 100.0% at 210-370 nm, 5.9 minutes

HRMS: calculated for C_{14}H_{20}F_{3}N_{3}O_{2}S + H+, 352.13011; found (ESI, [M+H]^+) 352.1301;
Example 77, *erf*-butyl 4-({[4-isopropyl-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate

[0335] In an analogous manner to example 74, 4-isopropyl-2-trifluoromethylaniline and 4-amino-piperidine-1-carboxylic acid tert-butyl ester were used to prepare *erf*-butyl 4-({[4-isopropyl-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate.

[0336] MS (ES-) m/z 448.9;
HPLC purity 100.0% at 210-370 nm, 10.6 minutes

Example 78, 4-isopropyl-V-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide

[0337] In an analogous manner to example 54, *erf*-7-butyl 4-({[4-isopropyl-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate was used to prepare 4-isopropyl-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide.

[0338] MS (ES-) m/z 348.8;
HPLC purity 100.0% at 210-370 nm, 7.1 minutes
HEMS: calculated for \(\text{C}_{15}\text{H}_{21}\text{F}_{3}\text{N}_{2}\text{O}_{2}\text{S} + \text{H}^+\), 351.13486; found (ESI, \([\text{M}+\text{H}]^+\)), 351.1347;

Example 79, \(N\)-[1-{(6-chloropyridin-3-yl)carbonyl}piperidin-4-yl]-4-fluoro-2-(trifluoromethyl)benzenesulfonamide

[0339] In an analogous manner to example 42, 4-fluoro-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare \(N\)-[1-{(6-chloropyridin-3-yl)carbonyl}piperidin-4-yl]-4-fluoro-2-(trifluoromethyl)benzenesulfonamide.

[0340] MS (ES+) m/z 465.7;
HPLC purity 99.4% at 210-370 nm, 8.6 minutes
HRMS: calculated for \(\text{C}_{18}\text{H}_{16}\text{ClF}_{4}\text{N}_{3}\text{O}_{3}\text{S} + \text{H}^+\), 466 06098; found (EST, \([\text{M}+\text{H}]^+\)), 466 0606;

Example 80, tert-butyl (2S)-2-{[4-(4-fluoro-2-...
In an analogous manner to example 45, 4-fluoro-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and BOC-L-proline were used to prepare \(\text{t}ro\)-butyl (2S)-2-\{4-([4-fluoro-2-(trifluoromethyl)phenylsulfonyl]amino)piperidin-1-yl\}carbonyl]pyrrolidine-1-carboxylate.

\[
\text{MS (ES-)} m/z 521.8;
\text{HPLC purity 100.0% at 210-370 nm, 9.1 minutes}
\]

Example 81, 4-(phenylsulfonyl)- \(N\)-(L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 54, \(\text{tert-butyl}\) (2S)-2-\{4-([4-(phenylsulfonyl)]-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl\}carbonyl]pyrrolidine-1-carboxylate was used to prepare 4-(phenylsulfonyl)- \(N\)-(L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

\[
\text{MS (ES+)} m/z 545.8;
\text{HPLC purity 97.9% at 210-370 nm, 7.7 minutes}
\]

HRMS: calculated for \(\text{C}_{23}\text{H}_{26}\text{F}_{3}\text{N}_{3}\text{O}_{5}\text{S}_{2} + \text{H}^{+}\), 546.13387; found (ESI, \([\text{M+H}]^{+}\)), 546.1357;

Example 82, 4-fluoro- \(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 54, \(\text{tert-butyl}\) 4-([4-fluoro-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate was used to prepare 4-fluoro- \(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide.

\[
\text{MS (ES+)} m/z 326.8;
\text{HPLC purity 100.0% at 210-370 nm, 5.4 minutes}
\]
Example 83, 3-([4-((4-cyano-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl)benzoic acid

[0347] In an analogous manner to example 42, 4-cyano-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonyamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-([4-((4-cyano-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl)benzoic acid.

[0348] MS (ES+) m/z 517.7;
HPLC purity 100.0% at 210-370 nm, 8.4 minutes
HRMS: calculated for C_{20}H_{18}F_{3}N_{4}O_{6}S_{2} + H+, 518.06619; found (ESI, [M+H]+), 518.0677;

Example 84, N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-4-cyano-2-(trifluoromethyl)benzenesulfonylamide

[0349] In an analogous manner to example 42, 4-cyano-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonyamide and 2-chloropyridine-5-carbonyl chloride were used to prepare N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-4-cyano-2-(trifluoromethyl)benzenesulfonylamide.

[0350] MS (ES+) m/z 472.7;
HPLC purity 100.0% at 210-370 nm, 8.3 minutes
HRMS: calculated for C_{19}H_{16}ClF_{3}N_{4}O_{3}S + H+, 473.06565; found (ESI, [M+H]+), 473.0662;

Example 85, tert-butyl (25)-2-([4-((4-cyano-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate

[0351] In an analogous manner to example 45, 4-cyano-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonyamide and BOC-L-proline were used to prepare tert-butyl (2S)-2-([4-((4-cyano-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate.
Example 86, 4-cyano-\(N\)-(1-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 54, \(\text{tert}\)-butyl (25)-2-\{[4-([4-cyano-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl\}carbonyl|pyrrolidine-1-carboxylate was used to prepare 4-cyano-\(N\)-(1-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

Example 87, 4-[\{1-[(3-carboxyphenyl)sulfonyl]piperidin-4-yl\}amino)sulfonyl]-3-(trifluoromethyl)benzoic acid

To a stirred solution of 3-\{[4-([4-cyano-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-y]sulfonfyl\}benzoic acid (0.10 g, 0.20 mmol) in glyme (1 mL) was added 2.5M KOH solution (0.5 mL, 1.25 mmol) and the resulting solution was heated to reflux overnight. The solution was acidified with 2N HCl solution, extracted with ethyl acetate and concentrated to give 4-\{[1-[(3-carboxyphenyl)sulfonfyl]piperidin-4-yl\}amino)sulfonyl]-3-(trifluoromethyl)benzoic acid (0.076 g, 70%).

Example 88, 3-(4-cyano-\(N\)-(1-L-allylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 55, \(\text{tert}\)-butyl (25)-2-\{[4-([4-cyano-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl\}carbonyl|pyrrolidine-1-carboxylate was used to prepare 4-cyano-\(N\)-(1-L-allylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

Example 89, 4-[\{1-[(3-carboxyphenyl)sulfonfyl]piperidin-4-yl\}amino)sulfonyl]-3-(trifluoromethyl)benzoic acid
Example 88, N-[l-(4-[[2-(dimethylamino)ethyl]amino]-2-fluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride

[0357]  N-[l-(2,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (Example 40, 200 mg, 0.446 mmol) and N,N-dimethylethylenediamine (d 0.807, 0.24 mL, 2.23 mmol) were combined in N,N-dimethylacetamide (1 mL) and heated at 200 °C (microwave) for 20 minutes. The reaction mixture was taken up in ethyl acetate (20 mL) and washed with 1N aqueous sodium hydroxide (20 mL), water (20 mL) and saturated brine (20 mL). The organic solution was dried (Na₂SO₄) and concentrated under vacuum. Flash column chromatography (10 g silica gel) eluting ethyl acetate followed by 10 % methanol (saturated with ammonia) in dichloromethane provided N-[l-(4-[[2-(dimethylamino)ethyl]amino]-2-fluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide. The free base was dissolved in ethyl acetate (ca. 1 mL) and treated with 1N hydrogen chloride-diethyl ether solution (1.0 M, 1.1 eq). The resulting precipitate was vacuum filtered to provide N-[l-(4-[[2-(dimethylamino)ethyl]amino]-2-fluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride (48 mg, 19 %) as a pale yellow solid. MS (ES) m/z 516.9 ([MH-H]⁺).

Example 89, N-[l-{4-[[2-(dimethylamino)ethyl](methyl)amino]-3-fluorobenzoyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride

[0358]  Starting from N-[l-(3,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (Example 41) in place of N-[l-(2,4-difluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide and N,N,N-trimethylethylenediamine in place of N,N-dimethylethylenediamine, N-[l-{4-[2-(dimethylamino)ethyl](methyl)amino]-3-fluorobenzoyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride was synthesized in essentially the same manner as described in Example 88. MS (ES) m/z 531.0 ([M+H]⁺).

Example 90, N-[l-(4-fluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide
Starting from \( \text{N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (Example 37, Step 2)} \) in place of 4-bromo-\( \text{N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride} \) and 4-fluorobenzoyl chloride in place of 3-cyanobenzenesulfonyl chloride, \( \text{N-[1-(4-fluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide} \) was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) \( m/z \) 430.7 ([M+H]+).

Example 91, \( \text{N-[1-(4-bromobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide} \)

Starting from \( \text{N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride (Example 37, Step 2)} \) in place of 4-bromo-\( \text{N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride} \) and 4-bromobenzoyl chloride in place of 3-cyanobenzenesulfonyl chloride, \( \text{N-[1-(4-bromobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide} \) was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) \( m/z \) 490.6 ([M+H]+).

Example 92, 4-(dimethylamino)-\( \text{\( \Lambda \)'-(l-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide} \)

In an analogous manner to example 54, \( \text{\textit{tert}-butyl (2.S)-2-{{[4-[(4-(dimethylamino)-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate} \) was used to prepare 4-(dimethylamino)-W-(l-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) \( m/z \) 448.9;
HPLC purity 100.0% at 210-370 nm, 6.3 minutes
HRMS: calculated for \( \text{C}_{39}\text{H}_{27}\text{F}_{3}\text{N}_{4}\text{O}_{3}\text{S} + \text{H}^+ \), 449.18287; found (ESI, [M+H]+), 449.1821;

Example 93, 3-\{4-\{4-(isopropyl-2-(trifluoromethyl)phenyl)sulfonyl]aniino)piperidini-1-yl]sulfonyl\}benzoi acid
In an analogous manner to example 42, 4-isopropyl-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-[[4-[[4-isopropyl-2-(trifluoromethyl)phenyl]sulfonyl]amino]piperidin-1-yl]sulfonyl]benzoic acid.

MS (ES+): m/z 534.7; HPLC purity 100.0% at 210-370 nm, 9.6 minutes
HRMS: calculated for C_{22}H_{25}F_3N_2O_6S_2 + H+, 535.1 1789; found (ESI, [M+H]^+), 535.1 182;

Example 94, N-{[1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-4-isopropyl-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 42, 4-isopropyl-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare N-\{[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}-4-isopropyl-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+): m/z 489.7; HPLC purity 100.0% at 210-370 nm, 9.6 minutes
HRMS: calculated for C_{21}H_{23}ClF_3N_3O_3S + H+, 490. 11735; found (ESI, [M+H]^+), 490. 1156;


In an analogous manner to example 45, 4-isopropyl-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and BOC-L-proline were used to prepare tert-butyl (2S)-2-[[4-[[4-isopropyl-2-(trifluoromethyl)phenyl]sulfonyl]amino]piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate.

MS (ES-): m/z 545.8; HPLC purity 100.0% at 210-370 nm, 10.0 minutes
Example 96, 4-isopropyl-L'-((L-prolyl)piperidin-4-yl)-2-
(trifluoromethyl)benzenesulfonamide

[0369] In an analogous manner to example 54, tert-butyl (2S)-2-[(4-((4-isopropyl-2-
(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate
was used to prepare 4-isopropyl-N-(L-prolyl)piperidin-4-yl-2-
(trifluoromethyl)benzenesulfonamide.

[0370] MS (ES+) m/z 447.9;
HPLC purity 100.0% at 210-370 nm, 7.5 minutes
HRMS: calculated for C_{20}H_{28}F_{3}N_{3}O_{3}S + H+, 448.18762; found (ESI, [M+H]^+), 448.1892;

Example 97, 2-[4-([(4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-
yl]acetamide

[0371] In an analogous manner to example 72, 4-bromo-N-piperidin-4-yl-2-
(trifluoromethyl)benzenesulfonamide and bromoacetamide were used to prepare 2-[4-([(4-
bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]acetamide.

[0372] MS (ES-) m/z 443.7;
HPLC purity 100.0% at 210-370 nm, 6.3 minutes
HRMS: calculated for C_{14}H_{17}BrF_{3}N_{3}O_{3}S + H+, 444.01988; found (ESI, 01+H^+), 444.0209;

Example 98, tert-butyl 4-([(4-chloro-2-
(trifluoromethyl)phenyl)sulfonyl]aniino)piperidine-1-carboxylate

[0373] In an analogous manner to example 74, 4-chloro-2-trifluoromethylaniline and 4-
amino-piperidine-1-carboxylic acid tert-butyl ester were used to prepare /el/7-butyl 4-([(4-
chloro-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate.

[0374] MS (ES-) m/z 440.8;
HPLC purity 100.0% at 210-370 nm, 10.3 minutes
Example 99, 3-[{4-([4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl}sulfonyl] benzoic acid

[0375] In an analogous manner to example 42, 4-fluoro-N-pipendin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-{{4-([4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl}sulfonyl}benzoic acid.

[0376] MS (ES+) m/z 510.7;
HPLC purity 100.0% at 210-370 nm, 8.7 minutes
HRMS: calculated for C_{i9}H_{i8}F_{i4}N_{i2}O_{i6}S_{i2} + H+, 511.06152; found (ESI, [M+H]^+), 511.0615;

Example 100, 4-fluoro-iV-(l-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

[0377] In an analogous manner to example 54, ter*-butyl (2S)-2-{{4-([4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl}carbonyl}pyrrolidine-l-carboxylate was used to prepare 4-fluoro-N-(l-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

[0378] MS (ES+) m/z 423.8;
HPLC purity 100.0% at 210-370 nm, 6.0 minutes
HRMS: calculated for C_{i17}H_{i2}F_{i4}N_{i3}O_{i3}S + H+, 424.13125; found (ESI, [M+H]^+), 424.1309;

Example 101, 4-[[l-[l-(tert-butoxycarbonyl)-L-prolyl]piperidin-4-yl]amino)sulfonyl]-3-(trifluoromethyl)benzoic acid

[0379] In an analogous manner to example 87, ter*-butyl (2S)-2-{{4-([4-cyano-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl}carbonyl}pyrrolidine-l-carboxylate was used to prepare 4-[[l-[l-(tert-butoxycarbonyl)-L-prolyl]piperidin-4-yl]amino)sulfonyl]-3-(trifluoromethyl)benzoic acid.
Example 102, 3-{{[4-(4-(dimethylamino)-2-
(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl}sulfonyl}benzoic acid

In an analogous manner to example 42, 4-(dimethylamino)-N-piperidin-4-yl-2-
(trifluoromethyl)benzenesulfonamide and 3-(chlorosulfonyl)benzoic acid was used to prepare
3-{{[4-(4-(dimethylamino)-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl}sulfonyl}benzoic acid.

Example 103, yV-{1-[[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-4-(diethylaminino)-2-
(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 42, 4-(dimethylamino)-N-piperidin-4-yl-2-
(trifluoromethyl)benzenesulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare N-{1-[6-chloropyridin-3-yl]carbonyl]piperidin-4-yl}-4-(dimethylamino)-2-
(trifluoromethyl)benzenesulfonamide.

Example 104, ferf-butyl (2S)-2-{{[4-(4-(dimethylamino)-2-
(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate
In an analogous manner to example 45, 4-(dimethylamino)-\textit{N}-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and BOC-L-proline were used to prepare \textit{t}or\textit{-}butyl (25)-2-\([4-([4-(dimethylamino)-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl\]carbonyl)pyrrolidine-1-carboxylate.

[0385] MS (ES-) \textit{m/z} 546.8;  
HPLC purity 100.0\% at 210-370 nm, 9.2 minutes

Example 105, 4-chloro-\textit{N}-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide

[0386] In an analogous manner to example 54, \textit{tert\textendash}butyl 4-\([4-([4-chloro-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidine-1-carboxylate was used to prepare 4-chloro-\textit{N}-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide.

[0387] MS (ES+) \textit{m/z} 342.8;  
HPLC purity 100.0\% at 210-370 nm, 6.2 minutes  
HRMS: calculated for \(\text{C}_{22}\text{H}_{14}\text{ClF}_{3}\text{N}_{2}\text{O}_{5}\) + H, 343.04893; found (ESI, [M+H]+), 343.0484;

Example 106, (25)-2-\([4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl\]carbonyl)-\textit{N}(\textit{tert\textendash}butyl)pyrrolidine-1-carboxamide

[0388] In an analogous manner to example 42, 4-bromo-\textit{N}(1-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide and \textit{tert\textendash}butylisocyanate were used to prepare \(\text{ZS}\)-2-\([4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl\]carbonyl)-\textit{N}(\textit{tert\textendash}butyl)pyrrolidine-1-carboxamide.

[0389] MS (ES-) \textit{m/z} 582.7;  
HPLC purity 100.0\% at 210-370 nm, 9.4 minutes  
HRMS: calculated for \(\text{C}_{29}\text{H}_{30}\text{BrF}_{3}\text{N}_{4}\text{O}_{4}\text{S}\) + H, 583.11960; found (ESI, [M+H]+), 583.1223;

Example 107, \textit{N}(1-\([3-(2 \textit{H}\textendash}tetrazol-5-yl)phenyl]sulfonyl)piperidin-4-yl)-2-
(trifluoromethyl)benzenesulfonamide

[0390] Azidotrimethylsilane (d 0.876, 0.083 mL, 0.632 mmol) and trimethyl aluminum-toluene solution (2.0 M, 0.316 mL) were mixed briefly at 23 °C and then added to a suspension of N-[1-[(3-cyanophenyl)sulfonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (Example 37, Step 3, 115 mg, 0.243 mmol) in dry toluene (0.20 mL) at 23 °C. The mixture was heated at 80 °C for 22 hours. At this time, the cooled solution was taken up in ethyl acetate and washed with 6 N aqueous hydrochloric acid, water and saturated brine, dried (Na2SO4), and concentrated under vacuum. The crude solid was briefly washed with hot ethyl acetate and vacuum-filtered to provide N-(1-[[3-(2H-tetrazol-5-yl)phenyl]sulfonyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide (80 mg, 63 %) as a pale yellow solid. MS (ES) m/z 516.6 ([M+H]^+).

Example 108, 4-bromo- N-(1-[[3-(2H-tetrazol-5-yl)phenyl]sulfonyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

[0391] Starting from 4-bromo- N-(1-[(3-cyanophenyl)sulfonyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide (Example 32, Step 3) in place of N-[1-[(3-cyanophenyl)sulfonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide, 4-bromo- N-(1-[[3-(2H-tetrazol-5-yl)phenyl]sulfonyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide was synthesized in essentially the same manner as described in Example 107. MS (ES) m/z 594.5 ([M+H]^+).

Example 109, N-[1-[(2i7-tetrazol-5-yl)benzoyl]piperidi 1-4-y1]-2-(trifluoromethyl)benzenesulfonamide

[0392] Starting from N-[1-(3-cyanobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (Example 38) in place of N-[1-[(3-cyanophenyl)sulfonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide, N-[1-[(2H-tetrazol-5-yl)benzoyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide was synthesized in essentially the same manner as described in Example 107. MS (ES) m/z 480 7 ([M+H]^+).
Example 110, tert-butyl 4-({[4-methoxy-2-
(trifluoro πethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate

[0393] To a stirred solution of tert-butyl 4-({[4-fluoro-2-
(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate (0.20 g, 0.47 mmol) in THF (1 mL) was added sodium methoxide 25% wt in methanol (1 mL). The resulting solution was heated overnight at 50°C and concentrated. Flash column separation using 0%-50% ethyl acetate/hexane gradient gave tert-butyl 4-({[4-methoxy-2-
(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate. (0.14 g, 68%).

[0394] MS (ES-) m/z 436.8;
HPLC purity 100.0% at 210-370 nm, 11.5 minutes

Example 111, 4-methoxy-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 54, tert-butyl 4-({[4-methoxy-2-
(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate was used to prepare 4-methoxy-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) m/z 338.9;
HPLC purity 100.0% at 210-370 nm, 6.4 minutes
HRMS: calculated for C_{13}H_{17}F_{3}N_{2}O_{3}S + H+, 339.09847; found (ESI, [M+H]^+), 339.0994;

Example 112, 3-{{[4-([4-chloro-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-
yl]sulfonyl}benzoic acid

[0395] In an analogous manner to example 42, 4-chloro-N-piperidin-4-yl-2-
(trifluoromethyl)benzenesulfonamide and 3-(chlorosulfonyl)benzoic acid was used to prepare 3-{{[4-([4-chloro-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]sulfonyl}benzoic acid.

[0396] MS (ES+) m/z 526.6;
HPLC purity 98.4% at 210-370 nm, 10.8 minutes
Example 113, 4-chloro- \( \text{N} \)-[1-{(6-chloropyridin-3-yl)carbonyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 42, 4-chloro- \( \text{N} \)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare 4-chloro- \( \text{N} \)-[1-{(6-chloropyridin-3-yl)carbonyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

Example 114, tert-butyl (2S)-2-{[4-({[4-chloro-2-(trifluoromethyl)phenyl}sulfonyl]amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate

In an analogous manner to example 45, 4-chloro- \( \text{N} \)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and BOC-L-proline were used to prepare tert-butyl (2S)-2-{[4-({[4-chloro-2-(trifluoromethyl)phenyl}sulfonyl]amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate.

Example 115, 4-chloro- \( \text{N} \)-(L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 54, tert-butyl (2S)-2-{[4-({[4-chloro-2-(trifluoromethyl)phenyl}sulfonyl]amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate was used to prepare 4-chloro- \( \text{N} \)-(L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.
Example 117, 3-[[4-([4-methoxy-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl]benzoic acid

In an analogous manner to example 42, 4-methoxy-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 3-(chlorosulfonyl)benzoic acid was used to prepare 3-[[4-([4-methoxy-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl]benzoic acid.

Example 118, A^\text{\`e}l-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-4-methoxy-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 42, 4-methoxy-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare A^\text{\`e}l-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-4-methoxy-2-(trifluoromethyl)benzenesulfonamide.


Example 114, 3-[[4-([4-methoxy-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]benzoic acid

Example 115, 3-[[4-([4-methoxy-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]benzoic acid
In an analogous manner to example 45, 4-methoxy-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and BOC-L-proline were used to prepare tert-butyl(2S)-2-\{4-\{4-methoxy-2-(trifluoromethyl)phenyl)sulfonyl\}amino)piperidin-1-ylcarbonyl\}pyrrolidine-1-carboxylate.

**Example 120, 4-methoxy-\(N\)-(L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide**

In an analogous manner to example 54, tert-butyl (2S)-2-\{4-\{4-methoxy-2-(trifluoromethyl)phenyl)sulfonyl\}amino)piperidin-1-ylcarbonyl\}pyrrolidine-1-carboxylate was used to prepare 4-methoxy-\(N\)-(L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

**Example 121, 4-bromo-\(N\)-(L-pyridin-3-ylmethyl)piperidin-4-yl)-2-(trifluoroniethyl)benzenesulfonamide**

To a stirred solution of 4-bromo-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide (0.09 g, 0.21 mmol) and triethylamine (0.1mL, 0.71 mmol) in THF (1 mL) was added 3-(bromomethyl)pyridine hydrobromide (0.054 g, 0.21 mmol) and the resulting solution was microwave irradiated for 20 min. at 120°C. The resulting solution was washed with sodium bicarbonate solution (sat.) and extracted with ethyl acetate. The organic layer was concentrated and flash column separation using 0%-5% methanol/dichloromethane gave 4-bromo-\(N\)-(L-pyridin-3-ylmethyl)piperidin-4-yl)-2-(trifluoroniethyl)benzenesulfonamide. (0.098 g, 96%).
Example 122, 4-bromo-iV-[l-(pyridin-4-ylmethyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 121, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 4-(bromomethyl)pyridine hydrobromide were used to prepare 4-bromo-N-[l-(pyridin-4-ylmethyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

Example 123, 4-bromo-yV-[l-(3-cyanobenzyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 121, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 3-bromomethylbenzonitrile were used to prepare 4-bromo-N-[l-(3-cyanobenzyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

Example 124, 2-fc/f-butyl-JV-piperidin-4-ylbenzenesulfonamide hydrochloride

Step 1: 0-(2-tert-butylphenyl) dimethylthiocarbamate
Potassium hydroxide (3.1 g, 55 mmol) was stirred in methanol (35 mL) at 23 °C. When it had dissolved, 2-/εr*-butylphenol (0.982, 5.7 mL, 37 mmol) was added at 23 °C. After 1.5 hours, dimethylthiocarbamoyl chloride (6.9 g, 56 mmol) was added at 23 °C. After 16 hours, the resulting solid was vacuum filtered and washed with methanol. The filtrate was concentrated under vacuum and the resulting oil was heated at 100-130 °C under high vacuum to remove starting phenol. The residue was pre-adsorbed on silica (25 g). Flash column chromatography on an ISCO (750 g silica gel) eluting ethyl acetate-hexanes (0-40 % solution @ 300 mL/min) provided 0-(2-tert-butylphenyl) dimethylthiocarbamate (2.3 g, 26 %) as a clear, yellow oil. MS (ES) m/z 238.0 ([M+H]⁺).

Step 2: 5-(2-tert-butyphenyl) dimethylthiocarbamate

0-(2-/εr-/butylphenyl) dimethylthiocarbamate (3.7 g, 16 mmol) was heated neat at 340-350 °C (sand bath) for 80 minutes. The cooled mixture was dissolved in dichloromethane and pre-adsorbed on silica gel (15 g). Flash column chromatography on an ISCO (330 g silica gel) eluting ethyl acetate-hexanes (0-40 % solution @ 100 mL/min) provided S-(2-tert-/butyl phenyl) dimethylthiocarbamate (2.4 g, 65 %) as an off-white solid. MS (ES) m/z 238.0 ([M+H]⁺).

Step 3: tert-buty 4-{{[2-tørf-butylphenyl)su.fonyl]amino}piperidine-1-carboxylate

A solution of 5-(2-/εr-/butylphenyl) dimethylthiocarbamate (2.7 g, 11 mmol) in 4:1 acetic acid-water (100 mL) was treated with chlorine gas at 0 °C during ca. 5 minutes and the reaction vessel was then sealed. After 1.5 hours, the reaction solution was taken up in dichloromethane (375 mL) and washed with water (2 x 375 mL), saturated aqueous sodium bicarbonate (375 mL) and saturated brine (375 mL), dried (Na₂SO₄) and concentrated under vacuum. The resulting orange solid was dissolved in dichloromethane (100 mL), triethylamine (0.726, 4.8 mL, 34 mmol) and 4-amino-l-Boc-piperidine (2.4 g, 12 mmol) were added and the mixture was stirred at 23 °C for 3.5 hours. At this time, the reaction solution was washed with 1 N aqueous sodium hydroxide (100 mL), water (100 mL) and saturated brine (100 mL), dried (Na₂SO₄) and concentrated under vacuum to provide an oil that was dissolved in dichloromethane and pre-adsorbed on silica gel (8 g). Flash column chromatography on an ISCO (80 g silica gel) eluting ethyl acetate-hexanes (20-75 % solution
@ 60 mL/min) provided tert-butyl 4-[(2-tert-butylphenyl)sulfonyl]amino]piperidine-1-carboxylate (3.4 g, 76%) as a yellow foam. MS (ES) m/z 395.0 ([M-H]).

**Step 4:** tert-butyl-N-piperidin-4-ylbenzenesulfonamide hydrochloride

[0420] Starting from tert-butyl 4-[(2-tert-butylphenyl)sulfonyl]amino]piperidine-1-carboxylate in place of tert-butyl 4-[(4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino]piperidine-1-carboxylate, tert-butyl-N-piperidin-4-ylbenzenesulfonamide hydrochloride was synthesized in essentially the same manner as described in Example 32, Step 2. MS (ES) m/z 297.0 ([M+H]+).

Example 125, 2,4-di-tert-butyl-/l-piperidin-4-ylbenzenesulfonamide hydrochloride

**Step 1:** 0-(2,4-di-tert-butylphenyl) dimethylthiocarbamate

[0421] Starting from 2,4-di-tert-butylphenol in place of 2-tert-butylphenol and dimethylthiocarbamoyl chloride, 0-(2,4-di-tert-butylphenyl) dimethylthiocarbamate was synthesized in essentially the same manner as described in Example 124, Step 1. MS (ES) m/z 294.0 ([M+H]+).

**Step 2:** S-(2,4-di-tert-butylphenyl) dimethylthiocarbamate

[0422] Starting from 0-(2,4-di-tert-butylphenyl) dimethylthiocarbamate in place of O-(2,4-di-tert-butylphenyl) dimethylthiocarbamate, S-(2,4-di-tert-butylphenyl) dimethylthiocarbamate was synthesized in essentially the same manner as described in Example 124, Step 2. MS (ES) m/z 294.1 ([M+H]+).

**Step 3:** tert-butyl 4-[(2,4-di-tert-butylphenyl)sulfonyl]amino]piperidine-1-carboxylate

[0423] Starting from S-(2,4-di-tert-butylphenyl) dimethylthiocarbamate in place of S-(2-tert-butylphenyl) dimethylthiocarbamate, tert-butyl 4-[(2,4-di-tert-butylphenyl)sulfonyl]amino]piperidine-1-carboxylate was synthesized in essentially the same
manner as described in Example 124, Step 3. MS (ES) m/z 451.0 ([M-H]').

**Step 4:** 2,4-di-^rf-butyl- N-piperidin-4-ylbenzenesulfonamide hydrochloride

[0424] Starting from tert-butyl 4-[[2,4-di-^rf-butylphenyl)sulfonyl]amino]piperidine-1-carboxylate in place of ter/-butyl 4-[[4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate, 2,4-di-^rf-butyl- N-piperidin-4-ylbenzenesulfonamide hydrochloride was synthesized in essentially the same manner as described in Example 32, Step 2. MS (ES) m/z 353.0 ([M^+H]^+).

Example 126, tert-butyl 4-[[4-phenoxy-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate

[0425] To a stirred solution of few-butyl 4-[[4-fluoro-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate (0.60 g, 1.4 mmol) and phenol (0.20 g, 2.1 mmol) in glyme (1 mL) was added potassium carbonate (0.97 g, 7.0 mmol) dissolved in water (2 mL) and the resulting solution was microwave irradiated for 10 min. at 180°C. The resulting solution was washed with ammonium chloride solution (sat.) and extracted with ethyl acetate. The organic layer was concentrated and flash column separation using 0%-30% ethyl acetate/hexane gave tert-butyl 4-[[4-phenoxy-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate (0.32 g, 45%).

[0426] MS (ES-) m/z 498.9;
HPLC purity 96.9% at 210-370 nm, 12.1 minutes

Example 127, 4-phenoxy- N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide

[0427] In an analogous manner to example 54, tert-/butyl 4-[[4-phenoxy-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate was used to prepare 4-phenoxy- N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide.

[0428] MS (ES+) m/z 400.9;
HPLC purity 98.0% at 210-370 nm, 8.7 minutes
HRMS: calculated for C_{20}H_{21}BrF_{3}N_{3}O_{4}S + H+, 536.04610; found (ESI, [M+H]^+), 536.0454.

Example 129, 1-yV-[l-(6-ethoxypyridin-3-yl)carbonyl]piperidin-4-yl]-4-isopropyl-2-(trifluoromethyl)benzenesulfonamide

[0429] Step 1: In an analogous manner to example 42, piperidin-4-yl-carbamic acid tert-butyl ester and 2-chloropyridine-5-carbonyl chloride were used to prepare [l-(6-Chloropyridine-3-carbonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.

[0430] Step 2: In an analogous manner to example 54, [l-(6-Chloro-pyridine-3-carbonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester was used to prepare 1-{(6-chloropyridin-3-yl)carbonyl}piperidin-4-amine.

[0431] Step 3: To a stirred solution of 1-{(6-chloropyridin-3-yl)carbonyl}piperidin-4-amine (0.40 g, 1.45 mmol) in Ethanol (3 mL) was added sodium ethoxide 21% wt in ethanol (5 mL) and the resulting solution was stirred overnight room temperature. The solution was diluted with water and extracted with ethyl acetate. The organic phase was concentrated to give (4-Amino-piperidin-1-yl)-(6-ethoxy-pyridin-3-yl)-methanone. (0.13 g, 36%).

[0432] Step 4: In an analogous manner to example 42, (4-Amino-piperidin-1-yl)-(6-ethoxy-pyridin-3-yl)-methanone and 4-bromo-2-trifluoromethylbenzene sulfonyl chloride were used to prepare 4-bromo-1-{(6-ethoxypyridin-3-yl)carbonyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

[0433] MS (ES-) m/z 535.7;

HPLC purity 93.2% at 210-370 nm, 10.7 minutes

HRMS: calculated for C_{20}H_{21}BrF_{3}N_{3}O_{4}S + H+, 536.04610; found (ESI, [M+H]^+), 536.0454.
[0434] Step 1: In an analogous manner to example 74 step 1, 4-isopropyl-2-trifluoromethylaniline was used to prepare 4-isopropyl-2-trifluoromethylbenzenesulfonyl chloride.

[0435] Step 2: In an analogous manner to example 128 step 4, 4-isopropyl-2-trifluoromethylbenzenesulfonyl chloride and (4-Amino-piperidin-1-yl)-(6-ethoxy-pyridin-3-yl)-methanone were used to prepare \(N\)-[1-[(6-ethoxy-pyridin-3-yl)carbonyl]piperidin-4-yl]-4-isopropyl-2-(trifluoromethyl)benzenesulfonamide.

[0436] MS (ES+) \(m/z\) 500.0;
HPLC purity 93.8% at 210-370 nm, 11.0 minutes
HRMS: calculated for \(C_{22}H_{28}F_3N_3O_4S + H^+\), 500.18254; found (ESI, [M+H]+), 500.1816;

Example 130, (25)-2-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]carbonyl]-\(N\)-tert-butyl-5-oxopyrrolidine-1-carboxamide

[0437] To a stirred solution of 4-bromo-JV-[1-(5-oxo-L-prolyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (0.10 g, 0.20 mmol) in DMF (1mL) was added sodium hydride (0.018 g (60%), 0.441 mmol) at O°C and the resulting solution was stirred 5 minutes. To this was added tert-butylisocyanate (0.02 g, 0.20 mmol) and solution was stirred 30 minutes at room temperature. The reaction was quenched with ammonium chloride solution (sat), and extracted several times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Flash column separation using 0%-100% ethyl acetate/hexane gradient gave (25)-2-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]carbonyl]-\(N\)-tert-butyl-5-oxopyrrolidine-1-carboxamide. (0.045 g, 38%).

[0438] MS (ES-) \(m/z\) 594.9;
HPLC purity 100.0% at 210-370 nm, 9.6 minutes
HRMS: calculated for \(C_{22}H_{28}BrF_3N_3O_5S + H^+\), 597.09886; found (ESI, [M+H]+), 597.0994;
Example 131, 2-isopropyl-N-piperidin-4-ylbenzenesulfonamide hydrochloride

Step 1: 0-(2-isopropylphenyl) dimethylthiocarbamiate

[0439] Starting from 2-isopropylphenol in place of 2-tert-butylphenol and dimethylthiocarbamoyl chloride, 0-(2-isopropylphenyl) dimethylthiocarbamate was synthesized in essentially the same manner as described in Example 124, Step 1. MS (ES) m/z 223.9 ([M+H]+).

Step 2: S-(2-isopropylphenyl) dimethylthiocarbamate

Starting from O-(2-isopropylphenyl) dimethylthiocarbamate in place of O-(2-tert-butylphenyl) dimethylthiocarbamate, S-(2-isopropylphenyl) dimethylthiocarbamate was synthesized in essentially the same manner as described in Example 124, Step 2. MS (ES) m/z 224.0 ([M+H]+).

Step 3: tert-butyl 4-{{[(2-isopropylphenyl)sulfonyl]amino}piperidine-1-carboxylate

[0440] Starting from 5-(2-isopropylphenyl) dimethylthiocarbamate in place of S-(2-tert-butylphenyl) dimethylthiocarbamate, fe7-butyl 4-{{[(2-isopropylphenyl)sulfonyl]amino}piperidine-1-carboxylate was synthesized in essentially the same manner as described in Example 124, Step 3. MS (ES) m/z 381.0 ([M-H]-).

Step 4: 2-isopropyl-N-piperidin-4-ylbenzenesulfonamide hydrochloride

[0441] Starting from /e/7-butyl 4-{{[(2-isopropylphenyl)sulfonyl]amino}piperidine-1-carboxylate in place of fofr-butyl 4-{{[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl}amino}piperidine-1-carboxylate, 2-isopropyl-N-piperidin-4-ylbenzenesulfonamide hydrochloride was synthesized in essentially the same manner as described in Example 32, Step 2. MS (ES) m/z 283.1 ([M+H]+).

Example 132, 3-{{4-{[(4-phenoxy-2-(trifluoromethyl)phenyl)sulfonyl]amino}piperidin-1-yl}sulfonyl} benzoic acid
In an analogous manner to example 42, 4-phenoxy-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 3-(chlorosulfonyl)benzoic acid was used to prepare 3-\{4-\{4-phenoxy-2-(trifluoromethyl)phenyl\}sulfonyl\}amino)piperidin-1-yl)sulfonyl\}benzoic acid.

MS (ES+) \(m/z\) 585.0;
HPLC purity 100.0% at 210-370 nm, 11.8 minutes
HRMS: calculated for \(C_{25}H_{23}F_3N_2O_7S_2 + H+\), 585.09715; found (ESI, [M+H]^+), 585.0975;

Example 133, yV-{l-[\{6-chloropyridin-3-yl\}carbonyl\}piperidin-4-yl]-4-phenoxy-2-(trifluoromethyl)benzenesulfo amide

In an analogous manner to example 42, 4-phenoxy-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare \(N\)-\{4-\{4-phenoxy-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) \(m/z\) 540.0;
HPLC purity 98.9% at 210-370 nm, 12.5 minutes
HRMS: calculated for \(C_{23}H_{23}ClF_3N_3O_4S + H+\), 540.09661; found (ESI, [M+H]^+), 540.0964;

Example 134, terf-butyl \((2S)-2-\{4-\{4-phenoxy-2-(trifluoromethyl)phenyl\}sulfonyl\}amino)piperidin-1-yl\{carbonyl\}pyrrolidine-l-carboxylate

In an analogous manner to example 45, 4-phenoxy-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and BOC-L-proline were used to prepare ferf-butyl \((2S)-2-\{4-\{4-phenoxy-2-(trifluoromethyl)phenyl\}sulfonyl\}amino)piperidin-1-yl\{carbonyl\}pyrrolidine-l-carboxylate.

MS (ES-) \(m/z\) 596.1;
HPLC purity 97.4% at 210-370 nm, 13.2 minutes
Example 135, 3-[[2-isopropylphenyl)sulfonyl]amino]piperidin-1-yl)sulfonyl]benzoic acid

[0448] Starting from 2-isopropyl-N-piperidin-4-ylbenzenesulfonamide hydrochloride (Example 131, Step 4) in place of 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride and 3-(chlorosulfonyl)benzoic acid in place of 3-cyanobenzenesulfonyl chloride, 3-[[2-isopropylphenyl)sulfonyl]amino]piperidin-1-yl)sulfonyl]benzoic acid was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) m/z 467.1 ([M+H]+).

Example 136, 3-[[2-t-butylphenyl)sulfonyl]amino]piperidin-1-yl)sulfonyl]benzoic acid

[0449] Starting from 2-ter/-butyl- N-piperidin-4-ylbenzenesulfonamide hydrochloride (Example 124, Step 4) in place of 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride and 3-(chlorosulfonyl)benzoic acid in place of 3-cyanobenzenesulfonyl chloride, 3-[[2-(tert-butylphenyl)sulfonyl]amino]piperidin-1-yl)sulfonyl]benzoic acid was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) m/z 481.1 ([M+H]+).

Example 137, 3-[[2,4-di-terf-butylphenyl)sulfonyl]amino]piperidin-1-yl)sulfonyl] benzoic acid

[0450] Starting from 2,4-di-ter/-butyl- N-piperidin-4-ylbenzenesulfonamide hydrochloride (Example 125, Step 4) in place of 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride and 3-(chlorosulfonyl)benzoic acid in place of 3-cyanobenzenesulfonyl chloride, 3-[[2,4-di-terf-butylphenyl)sulfonyl]amino]piperidin-1-yl)sulfonyl]benzoic acid was synthesized in
essentially the same manner as described in Example 32, Step 3. MS (ES) m/z 537.2 (PW-H)^+.

Example 138, 3-[[4-([4'-chloro-3-(trifluoromethyl)biphenyl-4-y]l)sulfonylamino]piperidin-1-yl]sulfonyl]benzoic acid

[0451] In an analogous manner to example 53, 3-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonylamino)piperidin-1-yl]sulfonyl]benzoic acid and 4-chlorophenyl boronic acid were used to prepare 3-[[4-([4'-chloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonylamino)piperidin-1-yl]sulfonyl]benzoic acid.

[0452] MS (ES+) m/z 603.0;
HPLC purity >99.9% at 210-370 nm, 10.5 minutes
HRMS: calculated for C_{25}H_{22}ClF_{3}N_{2}O_{6}S_{2} + H+, 603.0626; found (ESI, PwH-H)^+, 603.0639;

Example 139, 3-[[4-([3'-chloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonylamino)piperidin-1-yl]sulfonyl]benzoic acid

[0453] In an analogous manner to example 53, 3-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonylamino)piperidin-1-yl]sulfonyl]benzoic acid and 3-chlorophenyl boronic acid were used to prepare 3-[[4-([3'-chloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonylamino)piperidin-1-yl]sulfonyl]benzoic acid.

[0454] MS (ES+) m/z 603.0;
HPLC purity 96.0% at 210-370 nm, 10.5 minutes
HRMS: calculated for C_{25}H_{22}ClF_{3}N_{2}O_{6}S_{2} + H+, 603.0626; found (ESI, pD+H)^+, 603.0628;

Example 140, 3-[[4-([2'-chloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonylamino)piperidin-1-yl]sulfonyl]benzoic acid

[0455] In an analogous manner to example 53, 3-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonylamino)piperidin-1-yl]sulfonyl]benzoic acid and 2-
chlorophenyl boronic acid were used to prepare 3-\{4-([2'-chloro-3-(trifluoromethyl)biphenyl-4-yl)sulfonylamino)piperidin-1-yl\}sulfonylbenzoic acid.

\[0456\] M.S (ES+) \textit{m/z} 603.0;  
HPLC purity 96.8\% at 210-370 nm, 10.2 minutes  
HRMS: calculated for C\textsubscript{25}H\textsubscript{22}ClF\textsubscript{3}N\textsubscript{2}O\textsubscript{6}S\textsubscript{2} + H\textsuperscript{+}, 603.06326; found (ESI, [M\textsuperscript{+}H\textsuperscript{+}]), 603.0623;

Example 141, 3-\{4-([4'-methoxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonylamino)piperidin-1-yl\}sulfonylbenzoic acid

\[0457\] In an analogous manner to example 53, 3-\{4-([4'-bromo-2-(trifluoromethyl)phenyl)sulfonylamino)piperidin-1-yl\}sulfonylbenzoic acid and 4-methoxyphenyl boronic acid were used to prepare 3-\{4-([4'-methoxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonylamino)piperidin-1-yl\}sulfonylbenzoic acid.

\[0458\] M.S (ES+) \textit{m/z} 599.1;  
HPLC purity 100.0\% at 210-370 nm, 10.0 minutes  
HRMS: calculated for C\textsubscript{26}H\textsubscript{25}F\textsubscript{3}N\textsubscript{2}O\textsubscript{7}S\textsubscript{2} + H\textsuperscript{+}, 599.1280; found (ESI, [M+H\textsuperscript{+}]), 599.126;

Example 142, 3-\{4-([3'-methoxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonylamino)piperidin-1-yl\}sulfonylbenzoic acid

\[0459\] In an analogous manner to example 53, 3-\{4-([4'-bromo-2-(trifluoromethyl)phenyl)sulfonylamino)piperidin-1-yl\}sulfonylbenzoic acid and 3-methoxyphenyl boronic acid were used to prepare 3-\{4-([3'-methoxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonylamino)piperidin-1-yl\}sulfonylbenzoic acid.

\[0460\] M.S (ES+) \textit{m/z} 599;  
HPLC purity 89.1\% at 210-370 nm, 10.1 minutes  
HRMS: calculated for C\textsubscript{26}H\textsubscript{25}F\textsubscript{3}N\textsubscript{2}O\textsubscript{7}S\textsubscript{2} + H\textsuperscript{+}, 599.1280; found (ESI, [M+H\textsuperscript{+}]), 599.123;

Example 143, 3-\{4-([2'-methoxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonylamino)piperidin-1-yl\}sulfonylbenzoic acid
In an analogous manner to example 53, 3-{

[4-(4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino}piperidin-l-y]sulfonyl]benzoic acid and 2-methoxyphenyl boronic acid were used to prepare 3-{


MS (ESI+) m/z 599;
HPLC purity >99.9% at 210-370 nm, 10.0 min.;
HRMS: calculated for C_{26}H_{23}F_{3}N_{2}O_{7}S_{2} + H+, 599.1280; found (ESI, [M+H]^{+}), 599.1115;

Example 144, 3-{

[4'(cyano-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amine}piperidin-l-y]sulfonyl]benzoic acid

In an analogous manner to example 53, 3-{

[4-(4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino}piperidin-l-y]sulfonyl]benzoic acid and 4-cyanophenyl boronic acid were used to prepare 3-{


MS (ESI+) m/z 594.1;
HPLC purity 93.2% at 210-370 nm, 9.5 minutes
HRMS: calculated for C_{26}H_{22}F_{3}N_{3}O_{6}S_{2} + H+, 594.09749; found (ESI, [M+H]^{+}), 594.0968;

Example 145, 3-{

[3'(cyano-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amine}piperidin-l-y]sulfonyl]benzoic acid

In an analogous manner to example 53, 3-{

[4-(4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino}piperidin-l-y]sulfonyl]benzoic acid and 3-cyanophenyl boronic acid were used to prepare 3-{


MS (ESI+) m/z 594.1;
HPLC purity >99.9% at 210-370 nm, 9.6 minutes
HRMS: calculated for $C_{26}H_{22}F_{3}N_{3}O_{6}S_{2}^+ + H^+$, 594.09749; found (ESI, $\text{[M+H]}^+$), 594.0971;

Example 146, 3-{$[4-([2'-\text{carbamoyl}-3-(\text{trifluoromethyl})\text{biphenyl-4-yl}]\text{sulfonyl}amino)\text{piperidin-1-yl}]\text{sulfonyl}\text{benzoic acid}$

[0467] In an analogous manner to example 53, 3-{$[4-([4'-\text{bromo}-2-(\text{trifluoromethyl})\text{phenyl}]\text{sulfonyl}amino)\text{piperidin-1-yl}]\text{sulfonyl}\text{benzoic acid}$ and 2-cyanophenyl boronic acid were used to prepare 3-{$[4-([2'-\text{carbamoyl}-3-(\text{trifluoromethyl})\text{biphenyl-4-yl}]\text{sulfonyl}amino)\text{piperidin-1-yl}]\text{sulfonyl}\text{benzoic acid}$.

[0468] MS (ES+) $m/z$ 612.1;
HPLC purity 100.0% at 210-370 nm, 8.2 minutes
HRMS: calculated for $C_{26}H_{24}F_{3}N_{2}O_{7}S_{2}^+$, 612.10805; found (ESI, $\text{[M+H]}^+$), 612.1068;

Example 147, 3-{$[4-([4'-\text{tert-butyl}-3-(\text{trifluoromethyl})\text{biphenyl-4-yl}]\text{sulfonyl}amino)\text{piperidin-1-yl}]\text{sulfonyl}\text{benzoic acid}$

[0469] In an analogous manner to example 53, 3-{$[4-([4'-\text{bromo}-2-(\text{trifluoromethyl})\text{phenyl}]\text{sulfonyl}amino)\text{piperidin-1-yl}]\text{sulfonyl}\text{benzoic acid}$ and 4-tert-butylphenyl boronic acid were used to prepare 3-{$[4-([4'-\text{tert-butyl}-3-(\text{trifluoromethyl})\text{biphenyl-4-yl}]\text{sulfonyl}amino)\text{piperidin-1-yl}]\text{sulfonyl}\text{benzoic acid}$.

[0470] MS (ES+) $m/z$ 625.1;
HPLC purity >99.9% at 210-370 nm, 11.1 minutes
HRMS: calculated for $C_{27}H_{31}F_{3}N_{2}O_{7}S_{2}^+$, 625.16484; found (ESI, $\text{[M+H]}^+$), 625.1646;

Example 148, 3-{$[4-([4-(1-\text{naphthyl})-2-(\text{trifluoromethyl})\text{phenyl}]\text{sulfonyl}amino)\text{piperidin-1-yl}]\text{sulfonyl}\text{benzoic acid}$

[0471] In an analogous manner to example 53, 3-{$[4-([4'-\text{bromo}-2-(\text{trifluoromethyl})\text{phenyl}]\text{sulfonyl}amino)\text{piperidin-1-yl}]\text{sulfonyl} \text{benzoic acid}$ and 1-naphthylboronic acid were used to prepare 3-{$[4-([4-(1-\text{naphthyl})-2-(\text{trifluoromethyl})\text{phenyl}]\text{sulfonyl}amino)\text{piperidin-1-yl}]\text{sulfonyl}\text{benzoic acid}$.
Example 149, 3-{[4-([4-(2-naphthyl)-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl}sulfonyl]benzoic acid

In an analogous manner to example 53, 3-{[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl}sulfonyl]benzoic acid and 2-naphthylboronic acid were used to prepare 3-{[4-([4-(2-naphthyl)-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl}sulfonyl]benzoic acid.

Example 150, 3-{[4-([3-(trifluoromethyl)-1,1',3',1"-terphenyl-4-yl]sulfonyl)amino]piperidin-1-yl}sulfonyl]benzoic acid

In an analogous manner to example 53, 3-{[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl}sulfonyl]benzoic acid and 4-biphenylboronic acid were used to prepare 3-{[4-([3-(trifluoromethyl)-1,1',3',1"-terphenyl-4-yl]sulfonyl)amino]piperidin-1-yl}sulfonyl]benzoic acid.

Example 151, 3-{[4-([3-(trifluoromethyl)-1,1',3',1"-terphenyl-4-yl]sulfonyl)amino]piperidin-1-yl}sulfonyl]benzoic acid
In an analogous manner to example 53, 3-[[4-(((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl)sulfonyl]benzoic acid and 3-biphenylboronic acid were used to prepare 3-[[4-(((3-(trifluoromethyl)-1,3,4-terphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl]benzoic acid.

MS (ES+) m/z 645.1;
HPLC purity >99.9% at 210-370 nm, 11.0 minutes

HRMS: calculated for C_{31}H_{27}F_{3}N_{2}O_{6}S_{2} +H+ 645.13354; found (ESI, [M+H]^+) 645.133;

Example 152, 3-[[3',5'-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid

In an analogous manner to example 53, 3-[[4-(((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl)sulfonyl]benzoic acid and 3,5-dichlorophenylboronic acid were used to prepare 3-[[4-(((3',5'-dichloro-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]sulfonyl]benzoic acid.

MS (ES+) m/z 637.0;
HPLC purity 88.0% at 210-370 nm, 11.0 minutes

HRMS: calculated for C_{25}H_{21}Cl_{2}F_{3}N_{2}O_{6}S_{2} - H+ 635.00974; found (ESI-FTMS, [M-H])^- 635.00767;

Example 153, 3-[[4-pyridin-3-yl-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid

In an analogous manner to example 53, 3-[[4-(((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl)sulfonyl]benzoic acid and 3-pyridylboronic acid were used to prepare 3-[[4-(((4-pyridin-3-yl-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl]benzoic acid.

MS (ES+) m/z 570.1;
HPLC purity 100.0% at 210-370 nm, 8.5 minutes
HRMS: calculated for C\textsubscript{24}H\textsubscript{22}F\textsubscript{3}N\textsubscript{3}O\textsubscript{6}S\textsubscript{2} +H+, 570.09749; found (ESI, [M+H]+), 570.0961;

Example 154, 3-\{4-({[2',3'-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidin-l-yl\}sulfonyl]benzoic acid

[0483] In an analogous manner to example 53, 3-\{4-({[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidin-l-yl\}sulfonyl]benzoic acid and 2,3-dichlorophenylboronic acid were used to prepare 3-\{4-({[2',3'-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidin-l-yl\}sulfonyl]benzoic acid.

[0484] MS (ES+) m/z 637.0;
HPLC purity 95.6% at 210-370 nm, 10.6 minutes
HRMS: calculated for C\textsubscript{25}H\textsubscript{21}Cl\textsubscript{2}F\textsubscript{3}N\textsubscript{2}O\textsubscript{6}S\textsubscript{2} +H+, 637.02429; found (ESI, [M+H]+), 637.0241;

Example 155, 4-bromo-\Lambda\prime-\{1-[(6-chloropyridin-3-yl)methyl]piperidin-4-yl\}-2-(trifluoromethyl)benzenesulfonamide

[0485] To a stirred solution of 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide (0.15 g HCl salt, 0.36 mmol) and 6-chloropyridine-3-carboxaldehyde (0.05 g, 0.36 mmol) in methanol (1 mL) was added triacetoxy sodium borohydride (0.10 g, 0.50 mmol) and the resulting solution was stirred overnight at room temperature. The crude mixture was concentrated. Flash column separation using 0%-5% methanol/methylene chloride gradient gave 4-bromo-\Lambda\prime-\{1-[(6-chloropyridin-3-yl)methyl]piperidin-4-yl\}-2-(trifluoromethyl)benzenesulfonamide. (0.073 g, 40%).

[0486] MS (ES-) m/z 511.8;
HPLC purity 98.5% at 210-370 nm, 8.8 minutes
HRMS: calculated for C\textsubscript{18}H\textsubscript{18}BrCl\textsubscript{3}F\textsubscript{3}N\textsubscript{3}O\textsubscript{2}S + H+, 512.00165; found (ESI, [M+H]+), 512.0021;

Example 156, 4-bromo-N-\{1-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl\}-2-(trifluoromethyl)benzenesulfonamide
In an analogous manner to example 155, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 6-methoxypyridine-3-carboxaldehyde were used to prepare 4-bromo-N-[1-{(6-methoxypyridin-3-yl)methyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

MS (ES-) m/z 507.8;  
HPLC purity 99.2% at 210-370 nm, 8.6 minutes  
HRMS: calculated for C_{19}H_{21}BrF_{3}N_{3}O_{3}S + H+, 508.051 18; found (ESI, [M+H]⁺), 508.0519.

Example 157, 3-[[4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]methyl] benzoic acid

In an analogous manner to example 155, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 3-carboxybenzaldehyde were used to prepare 3-[[4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]methyl] benzoic acid.

MS (ES-) m/z 520.9;  
HPLC purity 100.0% at 210-370 nm, 8.2 minutes  
HRMS: calculated for C_{20}H_{20}BrF_{3}N_{2}O_{4}S + H+, 521.03520; found (ESI, [M+H]⁺), 521.0347.

Example 158, N-{[6-chloropyridin-3-yl]carbonyl}piperidin-4-yl)-2-isopropylbenzenesulfonamide

Starting from 2-isopropyl-N-piperidin-4-ylbenzenesulfonamide hydrochloride (Example 131, Step 4) in place of 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride and 6-chloronicotinoyl chloride in place of 3-cyanobenzenesulfonyl chloride, N-\{6-(chloropyridin-3-yl)carbonyl}piperidin-4-yl\)-2-isopropylbenzenesulfonamide was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) m/z 422.1 ([M+H]⁺).

Example 159, Z-tert-butyl- N-\{6-chloropyridin-S-yOcarbonyl}piperidiiM-
Starting from 2-tert-butyl-piperidin-4-ylbenzenesulfonamide hydrochloride (Example 124, Step 4) in place of 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride and 6-chloronicotinoyl chloride in place of 3-cyanobenzenesulfonyl chloride, 2-\(-\text{ter}^{-}\)-butyl-\(\text{L-}\end{alignat*}\{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}benzenesulfonamide was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) \(m/z\) 436.1 ([M+H]+).

Example 160, 2,4-di-tert-butyl-\(\text{L-}\end{alignat*}\{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}benzenesulfonamide

Starting from 2,4-di-\(\text{ter}^{-}\)-butyl-\(\text{V-}\end{alignat*}\)-piperidin-4-ylbenzenesulfonamide hydrochloride (Example 125, Step 4) in place of 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide hydrochloride and 6-chloronicotinoyl chloride in place of 3-cyanobenzenesulfonyl chloride, 2,4-di-\(-\text{ter}^{-}\)-butyl-\(\text{L-}\end{alignat*}\{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}benzenesulfonamide was synthesized in essentially the same manner as described in Example 32, Step 3. MS (ES) \(m/z\) 492.1 ([M+H]+).

Example 161, 5-bromo-4-isopropyl-\(\text{V-}\end{alignat*}\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide

To a stirred solution of 4-isopropyl-\(\text{N-}\end{alignat*}\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide (1.0 g, 2.6 mmol) in 90% concentrated sulfuric acid (25 mL) was added NBS (0.49 g, 2.8 mmol) portionwise. The resulting solution neutralized with sodium hydroxide and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated. Prep SFC gave 5-bromo-4-isopropyl-\(\text{N-}\end{alignat*}\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide. (0.28 g, 25%).

MS (ES-) \(m/z\) 428.9;
HPLC purity 100 0% at 210-370 nm, 9.6 minutes
HRMS: calculated for \(\text{C}_{15}\text{H}_{20}\text{BrF}_{3}\text{N}_{2}\text{O}_{2}\text{S} + \text{H}\), 429.04537; found (ESI, [M+H]+), 429.0447;
Example 162, 3-bromo-4-isopropyl-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide

[0496] In an analogous manner to example 161, 4-isopropyl-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide was used to prepare 3-bromo-4-isopropyl-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide.

[0497] MS (ES-) m/z 428.9;
HPLC purity 96.0% at 210-370 nm, 9.5 min.;
HRMS: calculated for C15H20BrF3N2O2S + H+, 429.04537; found (ESI, [M+H]+), 429.0445;

Example 163, 3-[[4-[[5-bromo-4-isopropyl-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid

[0498] In an analogous manner to example 42, 5-bromo-4-isopropyl-NV-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-[[4-[[5-bromo-4-isopropyl-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid.

[0499] MS (ES+) m/z 613.0;
HPLC purity 95.2% at 210-370 nm, 10.2 minutes
HRMS: calculated for C22H24BrF3N2O6S2 + H+, 613.02840; found (ESI, [M+H]+), 613.0289;

Example 164, tert-butyl 4-[[2'-methyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidine-1-carboxylate

[0500] In an analogous manner to example 53, tert-butyl 4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidine-1-carboxylate and 2-methylphenylboronic acid were used to prepare tert-butyl 4-[[2'-methyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidine-1-carboxylate.
Example 165, tert-butyl 4-([2'-ethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate

In an analogous manner to example 53, tert-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-ethylphenyl boronic acid were used to prepare tert-butyl 4-([2'-ethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate.

Example 166, tert-butyl 4-([2'-isopropyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate

In an analogous manner to example 53, tert-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-isopropyl phenyl boronic acid were used to prepare tert-butyl 4-([2'-isopropyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate.

Example 167, tert-butyl 4-([2'-fluoro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate

In an analogous manner to example 53, tert-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-fluorophenyl boronic acid were used to prepare tert-butyl 4-([2'-fluoro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate.
MS (ES-) m/z 501.3; 
HPLC purity 100.0% at 210-370 nm, 10.2 minutes

Example 168, ferf-butyl 4-([2'-acetyl-3-(trifluoromethyl)biphenyl-4-yl]sulfanyl)amino)piperidine-1-carboxylate

In an analogous manner to example 53, tert-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-acetylphenyl boronic acid were used to prepare tert-butyl 4-([2'-acetyl-3-(trifluoromethyl)biphenyl-4-yl]sulfanyl)amino)piperidine-1-carboxylate.

MS (ES-) m/z 525.4; 
HPLC purity 99.2% at 210-370 nm, 10.9 minutes
HRMS: calculated for C_{25}H_{29}F_{3}N_{2}O_{5}S + H+, 527.18220; found (ESI, [MH-H]^+), 527.1833;

Example 169, /erf/-butyl 4-([2'-ethoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfanyl)amino)piperidine-1-carboxylate

In an analogous manner to example 53, tert-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-ethoxyphenyl boronic acid were used to prepare /erl/-butyl 4-([2'-ethoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfanyl)amino)piperidine-1-carboxylate.

MS (ES-) m/z 521A; 
HPLC purity 98.4% at 210-370 nm, 11.4 minutes

Example 170, tert-butyl 4-([2'-propoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfanyl)amino)piperidine-1-carboxylate

In an analogous manner to example 53, tert-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-propoxyphenyl
boronic acid were used to prepare tert-butyl 4-[[2'-propoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidine-1-carboxylate.

[0512] MS (ES-) m/z 541.4; HPLC purity 99.5% at 210-370 nm, 11.3 minutes

Example 171, tert-butyl 4-[[2'-(methoxymethyl)-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidine-1-carboxylate

[0513] In an analogous manner to example 53, tert-butyl 4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidine-1-carboxylate and 2-methoxymethylphenyl boronic acid were used to prepare tert-butyl 4-[[2'-(methoxymethyl)-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidine-1-carboxylate.

[0514] MS (ES-) m/z 521.4; HPLC purity 99.2% at 210-370 nm, 11.1 minutes

Example 172, tert-butyl 4-[[2',6'-dimethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidine-1-carboxylate

[0515] In an analogous manner to example 53, tert-butyl 4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidine-1-carboxylate and 2,6-dimethylphenyl boronic acid were used to prepare tert-butyl 4-[[2',6'-dimethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidine-1-carboxylate.

[0516] MS (ES-) m/z 511.4; HPLC purity 90.5% at 210-370 nm, 11.2 minutes

Example 173, tert-butyl 4-[[2',5'-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidine-1-carboxylate

[0517] In an analogous manner to example 53, tert-butyl 4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidine-1-carboxylate and 2,5-dichlorophenyl boronic acid were used to prepare tert-butyl 4-[[2'-propoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidine-1-carboxylate.
boronic acid were used to prepare tert-butyl 4-({[2',5'-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate.

[0518] MS (ES-) m/z 551.3; HPLC purity 100.0% at 210-370 nm, 8.3 minutes

Example 174; 4-bromo-N-[1-(4-chlorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0519] In an analogous manner to example 4, example 15 was treated with 4-(chloro)benzoyl chloride to provide 4-bromo-N-[1-(4-chlorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (112 mg, 99%).

[0520] MS (ES+) m/z 525.0; HPLC purity 98.8%, R_t 10.2 minutes;

Example 175; 4-bromo-N-[1-[(4-chlorophenyl)sulfonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0521] In an analogous manner to example 4, example 15 was treated with 4-(chloro)benzenesulfonfyl chloride to provide 4-bromo-N-[1-[(4-chlorophenyl)sulfonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (109 mg, 90%).

[0522] MS (ES+) m/z 561.0; HPLC purity 100.0%, R_t 10.8 minutes;

Example 176; 4-bromo-N-[1-(4-fluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0523] To a stirred slurry of 4-amino-N-(4'-fluorobenzoyl)piperidine hydrochloride salt (129 mg, 0.5 mmol) in dichloromethane (10 mL) was added triethylamine (1.5 mmol) followed by 0.25 M dichloromethane solution of 4-bromo-2-trifluoromethylbenzenesulfonfyl
chloride (2 mL). The reaction was stirred at room temperature (4 h). The organic phase was washed with an aqueous IN hydrochloric acid solution (IN) and the aqueous phase was removed. The crude reaction mixture was concentrated and then purified by flash chromatography using a solvent gradient of ethyl acetate in hexane (0 to 20%, then 20 to 50%) affording 4-bromo-\(N\)-[1-(4-fluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (199 mg, 78%)

[0524] MS (ES+) \(m/z\) 509.1; 
HPLC purity 98.1%, \(R_t\) 9.8 minutes;

Example 177; 4-bromo-2-(trifluoromethyl)-\(N\)-[1-[4-(trifluoromethyl)benzoyl]piperidin-4-yl]benzenesulfonamide

[0525] In an analogous manner to example 176, 4-amino-\(N\)-(4'-trifluoromethyl)benzoyl)piperidine hydrochloride salt (0.5 mmol) was treated with 0.25 M dichloromethane solution of 4-bromo-2-trifluoromethylbenzenesulfonyl chloride (2 mL) to provide 4-bromo-2-(trifluoromethyl)- \(N\)-[1-[4-(trifluoromethyl)benzoyl]piperidin-4-yl]benzenesulfonamide (225 mg, 80%).

[0526] MS (ES+) \(m/z\) 559.1; 
HPLC purity 98.8%, \(R_t\) 10.3 minutes;

Example 178; 4-bromo-\(N\)-[1-(4-cyanobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 176, 4-amino-\(N\)-(4'-cyanobenzoyl)piperidine hydrochloride salt (0.5 mmol) was treated with 0.25 M dichloromethane solution of 4-bromo-2-trifluoromethylbenzenesulfonyl chloride (2 mL) to provide 4-bromo-\(N\)-[1-(4-cyanobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (182 mg, 70%).

[0527] MS (ES+) \(m/z\) 516.1; 
HPLC purity 100.0%, \(R_t\) 9.4 minutes;

Example 179; 4-bromo- \(N\)-[1-(4-te/t-butylbenzoyl)piperidin-4-yl]-2-
(trifluoromethyl)benzenesulfonamide

[0528] In an analogous manner to example 187, 4-amino-N-(4'-tert-butylbenzoyl)piperidine hydrochloride salt (0.5 mmol) was treated with 0.25 M dichloromethane solution of 4-bromo-2-trifluoromethylbenzenesulfonyl chloride (2 mL) to provide 4-bromo-N-[1-(4-fcr/-butylbenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (226 mg, 82%).

[0529] MS (ES) m/z 547.1;
HPLC purity 98.9%, Rₜ 10.9 minutes;

Example 180; 4-bromo- N-[1-14-(trifluoromethoxy)benzoyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0530] In an analogous manner to example 4, example 15 was treated with 4-(trifluoromethoxy)benzoyl chloride to provide 4-bromo- N-[1-[4-(trifluoromethoxy)benzoyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide (129 mg, 99%).

[0531] MS (ES) m/z 575.1;
HPLC purity 100.0%, Rₜ 10.4 minutes;

Example 181, 4-bromo-2-(trifluoromethyl)-N-[6-(trifluoromethyl)pyridin-3-yl]carbonyl]piperidin-4-yl]benzenesulfonamide

[0532] In an analogous manner to example 42, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 2-trifluoromethylpyridine-5-carbonyl chloride were used to prepare 4-bromo-2-(trifluoromethyl)- N-[6-(trifluoromethyl)pyridin-3-yl]carbonyl]piperidin-4-yl]benzenesulfonamide.

[0533] MS (ES+) m/z 560.0;
HPLC purity 100.0% at 210-370 nm, 9.7 minutes
HRMS: calculated for C₁₉H₁₆BrF₆N₃O₃S + H⁺, 560.00727; found (ESI, [M+H]⁺), 560.0088;
Example 182, 4-bromo-N-[1-(2-chloro-6-methylisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0534] In an analogous manner to example 42, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 2-chloro-6-methylpyridine-4-carbonyl chloride were used to prepare 4-bromo-N-[1-(2-chloro-6-methylisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

[0535] MS (ES+) m/z 540.0;
HPLC purity 100.0% at 210-370 nm, 9.6 minutes
HRMS: calculated for C_{19}H_{18}BrClF_{3}N_{3}O_{3}S + H+, 539.99656; found (ESI, [M+H]^+), 539.9985;

Example 183, 4-bromo-N-[1-(2-chloro-6-methoxyisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0536] In an analogous manner to example 42, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 2-chloro-6-methoxypyridine-4-carbonyl chloride were used to prepare 4-bromo-N-[1-(2-chloro-6-methoxyisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

[0537] MS (ES+) m/z 556.1;
HPLC purity 100.0% at 210-370 nm, 10.2 minutes
HRMS: calculated for C_{19}H_{18}BrClF_{3}N_{3}O_{4}S + H+, 555.99148; found (ESI, [M+H]^+), 555.9919;

Example 184, 4-bromo-N'-{1-[2,5-dichloropyridin-3-yl]carbonyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

[0538] In an analogous manner to example 42, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 2,5-dichloropyridine-3-carbonyl chloride were
used to prepare 4-bromo-\(N\)-[1-[(2,5-dichloropyridin-3-yl)carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

**Example 185**, 4-bromo-\(N\)-[1-[(6-pyrrolidin-1-ylpyridin-3-yl)carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

**Step 1:** In an analogous manner to example 42, piperidin-4-yl-carbamic acid tert-butyl ester and 2-chloropyridine-5-carbonyl chloride were used to prepare [l-(6-Chloropyridine-3-carbonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.

Step 2: In an analogous manner to example 75, [l-(6-Chloro-pyridine-3-carbonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester and pyrrolidine were used to prepare [l-(6-Pyrrolidin-1-yl-pyridine-3-carbonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.

**Step 2:** In an analogous manner to example 54, [l-(6-Pyrrolidin-1-yl-pyridine-3-carbonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester was used to prepare (4-Amino-piperidin-1-yl)-(6-pyrrolidin-1-yl-pyridin-3-yl)-methanone.

**Step 3:** In an analogous manner to example 42, (4-Amino-piperidin-1-yl)-(6-pyrrolidin-1-yl-pyridin-3-yl)-methanone and 4-bromo-2-trifluoromethylbenzene sulfonyl chloride were used to prepare 4-bromo-\(N\)-[1-[(6-pyrrolidin-1-ylpyridin-3-yl)carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

**Example 186**, 2'-methyl-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide
In an analogous manner to example 54, tert-butyl 4-{{[2'-methyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate was used to prepare 2'-methyl-\textit{N}-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

[0544] MS (ES+) \textit{m/z} 399.1; 
HPLC purity 98.7\% at 210-370 nm, 8.3 minutes 
HRMS: calculated for C_{19}H_{21}F_{3}N_{2}O_{2}S + H+, 399.13486; found (ESI, \([M+H]^+\)), 399.1339; 

Example 187, 2'-ethyl-\textit{N}-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0545] In an analogous manner to example 54, tert-butyl 4-{{[2'-ethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate was used to prepare 2'-ethyl-\textit{N}-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

[0546] MS (ES+) \textit{m/z} 412.8; 
HPLC purity 96.6\% at 210-370 nm, 8.7 minutes 
HRMS: calculated for C_{20}H_{23}F_{3}N_{2}O_{2}S + H+, 413.15051; found (ESI, \([M+H]^+\)), 413.1507; 

Example 188, 2'-isopropyl-\textit{N}-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0547] In an analogous manner to example 54, tert-butyl 4-{{[2'-isopropyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate was used to prepare 2'-isopropyl-\textit{N}-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

[0548] MS (ES+) \textit{m/z} 427.2; 
HPLC purity 100.0\% at 210-370 nm, 9.1 minutes 
HRMS: calculated for C_{21}H_{25}F_{3}N_{2}O_{2}S + H+, 427.16616; found (ESI, \([M+H]^+\)), 427.1679; 

Example 189, 2'-fluoro-\textit{N}-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide
In an analogous manner to example 54, tert-butyl 4-([2’-fluoro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate was used to prepare 2’-fluoro-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) m/z 403.0;
HPLC purity 99.5% at 210-370 nm, 7.9 minutes
HRMS: calculated for C_{18}H_{18}F_{4}N_{2}O_{2}S + H+, 403.1079; found (ESI, [M+H]), 403.1086;

Example 190, 2’-acetyl-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 54, tert-butyl 4-([2’-acetyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate was used to prepare 2’-acetyl-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) m/z 427.1;
HPLC purity 100.0% at 210-370 nm, 7.1 minutes
HRMS: calculated for C_{20}H_{21}F_{3}N_{2}O_{3}S + H+, 427.12977; found (ESI, [M+H]^+), 427.1306;

Example 191, 2’-ethoxy-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 54, tert-butyl 4-([2’-ethoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate was used to prepare 2’-ethoxy-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) m/z 428.9;
HPLC purity 99.4% at 210-370 nm, 8.5 minutes
HRMS: calculated for C_{20}H_{23}F_{3}N_{2}O_{3}S + H+, 429.14542; found (ESI, [M+H]^+), 429.1452;

Example 192, N-piperidin-4-yl-2’-propoxy-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 54, tert-butyl 4-([2’-propoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate was used to prepare N-piperidin-4-yl-2’-propoxy-3-(trifluoromethyl)biphenyl-4-sulfonamide.
Example 193, 2′-(methoxymethyl)-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 54, tert-butyl 4-{[2′-(methoxymethyl)-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate was used to prepare 2′-(methoxymethyl)-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

Example 194, 2′,6′-dimethyl-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 54, tert-butyl 4-{[2′,6′-dimethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate was used to prepare 2′,6′-dimethyl-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

Example 195, 2′,5′-dichloro-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 54, tert-butyl 4-{[2′,5′-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate was used to prepare 2′,5′-dichloro-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

Example 196, 2′,5′-dichloro-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 54, tert-butyl 4-{[2′,5′-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate was used to prepare 2′,5′-dichloro-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.
Example 196, IV-1-{(6-chloropyridin-3-yl)carbonylpiperidin-4-yl}-2’-methyl-S-(trifluoromethyl)biphenyl-4-sulfonamide

[0563] In an analogous manner to example 42, 2’-methyl- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare N-{1-JX6-chloropyridin-3-ylOcarbonylpiperidin^4-yI^4-methyl-S-(trifluoromethyl)biphenyl-4-sulfonamide.

Example 197, N-{1-{[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-2’-ethyl-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0565] In an analogous manner to example 42, 2’-ethyl- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare N-{1-I[(6-chloropyridin-3-yl)carbonylpiperidin^4-yI^4-ethyl-S-(trifluoromethyl)biphenyl-4-sulfonamide.

Example 198, N-{1-{[(6-chloropyridin-3-yl)carbonylpiperidin-4-yl}-2’-isopropyl-3-(trifluoromethyl)biphenyl-4-sulfonamide
In an analogous manner to example 42, 2'-isopropyl-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare N-1-{1-[6-chloropyridin-3-yl]carbonyl}piperidin-4-yl}-2'-isopropyl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) m/z 566.2;
HPLC purity 97.7% at 210-370 nm, 10.8 minutes

Example 199, N-1-{[6-chloropyridin-3-yl]carbonyl}piperidin-4-yl}-2'-fluoro-S-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 42, 2'-fluoro-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare N-1-{1-[6-chloropyridin-3-yl]carbonyl}piperidin-4-yl}-2'-fluoro-S-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) m/z 542.2;
HPLC purity 99.0% at 210-370 nm, 10.1 minutes
HRMS: calculated for C_{24}H_{20}ClF_{3}N_{3}O_{4}S + H+, 542.09228; found (ESI, [M+H]^+), 542.0928;

Example 200, 2'-acetyl-N-1-{(6-chloropyridin-3-yl)carbonyl}piperidin-4-yl}-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 42, 2'-acetyl-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare 2'-acetyl-N-1-[{6-chloropyridin-3-yl]carbonyl}piperidin-4-yl}-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) m/z 566.2;
HPLC purity 100.0% at 210-370 nm, 9.3 minutes
HRMS: calculated for C_{26}H_{23}ClF_{3}N_{3}O_{4}S + H+, 566.1226; found (ESI, [M+H]^+), 566.1 132;
Example 201. \( \mathcal{N}-\{1-[6\text{-chloropyridin-S-yOcarbonylpiperidin-yl}]l'-\text{ethoxy-S-(trifluoromethyl)biphenyl-4-sulfonamide} \)

[0573] In an analogous manner to example 42, 2'-ethoxy-\( \mathcal{N}\)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare \( \mathcal{N}-\{1-[6\text{-chloropyridin-3-yl}])\text{carbonylpiperidin-4-yl}\}-2'\text{-ethoxy-3-}
(trifluoromethyl)biphenyl-4-sulfonamide.

[0574] MS (ES+) \( m/z \) 568.2;
HPLC purity 100.0% at 210-370 nm, 10.5 minutes
HRMS: calculated for \( \text{C}_{26}\text{H}_{25}\text{ClF}_{3}\text{N}_{3}\text{O}_{4}\text{S} + \text{H}^+ \), 568.12791; found (ESI, [M+H]^+), 568.1267;

Example 202. \( \mathcal{N}-\{1-[6\text{-chloropyridin-S-yOcarbonylpiperidin-yl}]l'-\text{propoxy-S-(trifluoromethyl)biphenyl-4-sulfonamide} \)

[0575] In an analogous manner to example 42, \( \mathcal{N}\)-piperidin-4-yl-2'-propoxy-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare \( \mathcal{N}-\{1-[6\text{-chloropyridin-3-yl}])\text{carbonylpiperidin-4-yl}\}-2'\text{-propoxy-3-}
(trifluoromethyl)biphenyl-4-sulfonamide.

[0576] MS (ES+) \( m/z \) 582.2;
HPLC purity 100.0% at 210-370 nm, 10.8 minutes
HRMS: calculated for \( \text{C}_{27}\text{H}_{27}\text{ClF}_{3}\text{N}_{3}\text{O}_{4}\text{S} + \text{H}^+ \), 582.14356; found (ESI, [M+H]^+), 582.1447;

Example 214. \( \mathcal{N}-\{1-[6\text{-chloropyridin-3-yl}])\text{carbonylpiperidin-4-yl}\}-2'\text{-}(\text{methoxymethyl})-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0577] In an analogous manner to example 42, 2'-(methoxymethyl)-\( \mathcal{N}\)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare \( \mathcal{N}-\{1-[6\text{-chloropyridin-S-yOcarbonylpiperidin-yl}]l'^{\text{methoxymethyl}}\text{OS-(trifluoromethyl)biphenyl-4-sulfonamide}. \)
Example 204, N-{[(r(6-chloropyridin-3-yl)carbonyl)piperidin-4-yl]-2',6'-dimethyl-3-(trifluoromethyl)biphenyl-4-sulfonamide

Example 205, tert-butyl 4-({[2'-carbamoyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate
In an analogous manner to example 53, tert-butyl 4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate and 2-(aminocarbonyl)phenyl boronic acid were used to prepare tert-butyl 4-((2′-carbamoyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidine-1-carboxylate.

MS (ES+) m/z 428.1;
HPLC purity 98.6% at 210-370 nm, 9.1 minutes
HRMS: calculated for C_{24}H_{28}F_{3}N_{3}O_{5}S + H+, 528.17745; found (ESI, [M+H]^+), 528.1765;

Example 207, (55)-N-tert-butyl-2-oxo-5-((4-((3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl)carbonyl]pyrrolidine-1-carboxamide

In an analogous manner to example 53, (20)-2-((4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl)carbonyl)-N-tert-butyl-5-oxopyrrolidine-1-carboxamide and phenyl boronic acid were used to prepare (55)-N-tert-butyl-2-oxo-5-((4-((3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl)carbonyl]pyrrolidine-1-carboxamide.

MS (ES+) m/z 595.3;
HPLC purity 93.8% at 210-370 nm, 10.2 minutes
HRMS: calculated for C_{24}H_{25}F_{3}N_{3}O_{6}S_{2} + H+, 595.21965; found (ESI, [M+H]^+), 595.2199;

Example 208, 3-((4-((2′-methyl-3-(trifluoroniethyl)biphenyl-4-yl)sulfonyl)benzoyl)amino)piperidin-1-yl)sulfonil]benzoic acid

In an analogous manner to example 42, 2′-methyl- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-((4-((2′-methyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl)sulfonil]benzoic acid.

HPLC purity 90.4% at 210-370 nm, 10.1 minutes
HRMS: calculated for C_{28}H_{25}F_{3}N_{2}O_{6}S_{2} + H+, 583.1 1789; found (ESI, [M+H]^+), 583.1 194;
Example 209, 3-\{4-\{[2'-ethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}\ammino\}piperidin-1-yl\sulfonyl\benzoic acid

[0589] In an analogous manner to example 42, 2'-ethyl-\textit{N}-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-\{4-\{[2'-ethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl\}amino\}piperidin-1-yl\sulfonyl\benzoic acid.

HPLC purity 91.7% at 210-370 nm, 10.3 minutes
HRMS: calculated for C_{27}H_{27}F_{3}N_{2}O_{6}S_{2} + H+, 597.13354; found (ESI, [M+H]^{+}), 597.133 1;

Example 210, 3-\{4-\{[2'-isopropyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl\}ammino\}piperidin-1-yl\sulfonyl\benzoic acid

[0591] In an analogous manner to example 42, 2'-isopropyl-\textit{N}-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-\{4-\{[2'-isopropyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl\}amino\}piperidin-1-yl\sulfonyl\benzoic acid.

HPLC purity 95.8% at 210-370 nm, 10.5 minutes
HRMS: calculated for C_{27}H_{27}F_{3}N_{2}O_{6}S_{2} + H+, 611.14919; found (ESI, [M+H]^{+}), 611.1501;

Example 211, 3-\{4-\{[2'-fluoro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl\}ammino\}piperidin-1-yl\sulfonyl\benzoic acid

[0592] In an analogous manner to example 42, 2'-fluoro-\textit{N}-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-\{4-\{[2'-fluoro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl\}amino\}piperidin-1-yl\sulfonyl\benzoic acid.

HPLC purity 97.5% at 210-370 nm, 9.9 minutes
HRMS: calculated for C_{25}H_{22}F_{4}N_{2}O_{6}S_{2} + H+, 587.09282; found (ESI, [M+H]^{+}), 587.0930;
Example 212, 3-[[4-([[2'-acetyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid

[0595] In an analogous manner to example 42, 2'-acetyl-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-[[4-([[2'-acetyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid.

[0596] HPLC purity 92.8% at 210-370 nm, 9.2 minutes
HRMS: calculated for C_{27}H_{25}F_{3}N_{2}O_{7}S_{2} - H^+, 609.09825; found (ESI, [M-H]), 609.0978;

Example 213, 3-[[4-([[2'-ethoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid

[0597] In an analogous manner to example 42, 2'-ethoxy-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-[[4-([[2'-ethoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid.

[0598] HPLC purity 94.1% at 210-370 nm, 10.2 minutes
HRMS: calculated for C_{27}H_{27}F_{3}N_{2}O_{7}S_{2} + H^+, 613.12845; found (ESI, [M+H]^+), 613.1285;

Example 214, 3-[[4-([[2'-propoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid

[0599] In an analogous manner to example 42, N-piperidin-4-yl-2'-propoxy-3-(trifluoromethyl)biphenyl-4-sulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-[[4-([[2'-propoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid.

[0600] HPLC purity 95.8% at 210-370 nm, 10.5 minutes
HRMS: calculated for C_{29}H_{29}F_{3}N_{2}O_{7}S_{2} + H^+, 627.14410; found (ESI, [M+H]^+), 627.1435;
Example 215, 3-{[4-{[2'-(methoxymethyl)-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino]l-piperidin-1-yl}sulfonyl]benzoic acid

[0601] In an analogous manner to example 42, 2'-(methoxymethyl)-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-{[4-{[2'-(methoxymethyl)-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino]piperidin-1-yl]sulfonyl]benzoic acid.

Example 216, 3-{[4-{[2',6'-dimethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino]piperidin-1-yl}sulfonyl]benzoic acid

[0602] HPLC purity 95.1% at 210-370 nm, 9.7 minutes
HRMS: calculated for C_{27}H_{27}F_{3}N_{2}O_{7}S_{2} + H+, 613.12845; found (ESI, [M+H]), 613.1279;

Example 216, 3-{[4-{[2',6'-dimethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino]piperidin-1-yl}sulfonyl]benzoic acid

[0603] In an analogous manner to example 42, 2',6'-dimethyl-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 3-(chlorosulfonyl)benzoic acid were used to prepare 3-{[4-{[2',6'-dimethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino]piperidin-1-yl]sulfonyl]benzoic acid.

Example 217, 3-{[4-{[2',5'-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino]piperidin-1-yl}sulfonyl]benzoic acid

[0604] HPLC purity 89.9% at 210-370 nm, 10.2 minutes
HRMS: calculated for C_{25}H_{21}Cl_{2}F_{3}N_{2}O_{6}S_{2} - H-, 595.11899; found (ESI, [M-H]), 595.1196;

Example 217, 3-{[4-{[2',5'-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino]piperidin-1-yl}sulfonyl]benzoic acid

[0605] In an analogous manner to example 42, 2',5'-dichloro-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare 3-{[4-{[2',5'-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino]piperidin-1-yl]sulfonyl]benzoic acid.

[0606] HPLC purity 83.4% at 210-370 nm, 10.6 minutes
HRMS: calculated for C_{25}H_{21}Cl_{2}F_{3}N_{2}O_{6}S_{2} - H-, 635.00974; found (ESI, [M-H]), 635.0097;
Example 218, 4’-[(piperidin-4-ylamino)sulfonyl]-3’-(trifluoromethyl)biphenyl-2-carboxamide

[0607] In an analogous manner to example 54, tert-butyl 4-(((2’-carbamoyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidine-1-carboxylate was used to prepare 4’-[(piperidin-4-ylamino)sulfonyl]-3’-(trifluoromethyl)biphenyl-2-carboxamide.

[0608] HPLC purity 98.2% at 210-370 nm, 5.7 minutes
HRMS: calculated for C_{19}H_{20}F_{3}N_{3}O_{3}S + H+, 428.12502; found (ESI, [M+H]^+), 428.1260;

Example 219, 4’-[(1-(6-chloropyridin-3-yl)carbonyl)piperidin-4-yl]amino)sulfonyl]-3’-(trifluoromethyl)biphenyl-2-carboxamide

[0609] In an analogous manner to example 42, 4’-[(piperidin-4-ylamino)sulfonyl]-3’-(trifluoromethyl)biphenyl-2-carboxamide and 2-chloropyridine-5-carbonyl chloride were used to prepare 4’-[(1-(6-chloropyridin-3-yl)carbonylpiperidin-4-yl]amino)sulfonyl]-3’-(trifluoromethyl)biphenyl-2-carboxamide.

[0610] HPLC purity 100.0% at 210-370 nm, 8.0 minutes
HRMS: calculated for C_{25}H_{22}ClF_{3}N_{4}O_{4}S - H+, 565.09296; found (ESI, [M-H]^-), 565.0920;

Example 220, 4-bromo-N(1-[6-(dimethylamino)pyridin-3-yl]carbonyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

[0611] Step 1: In an analogous manner to example 42, piperidin-4-yl-carbamic acid tert-butyl ester and 2-chloropyridine-5-carbonyl chloride were used to prepare 1-(6-Chloropyridine-3-carbonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.

[0612] Step 2: In an analogous manner to example 75, [1-(6-Chloro-pyridine-3-carbonyl)piperidin-4-yl]-carbamic acid tert-butyl ester and dimethylamine were used to tert-butyl 1-(6-(dimethylamino)nicotinoyl)piperidin-4-ylcarbamate.
Step 2: In an analogous manner to example 54, tert-butyl 1-(6-(dimethylamino)nicotinoyl)piperidin-4-ylcarbamate was used to prepare (4-aminopiperidin-1-yl)(6-(dimethylamino)pyridin-3-yl)methanone.

Step 3: In an analogous manner to example 42, (4-aminopiperidin-1-yl)(6-(dimethylamino)pyridin-3-yl)methanone and 4-bromo-2-trifluoromethylbenzene sulfonyl chloride were used to prepare 4-bromo-N-(1-{6-(dimethylamino)pyridin-3-yl}carbonyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

HPLC purity 100.0% at 210-370 nm, 9.2 minutes
HRMS: calculated for C_{20}H_{22}BrF_{3}N_{4}O_{3}S - H+, 533.04753; found (ESI, [M-H]), 533.0466;

Example 221, N-(1-{6-(dimethylamino)pyridin-3-yl}carbonyl)piperidin-4-yl)-3-(trifluoromethyl)benzyl-4-sulfonamide

Step 4: In an analogous manner to example 53, 4-bromo-N-(1-{6-(dimethylamino)pyridin-3-yl}carbonyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide and phenyl boronic acid were used to prepare N-(1-{6-(dimethylamino)pyridin-3-yl}carbonyl)piperidin-4-yl)-3-(trifluoromethyl)benzyl-4-sulfonamide.

HPLC purity 97.4% at 210-370 nm, 10.0 minutes
HRMS: calculated for C_{26}H_{27}F_{3}N_{4}O_{3}S - H+, 531.16832; found (ESI, [M-H]), 531.1680;

Example 222, 4-bromo-7N-(1-[4-(dimethylamino)benzoyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

Step 5: In an analogous manner to example 42, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 4-dimethylaminobenzoyl chloride were used to prepare 4-bromo-N-{1-[4-(dimethylamino)benzoyl]piperidin-4-yl}-2-(trifluoromethyl)benzenesulfonamide.

HPLC purity 100.0% at 210-370 nm, 10.1 minutes
HRMS: calculated for C$_{21}$H$_{23}$BrF$_3$N$_3$O$_3$S-H$^+$, 532.05228; found (ESI, [M-H]-), 532.0511.

Example 223, $\mathcal{N}$-[1-[4-(dimethylamino)benzoyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0620] In an analogous manner to example 42, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 4-dimethylaminobenzoyl chloride were used to prepare $\mathcal{N}$-[1-[4-(dimethylamino)benzoyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

[0621] HPLC purity 99.4% at 210-370 nm, 10.6 minutes
HRMS: calculated for C$_{27}$H$_{28}$F$_3$N$_3$O$_3$S-H$^+$, 530.17307; found (ESI, [M-H]O), 530.1733;

Example 224, $\mathcal{N}$-[1-[(2-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0622] In an analogous manner to example 42, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloronicotinoyl chloride were used to prepare $\mathcal{N}$-ll^-chloropyridin-S-yOcarbonylpiperidin^-yl^-trifluoromethylObiphenyM-sulfonamide.

[0623] MS (ES+) m/z 524.1;
HPLC purity 100.0% at 210-370 nm, 9.8 minutes
HRMS: calculated for C$_{24}$H$_{21}$ClF$_3$N$_3$O$_3$S + H$, 524.10170; found (ESI-FTMS, [M+H]$^{1+}$), 524.10293;

Example 225, $\mathcal{N}$-[l-[6-(methylamino)pyridin-3-yl]carbonylpiperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0624] In an analogous manner to example 75, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and methyl amine in ethanol were used to prepare $\mathcal{N}$-[l-[6-(methylamino)pyridin-3-yl]carbonylpiperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.
Example 226, $N$-(I-{[2-(methylamino)pyridin-3-yl]carbonyl}piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 75, $N$-{1-[(2-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-3-(trifluoromethyl)biphenyl-4-sulfonamide and methyl amine in ethanol were used to prepare $N$-(I-{[2-(methylamino)pyridin-3-yl]carbonyl}piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide.

Example 227, $N$-(I-{[2-(dimethylamino)pyridin-3-yl]carbonyl}piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 75, $N$-{1-[(2-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-3-(trifluoromethyl)biphenyl-4-sulfonamide and dimethylamine were used to prepare $N$-(I-{[2-(dimethylamino)pyridin-3-yl]carbonyl}piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide.
Example 228, 4-bromo-\( \Lambda \)-\( l \)-[3-(dimethylamino)benzoyl]piperidin-4-yl]-2-(trifluoroethyl)benzenesulfonamide

[0630] In an analogous manner to example 42, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 3-dimethylaminobenzoyl chloride were used to prepare 4-bromo-\( \Lambda \)-\( l \)-[3-(dimethylamino)benzoyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

[0631] HPLC purity 100.0% at 210-370 nm, 10.1 minutes
HRMS: calculated for C21H23BrF3N3O3S + H+, 534.06683; found (ESI, [M+H]⁺), 534.0666;

Example 229, \( \psi \)-\( l \)-[3-(dimethylamino)benzoyl]piperidin-4-yl]-3-(trifluoromethyl)benzenesulfonamide

[0632] In an analogous manner to example 42, N-piperidin-4-yl-3-(trifluoromethyl)benzenesulfonamide and 3-dimethylaminobenzoyl chloride were used to prepare \( \Lambda \)-\( l \)-[3-(dimethylamino)benzoyl]piperidin-4-yl]-3-(trifluoromethyl)benzenesulfonamide.

[0633] HPLC purity 99.0% at 210-370 nm, 10.7 minutes
HRMS: calculated for C27H28F3N3O3S + H+, 532.18762; found (ESI, [M+H]⁺), 532.1870;

Example 230, 2'-chloro-N-piperidin-4-yl-3-(trifluoromethyl)benzenesulfonamide

[0634] In an analogous manner to example 54, \( \alpha \)\( \text{et} \)/butyl 4-([2'-chloro-3-(trifluoromethyl)benzenesulfonamido]piperidine-1-carboxylate was used to prepare 2'-chloro-N-piperidin-4-yl-3-(trifluoromethyl)benzenesulfonamide.

[0635] MS (ES⁺) \( m/z \) 419.0;
HPLC purity 92.7% at 210-370 nm, 8.3 minutes
HRMS: calculated for \( \text{C}_{18}\text{H}_{18}\text{ClF}_3\text{N}_2\text{O}_2\text{S} + \text{H}^+ \), 419.08023; found (ESI, \([\text{M+H}]^+\))\), 419.0799;

Example 231, 2'-methoxy- \( N \)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0636] In an analogous manner to example 54, \( \text{tert-buty}l \)\( 4\)\-(\(\{2'-\text{methoxy-}3\)-(trifluoromethyl)biphenyl-4-yl\}sulfonyl)amino)piperidine-1-carboxylate was used to prepare 2'-methoxy- \( N \)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

[0637] MS (ES+) \( m/z \) 415.1;
HPLC purity 100.0% at 210-370 nm, 7.9 minutes
HRMS: calculated for \( \text{C}_{19}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_3\text{S} + \text{H}^+ \), 415.12977; found (ESI, \([\text{M+H}]^+\))\), 415.1295;

Example 232, 2'-fluoro-6'-methoxy-IV-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0638] In an analogous manner to example 54, \( \text{iert-buty}l \)\( 4\)\-(\(\{2'-\text{fluoro-}6'-\text{methoxy-}3\)-(trifluoromethyl)biphenyl-4-yl\}sulfonyl)amino)piperidine-1-carboxylate was used to prepare 2'-fluoro-6'-methoxy- \( N \)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0639] MS (ES+) \( m/z \) 433.1;
HPLC purity 100.0% at 210-370 nm, 7.9 minutes
HRMS: calculated for \( \text{C}_{19}\text{H}_{20}\text{F}_4\text{N}_2\text{O}_3\text{S} + \text{H}^+ \), 433.12035; found (ESI, \([\text{M+H}]^+\))\), 433.1 199;

Example 233, \( N \)-piperidin-4-yl-2'-(trifluoromethoxy)-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0640] In an analogous manner to example 54, \( \text{tert-buty}l \)\( 4\)\-(\(\{2'-\text{(trifluoromethoxy)-}3\)-(trifluoromethyl)biphenyl-4-yl\}sulfonyl)amino)piperidine-1-carboxylate was used to prepare \( N \)-piperidin-4-yl-2'-((trifluoromethoxy)-3-(trifluoromethyl)biphenyl-4-sulfonamide.

[0641] MS (ES+) \( m/z \) 469.1;
HPLC purity 100.0% at 210-370 nm, 8.5 minutes
HRMS: calculated for \( \text{C}_{19}\text{H}_{18}\text{F}_{6}\text{N}_{2}\text{O}_{3}\text{S} + \text{H}^+ \), 469.10151; found (ESI, [M+H]^+), 469.101;

Example 234, \( \text{N} \)-piperidin-4-yl-3-(trifluoromethyl)-1,\( \text{r}',\text{l}'' \)-terphenyl-4-sulfonamide

[0642] In an analogous manner to example 54, tert-butyl 4-(((3-(trifluoromethyl)-1,\( \text{r},\text{l}'' \)-terphenyl-4-yl)sulfonyl)amino)piperidine-1-carboxylate was used to prepare \( \text{N} \)-piperidin-4-yl-3-(trifluoromethyl)-1,\( \text{r},\text{l}'' \)-terphenyl-4-sulfonamide.

[0643] MS (ES+) \( m/z \) 461.1;

HPLC purity 99.2% at 210-370 nm, 9.0 minutes

HRMS: calculated for \( \text{C}_{24}\text{H}_{23}\text{F}_{3}\text{N}_{2}\text{O}_{2}\text{S} + \text{H}^+ \), 461.15051; found (ESI, [M+H]^+), 461.1501;

Example 235, 2'-phenoxy- \( \text{N} \)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0644] In an analogous manner to example 54, tert-butyl 4-(((2'-phenoxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidine-1-carboxylate was used to prepare 2'-phenoxy- \( \text{N} \)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

[0645] MS (ES+) \( m/z \) 477.1;

HPLC purity 100.0% at 210-370 nm, 9.2 minutes

HRMS: calculated for \( \text{C}_{24}\text{H}_{23}\text{F}_{3}\text{N}_{2}\text{O}_{3}\text{S} + \text{H}^+ \), 477.14542; found (ESI, [M+H]^+), 477.1447;

Example 236, iV-\( \text{N} \)-{4'-(piperidin-4-ylamino)sulfonyl]-3'-(trifluoromethyl)biphenyl-2-yl}acetamide

[0646] In an analogous manner to example 54, tert-butyl 4-(((2'-acetamido-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidine-1-carboxylate was used to prepare \( \text{N} \)-{4'-(piperidin-4-ylamino)sulfonyl]-3'-(trifluoromethyl)biphenyl-2-yl}acetamide.

[0647] MS (ES+) \( m/z \) 442.1;

HPLC purity 99.1% at 210-370 nm, 6.0 minutes
Example 237, 2'-hydroxy-\textit{N}-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0648] In an analogous manner to example 54, \textit{tert-butyl} 4-((2'-hydroxy-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidine-1-carboxylate was used to prepare 2'-hydroxy-\textit{N}-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

[0649] MS (ES+) m/z 401.1;
HPLC purity 98.6\% at 210-370 nm, 7.3 minutes
HRMS: calculated for C_{18}H_{19}F_{3}N_{2}O_{2}S + H+, 401.1412; found (ESI, [M+H]^+), 401.1367;

Example 238, 4\textit{J}-(piperidin-4-ylamino)sulfonyl)-3'-{(trifluoromethyl)biphenyl-2-carboxylic acid

[0650] In an analogous manner to example 54, 4'-(((1-\textit{tert}-butoxycarbonyl)piperidin-4-yl)amino)sulfonyl)-3'-(trifluoromethyl)biphenyl-2-carboxylic acid was used to prepare 4'-((piperidin-4-ylamino)sulfonyl)-3'-(trifluoromethyl)biphenyl-2-carboxylic acid.

[0651] MS (ES+) m/z 429.1;
HPLC purity 98.7\% at 210-370 nm, 6.4 minutes
HRMS: calculated for C_{16}H_{18}F_{3}N_{2}O_{2}S_{2} + H+, 429.1094; found (ESI, [M+H]^+), 429.1084;

Example 239, \textit{N}-piperidin-4-yl-4-(2-thienyl)-2-(trifluoromethyl)benzenesulfonamide

[0652] In an analogous manner to example 54, \textit{tert-butyl} 4-((4-(2-thienyl)-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate was used to prepare \textit{N}-piperidin-4-yl-4-(2-thienyl)-2-(trifluoromethyl)benzenesulfonamide.

[0653] MS (ES+) m/z 391.0;
HPLC purity 100.0\% at 210-370 nm, 7.6 minutes
HRMS: calculated for C_{16}H_{18}F_{3}N_{2}O_{2}S_{2} + H+, 391.07563; found (ESI, [M+H]^+), 391.0751;
Example 240, tert-butyl 4-([2'-chloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate

[0654] In an analogous manner to example 53, tert-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-chlorophenyl boronic acid were used to prepare tert-butyl 4-([2'-chloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate.

[0655] MS (ES-) m/z 517.1;
HPLC purity 91.0% at 210-370 nm, 11.2 minutes
HRMS: calculated for C_{23}H_{26}ClF_{3}N_{2}O_{4}S + Na+, 541.1 1461; found (ESI, [M+Na]^+), 541.1135;

Example 241, tert-butyl 4-([2'-methoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate

[0656] In an analogous manner to example 53, tert-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-methoxyphenyl boronic acid were used to prepare tert-butyl 4-([2'-methoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate.

[0657] MS (ES-) m/z 513.2;
HPLC purity 100.0% at 210-370 nm, 10.9 minutes
HRMS: calculated for C_{24}H_{29}F_3N_2O_5S + Na+, 537.16415; found (ESI, [M+Na]^+), 537.165;

Example 242, tert-butyl 4-([2'-fluoro-6'-methoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate

[0658] In an analogous manner to example 53, tert-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-fluoro-6-methoxyphenyl boronic acid were used to prepare tert-butyl 4-([2'-fluoro-6'-methoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate.
HPLC purity 100.0% at 210-370 nm, 10.9 minutes

HRMS: calculated for C_{24}H_{28}F_{4}N_{2}O_{5}S + Na+, 555.15472; found (ESI, [M+Na]+), 555.1545;

Example 243, tert-butyl 4-({[2'-(trifluoromethoxy)-3-(trifluoroniethyl)biphenyl-4-yI]sulfonyl}amino)piperidine-1-carboxylate

In an analogous manner to example 53, tert-butyl 4-({[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate and 2-trifluoromethoxyphenyl boronic acid were used to prepare tert-butyl 4-({[2'-(trifluoromethoxy)-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate.

MS (ES-) m/z 567.1;
HPLC purity 100.0% at 210-370 nm, 11.1 minutes

HRMS: calculated for C_{24}H_{26}F_{6}N_{2}O_{4}S + Na+, 591.13588; found (ESI, [M+Na]+), 591.1352;

Example 244, tert-butyl 4-({[3-(trifluoromethyl)-1,2',1''-terphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate

In an analogous manner to example 53, tert-butyl 4-({[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate and 2-biphenyl boronic acid were used to prepare tert-butyl 4-({[3-(trifluoromethyl)-1,2\''-terphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate.

MS (ES-) m/z 559.2;
HPLC purity 90.0% at 210-370 nm, 11.5 minutes

HRMS: calculated for C_{25}H_{31}F_{3}N_{2}O_{4}S + Na+, 583.18488; found (ESI, [M+Na]+), 583.1843;

Example 245, tert-butyl 4-({[2'-phenoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate
In an analogous manner to example 53, tert-butyl 4-(([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-phenoxyphenyl boronic acid were used to prepare tert-butyl 4-(([2'-phenoxy-3-(trifluoromethyl)phenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate.

MS (ES-) m/z 575.2;
HPLC purity 100.0% at 210-370 nm, 11.5 minutes
HRMS: calculated for $C_{29}H_{31}F_3N_2O_5S + Na^+$, 599.17980; found (ESI, [M+Na]^+), 599.179;

Example 246, tert-butyl 4-(([2'-acetamido-3-(trifluoromethyl)phenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate

In an analogous manner to example 53, tert-butyl 4-(([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-acetamidophenyl boronic acid were used to prepare tert-butyl 4-(([2'-acetarnido-3-(trifluoromethyl)phenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate.

MS (ES-) m/z 540.1;
HPLC purity 98.8% at 210-370 nm, 9.5 minutes
HRMS: calculated for $C_{25}H_{29}F_3N_3O_5S + Na^+$, 564.17504; found (ESI, [M+Naf], 564.1756;

Example 247, tert-butyl 4-(([2'-hydroxy-3-(trifluoromethyl)phenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate

In an analogous manner to example 53, tert-butyl 4-(([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate and 2-hydroxyphenyl boronic acid were used to prepare tert-butyl 4-(([2'-hydroxy-3-(trifluoromethyl)phenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate.

MS (ES-) m/z 499.1;
HPLC purity 97.2% at 210-370 nm, 10.5 minutes
HRMS: calculated for $C_{23}H_{27}F_3N_2O_5S + Na^+$, 523.14850; found (ESI, [M+Na]^+), 523.1483;
Example 248, 4'-(\([1-(\text{tert-butoxycarbonyl}piperidin-4-yl)\text{aniino}]\text{sulfonyl}\))-3'-(trifluoroniethyl)biphenyl-2-carboxylic acid

[0670] In an analogous manner to example 53, tert-butyl 4-\((\{4\text{-bromo-2-(trifluoromethyl)}\text{phenyl}\text{sulfonyl}\}\text{amino})\text{piperidine-1-carboxylate}\) and 2-carboxyphenyl boronic acid were used to prepare 4'-(\([1-(\text{tert-butoxycarbonyl})\text{piperidin-4-yl}][\text{aniino}]\text{sulfonyl}\))-3'-(trifluoromethyl)biphenyl-2-carboxylic acid.

[0671] MS (ES-) \(m/z\) 527.1;
HPLC purity 97.6% at 210-370 nm, 9.8 minutes
HRMS: calculated for C\(_{24}\)H\(_{27}\)F\(_3\)N\(_2\)O\(_6\)S \(+\) Na\(^+\), 551.14341; found (ESI, [M+Na\(^+\)], 551.143;

Example 249, tert-butyl 4-\((\{4\text{-}(2-thienyl)}\text{-2-(trifluoromethyl)}\text{phenyl}\text{sulfonyl}\}\text{amino})\text{piperidine-1-carboxylate}

[0672] In an analogous manner to example 53, tert-butyl 4-\((\{4\text{-bromo-2-(trifluoromethyl)}\text{phenyl}\text{sulfonyl}\}\text{amino})\text{piperidine-1-carboxylate}\) and thiophene-2-boronic acid were used to prepare tert-butyl 4-\((\{4\text{-}(2-thienyl)}\text{-2-(trifluoromethyl)}\text{phenyl}\text{sulfonyl}\}\text{amino})\text{piperidine-1-carboxylate}.

[0673] MS (ES-) \(m/z\) 489.1;
HPLC purity 99.3% at 210-370 nm, 10.9 minutes
HRMS: calculated for C\(_{24}\)H\(_{25}\)F\(_3\)N\(_2\)O\(_4\)S \(+\) Na\(^+\), 513.1 1000; found (ESI, [M+Na\(^+\)], 513.1094;

Example 250, tert-butyl (4-\((\{4\text{-}(4\text{-bromo-2-(trifluoromethyl)}\text{phenyl}\text{sulfonyl}][\text{aniino})\text{piperidin-1-yl}\text{carbonyl}]\text{phenyl}\text{methylcarbamate}

[0674] In an analogous manner to example 45, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and N-BOC-4-(methylamino)benzoic acid were used to prepare tert-butyl (4-\((\{4(\text{bromo-2-(trifluoromethyl})\text{phenyl}\text{sulfonyl}[\text{amino})\text{piperidin-1-yl}\text{carbonyl}]\text{phenyl}\text{methylcarbamate}.

Example 251, terf-butyl methyl(4-[[4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidin-l-yl]carbonyl]phenyl)carbamate

In an analogous manner to example 45, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and and N-BOC-4-(methylamino)benzoic acid were used to prepare terf-butyl methyl(4-[[4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidin-l-yl]carbonyl]phenyl)carbamate.

Example 252, 4-bromo-N-{l-[4-(methylamino)benzoyl]piperidin-4-yl}-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 54, tert-butyl (4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-l-yl]carbonyl]phenyl)methylcarbamate was used to prepare 4-bromo-N-{l-[4-(methylamino)benzoyl]piperidin-4-yl}-2-(trifluoromethyl)benzenesulfonamide.

Example 253, N-{l-[4-(methylamino)benzoyl]piperidin-4-yl}-3-(trifluoromethyl)biphenyl-4-sulfonamide
In an analogous manner to example 54, tert-butyl methyl(4-[[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl)carbonyl)phenyl)carbamate was used to prepare *N*-{1-[4-(methylamino)benzoyl]piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.


In an analogous manner to example 45, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and BOC-D-proline were used to prepare tert-butyl (2/?)-2-[[4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate.

**Example 255**, 4-bromo-N-(1-D-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 54, tert-butyl (2R)-2-[[4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]Jaminolpiperidin-1-ylJcarbonyllpyrrolidine-1-carboxylate was used to prepare 4-bromo-N-(1-D-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

**Example 256**, tert-butyl (2/?)-2-[[4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate
HRMS: calculated for C\textsubscript{i7}H\textsubscript{21}BrF\textsubscript{3}N\textsubscript{3}O\textsubscript{3}S + H\textsuperscript{+}, 484.05118; found (ESI, [M+H]\textsuperscript{+}), 484.0507;

Example 257, (2R)-2-\{4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl\}carbonyl\}yV-fert-butylpyrrolidine-1-carboxamide

[0686] In an analogous manner to example 42, 4-bromo-N-(1-D-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide and tert-butylisocyanate were used to prepare (2R)-2-\{4-\{[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl\}carbonyl\}yN-tet butylpyrrolidine-1-carboxamide.

[0687] MS (ES+) \textit{m/z} 583.1;
HPLC purity 100.0% at 210-370 nm, 9.4 minutes

Example 258, ferf-butyl (2-\{4-\{[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl\}carbonyl\}phenyl)carbamate

[0688] In an analogous manner to example 45, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 2-(tert-butoxycarbonylamino)benzoic acid were used to prepare \textit{ferf}-butyl (2-\{4-\{[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl\}carbonyl\}phenyl)carbamate.

[0689] MS (ES+) \textit{m/z} 606.2;
HPLC purity 98.0% at 210-370 nm, 10.5 minutes

Example 259, terf-butyl (3-\{4-\{[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]aniino)piperidin-1-yl\}carbonyl\}phenyl)carbamate

[0690] In an analogous manner to example 45, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 3-(tert-butoxycarbonylamino)benzoic acid were used to prepare \textit{terf/-}butyl (3-\{4-\{[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl\}carbonyl\}phenyl)carbamate.
Example 260, terf-butyl (4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]carbonyl]phenyl)carbamate

In an analogous manner to example 45, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and 4-((tert-butoxycarbonylamino)benzoic acid were used to prepare /er/-butyl (4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]carbonyl]phenyl)carbamate.

Example 261, terf-butyl (2-[[4-(3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]carbonyl]phenyl)carbamate

In an analogous manner to example 45, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-((tert-butoxycarbonylamino)benzoic acid were used to prepare to/7-butyl (2-[[4-(3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]carbonyl]phenyl)carbamate.

Example 262, ferf-butyl (3-[[4-((3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]carbonyl]phenyl)carbamate

In an analogous manner to example 45, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 3-((tert-butoxycarbonylamino)benzoic acid were used to prepare tert-butyl (3-[[4-((3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]carbonyl]phenyl)carbamate.
Example 263, **tert-butyl (4-[[4-[[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino]piperidin-1-yl]carbonyl]phenyl)carbamate**

[0698] In an analogous manner to example 45, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 4-(tert-butoxycarbonylamino)benzoic acid were used to prepare tert-butyl (4-[[4-[[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino]piperidin-1-yl]carbonyl]phenyl)carbamate.

Example 264, **ferf-butyl 4-[[4-[[1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl]-2-(trifluoromethyl)phenyl]sulfonyl]amino]piperidine-1-carboxylate**

[0700] In an analogous manner to example 53, tert-butyl 4-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidine-1-carboxylate and 1-(tert-butoxycarbonyl)-1H-pyrrol-2-ylboronic acid were used to prepare tert-butyl 4-[[4-[[1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl]sulfonyl]amino]piperidine-1-carboxylate.

Example 265, **N-piperidin-4-yl-4-(1H-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide**
In an analogous manner to example 54, tert-buty-4-[(4-[(l-(te/-/-butoxycarbonyl)-1H-pyrrol-2-yl)-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidine-1-carboxylate was used to prepare \( N\)-piperidin-4-yl-4-((1 H-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) \( m/z \) 373.9; HPLC purity 94.0% at 210-370 nm, 6.9 minutes

Example 266, \( iV\)-[l-(2-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 54, tert-buty-2-[4-[(4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino]piperidin-l-yl]carbonyl]phenyl)carbamate was used to prepare \( N\)-[l-(2-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) \( m/z \) 505.8; HPLC purity 96.4% at 210-370 nm, 9.4 minutes

Example 267, \( iV\)-[l-(3-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 54, tert-buty-3-[4-(4-bromo-2-(trifluoromethyOphenyl)sulfonyl]amino]piperidin-1-yl]carbonyl]phenyl)carbamate was used to prepare \( N\)-[l-(3-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) \( m/z \) 505.8; HPLC purity 97.2% at 210-370 nm, 8.9 minutes

Example 268, \( /V\)-[l-(4-aminobenzoyl)pipendin-4-yl]-4-bronio-2-(trifluoromethyl)benzenesulfonamide
In an analogous manner to example 54, tert-butyl (4-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]carbonyl]phenyl)carbamate was used to prepare N-[l-(4-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) m/z 505.8;
HPLC purity 97.4% at 210-370 nm, 8.8 minutes

Example 269, N-[l-(2-aminobenzoyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 54, tert-butyl (2-[[4-[[3-(trifluoromethyl)obiphenyl]y]sulfonyl]amino)piperidin-1-yl]carbonyl]phenyl)carbamate was used to prepare N-[l-(2-aminobenzoyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) m/z 504.0;
HPLC purity 97.8% at 210-370 nm, 10.1 minutes

Example 270, N-[l-(3-aminobenzoyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 54, tert-butyl (3-[[4-[[3-(trifluoromethyl)obiphenyl]y]sulfonyl]amino)piperidin-1-yl]carbonyl]phenyl)carbamate was used to prepare N-[l-(3-aminobenzoyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) m/z 504.0;
HPLC purity 97.5% at 210-370 nm, 9.7 minutes

Example 271, N-[l-(4-aminobenzoyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide
In an analogous manner to example 54, tert-butyl (4-[[4-[[3-(trifluoromethyl)phenyl]sulfonyl]amino]piperidin-1-yl]carbonyl)phenyl carboxamido was used to prepare N-[1-(4-aminobenzoyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) m/z 504.0;
HPLC purity 98.4% at 210-370 nm, 9.6 minutes;

Example 272. 4-bromo-N-[1-{2-[(tert-butylcarbamoyl)amino]benzoyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 42, iV-[l-(2-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide and tert-butylisocyanate were used to prepare 4-bromo-N-[1-{2-[(tert-butylcarbamoyl)amino]benzoyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) m/z 604.8;
HPLC purity 94.4% at 210-370 nm, 10.1 minutes;

Example 273. 4-bromo-N-[1-{3-[(tert-butylcarbamoyl)amino]benzoyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 42, W-[l-(3-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide and tert-butylisocyanate were used to prepare 4-bromo-N-[1-{3-[(tert-butylcarbamoyl)amino]benzoyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) m/z 604.8;
HPLC purity 100.0% at 210-370 nm, 10.1 minutes;

Example 274. 4-bromo-N-[1-{4-[(tert-butylcarbamoyl)amino]benzoyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide
In an analogous manner to example 42, \( N\)-[1-(4-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide and tert-butylisocyanate were used to prepare 4-bromo-\( N\)-(1-[4-\{\text{tert-butylcarbamoyl}\}amino]benzoyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) \( m/z \) 604.8;
HPLC purity 100.0% at 210-370 nm, 10.0 minutes;

Example 275, \( N\)-[2-\{\text{tert-butylcarbamoyl}\}amino]benzoyl]piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 42, \( N\)-[1-(2-aminobenzoyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide and tert-butylisocyanate were used to prepare \( N\)-[1-\{2-[\{\text{tert-butylcarbamoyl}\}amino]benzoyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) \( m/z \) 603.0;
HPLC purity 98.3% at 210-370 nm, 10.6 minutes;

Example 276, \( N\)-[1-\{3-[\{\text{tert-butylcarbamoyl}\}amino]benzoyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 42, \( N\)-[1-(3-aminobenzoyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide and tert-butylisocyanate were used to prepare \( N\)-[1-\{3-\{\{\text{tert-butylcarbamoyl}\}amino]benzoyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) \( m/z \) 603.0;
HPLC purity 100.0% at 210-370 nm, 10.6 minutes;

Example 277, \( N\)-[4-\{\text{tert-butylcarbamoyl}\}amino]benzoyl]piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide
In an analogous manner to example 42, N-[l-(4-aminobenzoyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide and tert-butylisocyanate were used to prepare N-[(I-4-[(/er/-butylcarbamoyl)amino]benzoyle]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) m/z 603.0;
HPLC purity 100.0% at 210-370 nm, 10.5 minutes;

Example 278, Λ,l-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-4-(l/H-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 42, N-piperidin-4-yl-4-(1 H-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare N-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-4-(1 H-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) m/z 512.9;
HPLC purity 100.0% at 210-370 nm, 9.5 minutes;

Example 279, -1-[6-chloropyridin-3-yl]carbonyl]piperidin-4-yl]-4-(1/H-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 42, N-piperidin-4-yl-4-(1 H-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide and 2-chloropyridine-5-carbonyl chloride with ethyl acetate were used to prepare N-(1-acetyl)piperidin-4-yl)-4-(1/H-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide.

MS (ES+) m/z 415.9;
HPLC purity 96.0% at 210-370 nm, 8.5 minutes;

Example 280, 2'-chloro-Λr-{l-[6-chloropyridin-3-yl]carbonyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide
In an analogous manner to example 42, 2'-chloro-\(N\)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare 2'-chloro-\(N\)-(1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide.

Example 281, \(N\)-(1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl)-2'-methoxy-3-(trifluoromethyl)biphenyl-4-sulfonamide

\[
\text{MS (ES+)} \text{ m/z 557.8;}
\]
HPLC purity 92.4% at 210-370 nm, 10.4 minutes;

Example 282, \(N\)-(1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl)-2'-fluoro-6'-methoxy-3-(trifluoromethyl)biphenyl-4-sulfonamide

\[
\text{MS (ES+)} \text{ m/z 553.8;}
\]
HPLC purity 99.2% at 210-370 nm, 10.1 minutes;

Example 283, \(N\)-{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-2'-fluoro-3-(trifluoromethyl)biphenyl-4-sulfonamide

\[
\text{MS (ES+)} \text{ m/z 571.8;}
\]
HPLC purity 100.0% at 210-370 nm, 10.1 minutes;
In an analogous manner to example 42, \(N\)-piperidin-4-yl-2'(trifluoromethoxy)-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare \(N\)-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\]-2'(trifluoromethoxy)-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) \(m/z\) 607.8; HPLC purity 98.5% at 210-370 nm, 10.4 minutes;

Example 284, \(N\)-{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-3-(trifluoromethyl)-1,r,2',l"-terphenyl-4-sulfonamide

In an analogous manner to example 42, \(N\)-piperidin-4-yl-3-(trifluoromethyl)-1,r,2',l"-terphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare \(N\)-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\]-1,r,2',l"-terphenyl-4-sulfonamide.

MS (ES+) \(m/z\) 599.9; HPLC purity 98.6% at 210-370 nm, 10.8 minutes;

Example 285, \(N\)-{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-2'-phenoxy-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 42, 2'-phenoxy-\(N\)-piperidin-4-yl-3-(trifluorornethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare \(N\)-1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\]-2'-phenoxy-3-(trifluoromethyl)biphenyl-4-sulfonamide.

MS (ES+) \(m/z\) 615.9; HPLC purity 97.6% at 210-370 nm, 10.9 minutes;

Example 286, \(N\)-{4'-[(1-[6-chloropyridin-3-yl]carbonyl]piperidin-4-yl]amino}sulfonyl]-3'- (trifluoromethyl)biphenyl-2-yl}acetamide
In an analogous manner to example 42, \(N\)-\{4'-[(piperidin-4-ylamino)sulfonyl]-3'-(trifluoromethyl) biphenyl-2-yl\}acetamide and 2-chloropyridine-5-carbonyl chloride were used to prepare \(N\)-\{4'-[[1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]amino)sulfonyl]-3'-(trifluoromethyl)biphenyl-2-yl\}acetamide.

**Example 287**, \(N\)-\{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}-2'-hydroxy-3-(trifluoromethyl)biphenyl-4-sulfonamide

**Example 288**, 4\(l\)-\{[(1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]amino) sulfonfonyl]-3'-(trifluoromethyl)biphenyl-2-carboxylic acid

**Example 289**, \(N\)-\{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}-4-(2-thienyl)2-(trifluoromethyl)benzenesulfonamide
In an analogous manner to example 42, \(N\)-piperidin-4-yl-4-(2-thienyl)-2-(trifluoromethyl)benzenesulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare \(N\)-\{[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl\}-4-(2-thienyl)-2-(trifluoromethyl)benzenesulfonamide.

**Example 290.** ferf-butyl 4-\{[[2\text{-}f\text{-}cyano\text{-}3\text{-}(trifluoromethyl)biphenyl\text{-}4\text{-}yl]sulfonyl]amino\}piperidine\text{-}l\text{-}carboxylate

In an analogous manner to example 53, tert-butyl 4-\{[[4-bromo\text{-}2\text{-}(trifluoromethyl)phenyl]sulfonyl]amino\}piperidine\text{-}l\text{-}carboxylate and 2-cyanophenyl boronic acid 1,3-propanediol were used to prepare tert-butyl 4-\{[[2\text{-}cyano\text{-}3\text{-}(trifluoromethyl)biphenyl\text{-}4\text{-}yl]sulfonyl]amino\}piperidine\text{-}l\text{-}carboxylate.

**Example 291.** 2\text{-}cyano- \(N\)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 54, tert-butyl 4-\{[[2\text{-}cyano\text{-}3\text{-}(trifluoromethyl)biphenyl\text{-}4\text{-}yl]sulfonyl]amino\}piperidine\text{-}l\text{-}carboxylate was used to prepare 2\text{-}cyano-\(N\)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide.

**Example 292.** \(N\)-\{\{6\text{-}chloropyridin-3-yl\}carbonyl\}piperidin-4-yl\text{-}2\text{-}cyano\text{-}3\text{-}(trifluoromethyl)biphenyl-4-sulfonamide
In an analogous manner to example 42, 2'-cyano-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 2-chloropyridine-5-carbonyl chloride were used to prepare N-{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-2'-cyano-3-(trifluoromethyl)biphenyl-4-sulfonamide.

HPLC purity 97.4% at 210-370 nm, 9.4 minutes; HRMS: calculated for C_{25}H_{20}ClF_{3}N_{4}O_{3}S + H+, 549.0965; found (ESI, [M+H]^+), 549.0968

Example 293, 4-(1-acetyl-1H-pyrrol-2-yl)-N-{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-2-(trifluoromethyl)benzenesulfonamide

To a stirred solution of N-{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-4-(1H-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide (0.09 g, 0.175 mmol) in DMF (2 mL) was added sodium hydride (0.015 g, 60%, 0.386 mmol) and the resulting solution was stirred 10 minutes. To this was added acetic anhydride (0.021 g, 0.175 mmol) and the solution was stirred 30 minutes at room temperature. The reaction was quenched with water, extracted twice with ethyl acetate and the combined organic layers were washed several times with water and concentrated. Flash column separation using 0%-100% ethyl acetate/hexane gradient gave 4-(1-acetyl-1H-pyrrol-2-yl)-N-{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-2-(trifluoromethyl)benzenesulfonamide. (0.044 g, 45%).

MS (ES+) m/z 554.9;
HPLC purity 95.1% at 210-370 nm, 9.0 minutes;

Example 294, tert-butyl 2-[4-{[4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]-2-oxoethyl]carbamate

In an analogous manner to example 45, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and BOC-glycine were used to prepare tert-butyl 2-[4-{[4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]-2-oxoethyl]carbamate.

MS (ES+) m/z 543.8;
HPLC purity 100.0% at 210-370 nm, 9.5 minutes;
Example 295. ^bromo-\(N\{1\text{-glycylpiperidii-4-yl}\}\)-2-(trifluoroniethyl)benzenesulfonamide

[0761] In an analogous manner to example 54, teri-buty\(l\) (2-\([4\text{-bromo-2-(trifluoromethyl)phenyl}]\text{sulfonyl}\)amino)piperidin-1-yl]-2-oxoethyl\)carbamate was used to prepare 4-bromo-\(N\{1\text{-glycylpiperidin^-y1}^\}\)-trifluoromethyObenzenesulfonamide.

[0762] HPLC purity 100.0% at 210-370 nm, 6.7 minutes; HRMS: calculated for C\(_{i4}\)H\(_{17}\)BrF\(_3\)N\(_3\)O\(_3\)S + H+, 444.01988; found (ESI, [IVH-H]^+) 444.0199

Example 296. \(N\{1\text{-acetylpiperidin-4-yl}\}\)-4-(1-acetyl-litf-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide

[0763] In an analogous manner to example 293, \(N\{1\text{-acetylpiperidin-4-yl}\}\)-4-(1\(H\)-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide and acetic anhydride were used to prepare \(N\{1\text{-acetylpiperidin-4-yl}\}\)-4-(1-acetyl-1\(H\)-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide.

[0764] MS (ES+) \(m/\ell\) 458.0; HPLC purity 91.4% at 210-370 nm, 8.1 minutes;

Example 297. tert-butyl \(2\text{-oxo-2-}[4\text{-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidin-l-yl]ethyl\)carbamate

[0765] In an analogous manner to example 45, \(N\text{-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide}\) and BOC-glycine were used to prepare tert-butyl \(2\text{-oxo-2-}[4\text{-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidin-l-yl]ethyl\)carbamate.

[0766] HPLC purity 100.0% at 210-370 nm, 10.1 minutes; HRMS: calculated for C\(_{22}\)H\(_{30}\)F\(_3\)N\(_3\)O\(_3\)S + H+, 542.19310; found (ESI, [M+H]^+), 542.1932

Example 298. \(N\{1\text{-glycylpiperidin-4-yl}\}\)-3-(trifluoromethyl)biphenyl-4-sulfonamide
In an analogous manner to example 54, tert-butyl {2-oxo-2-[4-((3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]ethyl}carbamate was used to prepare \(N\)-(1-glycylpiperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide.

HPLC purity 99.7% at 210-370 nm, 7.9 minutes; HRMS: calculated for \(\text{C}_{20}\text{H}_{22}\text{F}_{3}\text{N}_{3}\text{O}_{3}\text{S} + \text{H}^+\), 442.14067; found (ESI, [M+H]^+), 442.141

Example 299, 4-bromo-\(\Lambda\)\{1\}-(tert-butylcarbamoyl)glycyl)piperidin-4-yl\}2-(trifluoromethyl)benzenesulfonamide

In an analogous manner to example 42, 4-bromo-\(N\)-(1-glycylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide and tert-butylisocyanate were used to prepare 4-bromo-\(N\)\{1\}-(tert-butylcarbamoyl)glycyl)piperidin-4-yl\}2-(trifluoromethyl)benzenesulfonamide.

HPLC purity 100.0% at 210-370 nm, 9.1 minutes; HRMS: calculated for \(\text{C}_{19}\text{H}_{26}\text{BrF}_{3}\text{N}_{4}\text{O}_{4}\text{S} + \text{H}^+\), 543.08830; found (ESI, [M+H]^+), 543.0887

Example 300, \(N\)\{1\}-(\(N\)Oert-butylcarbamoyl)glycyl)piperidin-4-yl\}S-(trifluoromethyl)biphenyl-4-sulfonamide

In an analogous manner to example 42, \(N\)-(1-glycylpiperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide and tert-butylisocyanate were used to prepare \(N\)\{1\}-(\(N\)-(tert-butylcarbamoyl)glycyl)piperidin-4-yl\}3-(trifluoromethyl)biphenyl-4-sulfonamide.

HPLC purity 100.0% at 210-370 nm, 9.9 minutes; HRMS: calculated for \(\text{C}_{25}\text{H}_{33}\text{F}_{3}\text{N}_{4}\text{O}_{4}\text{S} + \text{H}^+\), 541.20909; found (ESI, [M+H]^+), 541.2091

Example 301, 4-\{[4-([4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]carbonyl\}-N-tert-butylpiperidine-1-carboxamide

A suspension of 4-bromo-\(N\)\{1\}-(piperidin-4-ylcarbonyl)piperidin-4-yl\}2-(trifluoromethyl)benzenesulfonamide hydrochloride (200 mg, 0.374 mmol) in
dichloromethane (7.5 mL) was treated with triethylamine (d 0.726, 0.100 mL, 0.717 mmol), followed by tert-butylisocyanate (43 µL, d 0.868, 0.377 mmol) at 23 °C. After 3.5 hours, the reaction solution was washed with 1 N aqueous sodium hydroxide (7.5 mL), water (7.5 mL) and saturated brine (7.5 mL), dried (Na$_2$SO$_4$) to provide a white solid (182 mg). Flash chromatography on silica gel (6 g) eluting 75% ethyl acetate-hexanes, then 100% ethyl acetate provided 4-{[4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino]piperidin-1-yl}carbonyl]-N-tert-butylpiperidine-l-carboxamide (97 mg, 43%) as a white solid after recrystallization from ethyl acetate-hexanes.

[0774] MS (ES+) m/z 596.9.

Example 302, 4-{[4-{{4-bromo-2-(trifluoromethyl)phenyl}sulfonyl}amino]piperidin-1-yl}carbonyl]-N-tert-butylpiperidine-l-carbothioamide

[0775] In an analogous manner to example 270, tert-butylisothiocyanate was used to prepare 4-{[4-{{4-bromo-2-(trifluoromethyl)phenyl}sulfonyl}amino]piperidin-1-yl}carbonyl]-N-tert-butylpiperidine-l-carbothioamide.

[0776] MS (ES+) m/z 612.9.

Example 303, tert-butyl {2-[4-{{4-bromo-2-(trifluoromethyl)phenyl}sulfonyl}amino]piperidin-1-ylj-L,L-dimethyl-2-oxoethyl}carbamate

[0777] In an analogous manner to example 45, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and N-boc-2-aminoisobutyric acid were used to prepare tert-butyl {2-[4-{{4-bromo-2-(trifluoromethyl)phenyl}sulfonyl}amino]piperidin-1-ylj-L,L-dimethyl-2-oxoethyl}carbamate.

[0778] MS (ES+) m/z 572.0;
HPLC purity 100.0% at 210-370 nm, 9.7 minutes;
In a analogous manner to example 45, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and N-boc-2-aminoisobutyric acid were used to prepare tert-butyl {[1,l-dimethyl-2-oxo-2-[4-({[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidin-1-yl]ethyl}carbamate.

**[0779]**

**MS (ES+) m/z 570.2;**

**HPLC purity 99.2% at 210-370 nm, 10.3 minutes;**

**HRMS: calculated for C_{27}H_{34}F_3N_3O_5S + H+, 570.22440; found (ESI, [M+H]+), 570.2244;**

Example 305, N-[l-(2-methylalanyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide

In a analogous manner to example 54, tert-butyl {[1,l-dimethyl-2-oxo-2-[4-({[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidin-1-yl]ethyl}carbamate was used to prepare N-[l-(2-methylalanyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

**[0781]**

**MS (ES+) m/z 470.1;**

**HPLC purity 95.9% at 210-370 nm, 8.2 minutes;**

**HRMS: calculated for C_{22}H_{26}F_3N_3O_3S + H+, 470.17197; found (ESI, [M+H]+), 470.172;**

Example 306, 3-{{[4-({[2'-cyano-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidin-1-yl]sulfonyl}benzoic acid

In a analogous manner to example 42, 2'-cyano-N-piperidin-4-yl-3-(trifluorornethyl)biphenyl-4-sulfonamide and 3-(chlorosulfon)benzoic acid were used to prepare 3-{{[4-({[2'-cyano-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidin-1-yl]sulfonyl}benzoic acid.

In an analogous manner to example 42, N-(L-prolylpiperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide and tert-butyl isocyanate were used to prepare (2S)-N-tert-butyl-2-[[4-[[3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino]piperidine-1-yl]carbonyl]pyrrolidine-1-carboxamide.

Example 308, 4-bromo-N-[[1-[N-(tert-butyl carbamoyl)-2-methylalanyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide

Step 1: In an analogous manner to example 54, tert-butyl [2-[[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino]piperidine-1-yl]-1,1-dimethyl-2-oxoethyl]carbamate was used to prepare N-(L-[(2-amino-2-methylpropanoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide.

Step 2: In an analogous manner to example 42, N-(L-(2-amino-2-methylpropanoyl)piperidin-4-yl)-4-bromo-2-(trifluoromethyl)benzenesulfonamide and tert-butyl isocyanate were used to prepare 4-bromo-N-[[N-(tert-butyl carbamoyl)-2-methylalanyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide.
Example 309, \(y\)-V-[1-[N-(tert-butylcarbamoyl)-2-methylalanyI]piperidin-4-yl]-3-(trifluoronethyl)biphenyl-4-sulfonamide

[0790] In an analogous manner to example 42, \(N\)-[1-(2-methylalanyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide and tert-butyl isocyanate were used to prepare \(N\)-[1-[\(N\)-(tert-butylcarbamoyl)-2-methylalanyI]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

[0791] MS (ES+) \(m/z\) 569.2;
HPLC purity 99.5\% at 210-370 nm, 10.1 minutes;
HRMS: calculated for \(C_{29}H_{35}F_{3}N_{4}O_{4}S + H^+\), 569.2403; found (ESI, \([M+H]^+\)), 569.2409;

Example 310, \(i\)-V-[1-[(6-aminopyridin-3-yl)carbonyl]piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide

[0792] Step 1: To a stirred solution of 6-aminonicotinic acid (0.70 g, 5.0 mmol) in THF (25 mL) was added triethylamine (1 mL, 7.1 mmol) and BOC anhydride (2.40 g, 11.0 mmol) and the solution was stirred overnight at room temperature. To the solution was added 2N sodium hydroxide followed by 2N HCl until acidic. The mixture was diluted with water and extracted with ethyl acetate. Flash column separation using 0\%-100\% ethyl acetate/hexane gradient gave a compound weight corresponded with a di-BOC protected intermediate which was carried on to the next step.

[0793] Step 2: In an analogous manner to example 45, the above material and 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide were used to prepare an intermediate that was treated with HCl in an analogous manner to example 54 to give \(N\)-[1-[(6-aminopyridin-3-yl)carbonyl]piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide.

[0794] MS (ES+) \(m/z\) 506.8;
HPLC purity 90.8\% at 210-370 nm, 7.8 minutes;
Example 311. **tert-butyl (35)-3-{(4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate**

[0795] In an analogous manner to example 45, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and (S)-N-Boc-pyrrolidine-3-carboxylic acid were used to prepare **tert-butyl (3£)-3-{(4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate**.

[0796] MS (ES-) m/z 583.8;
HPLC purity 100.0% at 210-370 nm, 9.9 minutes;

Example 312. **tert-butyl (3I?)-3-{(4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate**

[0797] In an analogous manner to example 45, 4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide and (R)-N-Boc-pyrrolidine-3-carboxylic acid were used to prepare **/er/-butyl (37?)-3-{(4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate**.

[0798] MS (ES-) m/z 583.8;
HPLC purity 100.0% at 210-370 nm, 9.9 minutes;

Example 313. **4-bromo-N-{l-[3S]-pyrroIidin-3-yl]carbonyl}piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide**

[0799] In an analogous manner to example 54, /er/-butyl (35)-3-{(4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]carbonyl}pyrrolidine-1-carboxylate was used to prepare 4-bromo-N-{l-[3S]-pyrroIidin-3-yl]carbonyl}piperidin-4-yl] 2-(trifluoromethyl)benzenesulfonamide.
**Example 314, 4-bromo-**  
\(\text{N}^{-}[1-[(3R)-\text{pyrrolidin-3-yl} \text{carbonyl}] \text{piperidin-4-yl}] - 2-\)  
**trifluoromethyl** \(\text{benzenesulfonamide}\)

**Example 315, tert-butyl**  
\(\text{N}^{-}[1-[(3R)-\text{pyrrolidin-3-yl} \text{carbonyl}] \text{piperidin-4-yl}] - 2-\)  
**trifluoromethyl** \(\text{benzenesulfonamide}\)
Example 317, \(N\{-[l-(3\,S)-pyrrolidin-3-ylcarbonyl]piperidin-4-yl\}-3-(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide}\)

In an analogous manner to example 54, tert-butyl (35)-3-\{4-([3-(trifluoromethyl)biphenyl-4-y]sulfonyl]amino)piperidin-l-yl]carbonyl]pyrrolidine-l-carboxylate was used to prepare \(N\{-l-[3\,S]-pyrrolidin-3-ylcarbonyl]piperidin-4-yl\}-3-(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide}\).

Example 318, \(N\{-l-[3\,R]-pyrrolidin-3-ylcarbonyl]piperidin-4-yl\}-3-(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide}\)

In an analogous manner to example 54, tert-butyl (3)/-butyl (3/)-3-\{4-([3-(trifluoromethyl)biphenyl-4-y]sulfonyl]amino)piperidin-l-yl]carbonyl]pyrrolidine-l-carboxylate was used to prepare \(N\{-l-[3\,R]-pyrrolidin-3-ylcarbonyl]piperidin-4-yl\}-3-(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide}\).

Example 319, \((2S\,J\,y\,V\text{-}\text{tert-butyl}-l-i^{\neq}\text{-CiP'}\text{-cyano-S-C}\text{trifluoromethyObiphenyl}^{\text{-}}\text{ylsulfonyl}jaiiino\text{piperidin-l-ylcarbonyl}l-S-oxypyrrolidine-l-carboxamide}\)

In an analogous manner to example 53, (25)-2-\{4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-l-yl]carbonyl\}-\(N\text{-ter}<\text{butyl}-5-\text{oxypyrrolidine-1-carboxamide}\) and 2-cyanophenyl boronic acid 1,3-propanediol were used to
prepare (25)-\textit{N/\textit{tert}-butyl-2-[[4-((2'-cy ano-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]carbonyl}-5-oxopyrrolidine-1-carboxamide.

**[0812]** MS (ES+) \textit{m/z} 619.9;
HPLC purity 99.4% at 210-370 nm, 9.6 minutes

Example 320, (2\textit{S})-\textit{N/\textit{tert}-butyl-2-[[4-([4'-fluoro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]carbonyl}-5-oxopyrrolidine-1-carboxamide

**[0813]** In an analogous manner to example 53, (25)-2-[[4-((4'-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]carbonyl]-\textit{N/\textit{tert}-butyl-5-oxopyrrolidine-1-carboxamide and 4-fluorophenyl boronic acid were used to prepare (25)-\textit{N/\textit{tert}-butyl-2-[[4-([4-fluoro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]carbonyl}-5-oxopyrrolidine-1-carboxamide.

**[0814]** MS (ES+) \textit{m/z} 613.0;
HPLC purity 97.7% at 210-370 nm, 10.2 minutes

Example 321, (2\textit{S})-\textit{N/\textit{tert}-butyl-2-[[4-([2',4'-difluoro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]carbonyl}-5-oxopyrrolidine-1-carboxamide

**[0815]** In an analogous manner to example 53, (25)-2-[[4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]carbonyl]-\textit{N/\textit{tert}-butyl-5-oxopyrrolidine-1-carboxamide and 2,4-difluorophenyl boronic acid were used to prepare (25)-\textit{N/\textit{tert}-butyl-2-[[4-([2',4'-difluoro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]carbonyl}-5-oxopyrrolidine-1-carboxamide.

**10816** MS (ES+) \textit{m/z} 630.9;
HPLC purity 97.9% at 210-370 nm, 10.3 minutes

Example 322, (2\textit{S})-2-[[4-([2\textit{3}-bis(tri\textit{fluoromethyl})biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]carbonyl]-\textit{N/\textit{tert}-butyl-5-oxopyrrolidine-1-carboxamide
In an analogous manner to example 53, (25)-2-[[4-{([4-bromo-2-
(trifluoromethyl)phenylsulfonyl]amino)piperidin-1-yl}carbonyl]-
N-tert-buty1-5-
oxopyrrolidine-1-carboxamide and 2-trifluoromethylphenyl boronic acid were used to
prepare (25)-2-[[4-([2',3-bis(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-
yl]carbonyl]-N-tert-buty1-5-oxopyrrolidine-1-carboxamide.

MS (ES+) m/z 662.9;
HPLC purity 97.8% at 210-370 nm, 10.4 minutes

Example 323, 2'-cyano-3-(trifluoromethyl)-L-(6-(trifluoromethyl)pyridin-3-
yl]carbonyl)piperidin-4-yl)biphenyl-4-sulfonamide

In an analogous manner to example 42, 2'-cyano-N-piperidin-4-yl-3-
(trifluoromethyl)biphenyl-4-sulfonamide and 6-(trifluoromethyl)nicotinoyl chloride were
used to prepare 2'-cyano-3-(trifluoromethyl)-N-[6-(trifluoromethyl)pyridin-3-
yl]carbonyl)piperidin-4-yl)biphenyl-4-sulfonamide.

MS (ES+) m/z 583.1;
HPLC purity 98.0% at 210-370 nm, 9.7 minutes

Example 324, (35)-3-[[4-{([4-bromo-2-
(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl}carbonyl]-
N-tert-
butylpyrrolidine-1-carboxamide

In an analogous manner to example 42, 4-bromo-N-[(35)-pyrrolidin-3-
yl]carbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide and tert-butylisocyanate
were used to prepare (35)-3-[[4-{([4-bromo-2-
(trifluoromethyl)phenyl]sulfonyl]amino)piperidin-1-yl]carbonyl]-
N-tert-butylpyrrolidine-1-
carboxamide.

HPLC purity 100.0% at 210-370 nm, 9.3 minutes;
HRMS: calculated for C$_{22}$H$_{30}$BrF$_3$N$_4$O$_4$S + H+, 583.1 1960; found (ESI, [M+H]$^+$), 583.1206

Example 325, (3/?)-3-[[4-([4-bromo-2-
(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]carbonyl]-N-ferf-
butylpyrrolidine-1-carboxamide

[0823] In an analogous manner to example 42, 4-bromo- \( N \{1-[(3/?)-pyrrolidin-3-
ylcarbonyl]piperidin-4-yl \}-2-(trifluoromethyl)benzenesulfonamide \) and tert-butylisocyanate were used to prepare (3/?)-3-[[4-([4-bromo-2-
(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]carbonyl]- \( N \)-ter/-butylpyrrolidine-1-
carboxamide.

[0824] HPLC purity 100.0% at 210-370 nm, 9.3 minutes;
HRMS: calculated for C$_{22}$H$_{30}$BrF$_3$N$_4$O$_4$S + H+, 583.11960; found (ESI, [M+H]$^+$), 583.1 194

Example 326, (35)- \( N \)-tert-butyl-3-[[4-([3-(trifluoromethyl)biphenyl-4-

[0825] In an analogous manner to example 42, \( N \{1-[(35)-pyrrolidin-3-
ylcarbonyl]piperidin-4-yl \}-3-(trifluoromethyl)biphenyl-4-sulfonamide \) and tert-
butylisocyanate were used to prepare (3S)-\( N \)-tert-butyl-3-[[4-([3-(trifluoromethyl)biphenyl-

[0826] HPLC purity 100.0% at 210-370 nm, 10.0 minutes;
HRMS: calculated for C$_{28}$H$_{35}$F$_3$N$_4$O$_4$S + H+, 581 .24039; found (ESI, [M+H]$^+$), 581 .2401

Example 327, (3/?)- \( N \)-tert-butyl-3-[[4-([3-(trifluoromethyl)biphenyl-4-

[0827] In an analogous manner to example 42, \( N \{1-[(3 \text{R})-pyrrolidin-3-
ylcarbonyl]piperidin-4-yl \}-3-(trifluoromethyl)biphenyl-4-sulfonamide \) and tert-
butylisocyanate were used to prepare (3/?)-\( N \)-ter/-butyl-3-[[4-([3-(trifluoromethyl)biphenyl-
HPLC purity 100.0% at 210-370 nm, 10.0 minutes;
HRMS: calculated for C_{28}H_{35}F_{3}N_{4}O_{4}S + H+, 581.24039; found (ESI, [M+H]+), 581.2406

Example 328, N-[1-(pyridin-5-ylcarbonyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0829] In an analogous manner to example 45, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and pyrimidine-5-carboxylic acid were used to prepare N-[1-(pyrimidin-5-ylcarbonyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

HPLC purity 98.7% at 210-370 nm, 9.2 minutes

Example 329, JV-[1-(pyridazin-4-ylcarbonyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0831] In an analogous manner to example 45, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and 4-pyrazinecarboxylic acid were used to prepare N-[1-(pyridazin-4-ylcarbonyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

HPLC purity 100.0% at 210-370 nm, 9.0 minutes

Example 330, Λ-[1-(pyrazin-2-ylcarbonyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0833] In an analogous manner to example 42, N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide and pyrazine-2-carboxylic acid chloride were used to prepare N-[1-(pyrazin-2-ylcarbonyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide.

HPLC purity 99.4% at 210-370 nm, 9.4 minutes;
HRMS: calculated for $\text{C}_{23}\text{H}_{22}\text{BrF}_3\text{N}_4\text{O}_3\text{S} + \text{H}^+$, 491.13592; found (ESI, [M+H]$^+$), 491.1364

Example 331, 4-bromo-N-(l-[(3S)-l-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

[0835] In an analogous manner to example 42, 4-bromo-N-{1-[3S]-pyrrolidin-3-yl}carbonyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide and trimethylacetic anhydride were used to prepare 4-bromo-N-(l-[(3S)-l-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

[0836] MS (ES$^+$) m/z 567.7;
HPLC purity 100.0% at 210-370 nm, 9.3 minutes

Example 332, 4-bromo-N-(l-[(3R)-l-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide

[0837] In an analogous manner to example 42, 4-bromo-N-{1-[3R]-pyrrolidin-3-yl}carbonyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide and trimethylacetic anhydride were used to prepare 4-bromo-N-(l-[(3R)-l-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide.

[0838] MS (ES$^+$) m/z 567.7;
HPLC purity 100.0% at 210-370 nm, 9.3 minutes;
HRMS: calculated for $\text{C}_{23}\text{H}_{22}\text{BrF}_3\text{N}_4\text{O}_3\text{S} + \text{H}^+$, 568.10870; found (ESI, [M+H$^+$]), 568.1085

Example 333, N-(l-[(3S)-l-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl)piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide

[0839] In an analogous manner to example 42, N-{-[(3S)-l-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl)piperidin-4-yl}-3-(trifluoromethyl)biphenyl-4-sulfonamide and trimethylacetic anhydride were used to prepare N-(l-[(3S)-l-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl)piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide.
Example 334, N-[(3R)-1-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl]piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonaniide

[0841] In an analogous manner to example 42, N-[(3R)-pyrrolidin-3-ylcarbonyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide and trimethylacetic anhydride were used to prepare N-(l-[(3R)-1-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl]piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide.

Example 335: Biological Testing

**Fluorescence Polarization Binding Assay**

[0843] The affinity of test compounds for SFRP-I was determined using a fluorescence polarization binding assay. According to the assay design, a probe compound was bound to SFRP-I. The fluorescence anisotropy value of the probe compound is increased upon binding to SFRP-I. Upon the addition of a test compound, the fluorescence anisotropy value for the probe compound decreased due to competitive displacement of the probe by the test compound. The decrease in anisotropy as a function of increasing concentration of the test compound provides a direct measure of the test compound's binding affinity for SFRP-I.

[0844] To determine IC50 values, fluorescence polarization experiments were conducted in a 384-well format according to the following procedures. A 20 mM stock solution of the probe compound was prepared in 100% DMSO and dispensed in 10 µL aliquots for long-term storage at -20°C. The binding assay buffer was prepared by combining stock solutions of Tris-Cl, NaCl, glycerol, and NP40 at final concentrations of 25 mM Tris-Cl pH 7.4, 0.5 M...
NaCl, 5% glycerol and 0.002 % NP40. Master stock solutions of the test compounds were prepared in 100 % DMSO at final concentrations of 20 mM. Typically the working stock solutions of the test compounds were prepared by serially diluting the 20 mM master stock solution to 5 mM, 2.5 mM, 1.25 mM, 0.625 mM, 0.3125 mM, 0.156 mM, 78 µM, 39 µM, 19.5 µM, 9.8 µM, 4.9 µM, 2.44 µM, 1.22 µM, 0.31 µM, 76 nM, and 19 nM in DMSO. The working stock solutions of the test compounds were further diluted by combining 6 µL of the solutions with 24 µL of Milli-Q purity water, resulting in working stock solutions (10x compound stocks) in 20 % DMSO.

[0845] The assay controls were prepared as follows. A 2 µL aliquot of the 20 mM fluorescence probe compound was diluted 1000-fold in 100 % DMSO to a final concentration of 20 µM. 6 µL of the 20 µM probe was combined with 5.4 mL of the assay buffer, mixed well, and 18 µL of the resulting solution was dispensed into 384-well plates.

[0846] SFRP-1/probe complex was prepared by combining 11 µL of 20 µM probe compound with 9.9 mL of the assay buffer and SFRP-1 stock solution to final concentrations of 22 nM probe compound and 50 nM SFRP-1. 18 µL of the SFRP-1/probe complex was dispensed into the 384-well plates.

[0847] 2 µL aliquots of the test compounds from the 10x working stock solutions were removed and dispensed into the plate containing the SFRP-1/probe complex and the resultant solutions were mixed by pipetting up and down once. The final concentrations of SFRP-1 and probe in the assay solutions were 45 nM and 20 nM, respectively. In a typical experiment, each plate was used to test 14 compounds.

[0848] The plate was incubated in the dark for 15 minutes. The fluorescence of the SFRP-1/probe complexes was read in the Tecan Ultra plate reader at excitation and emission maxima of 485 and 535 nm. The plate reader settings were as follows:

Mode: Fluorescence Polarization
Plate definition: Matrical3841v.pdf
(pdf stands for Plate Definition File)
Excitation 485nm (bandwidth 20nm)
Emission 535nm (bandwidth 30nm)
G-factor: 1.03
Analysis of Results

[0849] Fluorescence anisotropy results from the emission of polarized light in the parallel and perpendicular directions when a fluorophore is excited with vertically polarized light. The anisotropy of the probe in the free and bound state was determined using the following equation:

\[ r = \frac{I(\perp) - I(\parallel)}{I(\perp) + 2I(\parallel)} \]

where \( I(\parallel) \) and \( I(\perp) \) are the parallel and perpendicular emission intensities, respectively.

[0850] Monitoring the anisotropy changes of the probe compound revealed that it bound saturably to SFRP-I with a \( K_D \) of 20-30 nM. The binding affinity was independently verified using a tryptophan fluorescence quenching assay.

[0851] The decrease in the anisotropy of the probe upon addition of the competing test compound was fitted to a sigmoidal dose response curve of the equation shown below:

\[ Y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom}) \cdot \text{Hillslope}}{(1 + 10^{(X - \log C_{50})})} \]

where "X" is the logarithm of concentration, "Y" is the anisotropy, and "Bottom" and "Top" correspond to the anisotropy values of the free and SFRP-1-bound probe prior to the addition of the test compound, respectively.

[0852] For automated IC\textsubscript{50} determinations, the equation shown above was used in the program GraphPad Prism. The "Hillslope" was kept constant at 1. The value for "Bottom" was fixed, but was determined by the blank (probe-only) wells in the plate. The values for "Top" and "IC50" were determined by the data fit. The value for "Top" was typically close to 120, equivalent to approximately 50 % bound probe, and the value for "Bottom" was around 30, due to free probe. If the test compound interfered with the probe in the
fluorescence assay at high concentrations, the range for the fitted data was limited to the lower concentration range.

[0853] The data obtained from the experiments are shown in the table below.

**Cell-based Assay for in vitro Measurement of SFRP-1/SRP2 Antagonist Activity**

[0854] The following cell-based assay can be used to identify inhibitors of SFRP-I.

**Materials and Methods**

**Cells**

[0855] The osteosarcoma cell line, U2OS (ATCC, HTB 96), was passaged twice a week with growth medium (McCoy's 5A medium containing 10% (v/v) fetal calf serum, 2mM GlutaMAX-1, and 1% (v/v) Penicillin- Streptomycin). The cells were maintained in vented flasks at 37°C inside a 5% CO₂/95% humidified air incubator. One day prior to transfection, the cells were plated with growth medium at 25,000 cells/well into 96-well plates and incubated at 37°C overnight.

**Routine Co-Transfection**

[0856] The growth medium was removed, and the cells were washed once with OPTI-MEM I (Gibco-BRL) medium (100 µL/well) to remove the serum and antibiotics. The wash medium was removed, and the cells were re-fed with OPTI-MEM I medium (100 µL/well). For each well of cells to be transfected, the following DNA's were diluted together in 25 µL OPTI-MEM I medium: 0.1 µg 16x TCF-tk-Luciferase reporter, 0.02 µg Wnt 3, Wnt3A, Wnt I or empty vector (Upstate Biotechnology), 0.075 µg hSFRP-1 or empty vector (pcDNA3.1, Invitrogen), and 0.025 µg CMV-βgal (Clonetech). For each well of cells to be transfected, 1µL of Lipofectamine 2000 reagent (Invitrogen) was diluted in 25 µl OPTI-MEM I medium and incubated at room temperature for 5 minutes. The diluted DNA's were then combined with the diluted Lipofectamine 2000 (LF2000), and the mixture was incubated at room temperature for 20 minutes. Fifty µL of the DNA-LF 2000 mixture was added to each well,
and the plate(s) were incubated at 37°C in a 5% C(V95% humidified air incubator for 4 hours. The cells were washed once with 150 µL/well of experimental medium (phenol red-free RPMI Medium 1640 containing 2% fetal bovine serum, 2mM GlutaMAX-1, and 1% Penicillin-Streptomycin). Finally, the cells were treated overnight at 37°C with 200 µL/well of experimental medium containing either vehicle (typically DMSO) or diluted compound in replicates of 8 wells/compound.

**Dosing**

[0857] Initial single dose screening of test compounds was done at 10 µM.

[0858] Dose-response experiments were initially performed with the compounds in log increases of concentration from 1-10,000 nM. From these dose-response curves, EC50 values were generated.

**Assay**

[0859] After treatment, the cells were washed twice with 150 µL/well of PBS without calcium or magnesium and were lysed with 50 µL/well of IX cell culture lysis reagent (Promega Corporation) on a shaker at room temperature for 30 minutes. Thirty µL aliquots of the cell lysates were transferred to 96-well luminometer plates, and luciferase activity was measured in a MicroLumat PLUS luminometer (EG&G Berthold), or a Victor (PerkinElmer Life Sciences) using 100 µL/well of luciferase substrate (Promega Corporation). Following the injection of substrate, luciferase activity was measured for 10 seconds after a 1.6 second delay. Similarly, 10 µL aliquots of the cell lysates were transferred to separate 96-well luminometer plates, and 50 µL of Galacton chemiluminescent substrate (Tropix) was added to each well. The plates were covered and incubated on a rotary shaker at room temperature for one hour, βgal activity was measured in a MicroLumat PLUS luminometer or Victor using 100 µL/well of Light Emission Accelerator (Tropix). Following the injection of the accelerator, βgal activity was measured for 10 seconds after a 1.6 second delay. The luciferase and βgal activity data were transferred from the luminometer to a PC and analyzed using the SAS/Excel program. After the luciferase activity was normalized to βgal, the
SAS/Excel program was used to determine the mean and standard deviation of each treatment, to analyze the data for statistical significance, and to determine EC\textsubscript{50} values (see the Table below).

**Large-Scale Co-Transfection**

[0860] As an alternative to co-transfection in a 96 well plate, the U2OS cells were transfected in T225 flasks and the transfected cells were frozen. The frozen cells were thawed and plated on a 96 well plate and the assay was carried out as detailed above. The growth medium was removed from the T225 flasks, and the cells were washed once with OPTI-MEM I medium (approx. 25 ml/flask) to remove the serum and antibiotics. The wash medium was removed, and the cells were re-fed with OPTI-MEM I medium (59 ml/flask). For each T225 flask of cells to be transfected, the following DNA’s were diluted together in 5.9 ml OPTI-MEM I medium: 70.3 µg 16x TCF-tk-Luciferase reporter, 14.06 µg WNT3, 3A or Wntl or empty vector, 52.8 µg hSFRP-1 or empty vector, and 17.58 µg CMV-βgal. Separately, for each flask of cells to be transfected, 354 µL of Lipofectamine 2000 reagent (Invitrogen) was diluted in 5.9 mL OPTI-MEM I medium and incubated at room temperature for 5 minutes. The diluted DNA’s were then combined with the diluted Lipofectamine 2000 (LF2000), and the mixture was incubated at room temperature for 20 minutes. 11.8 mL of the DNA-LF 2000 mixture was added to each flask, and the flask(s) were incubated at 37 °C in a 5% CO\textsubscript{2}/95% humidified air incubator for 4 hours. The medium was removed, and the cells were washed once with approximately 25 mL/flask of phenol red-free RPMI Medium 1640, then re-fed with 50 mL/flask of experimental medium (phenol red-free RPMI Medium 1640 containing 2% fetal bovine serum, 2 mM GlutaMAX-1, and 1% Penicillin-Streptomycin) and incubated at 37 °C overnight.

**Freezing Cells**

[0861] The transfected cells were washed twice with 25 mL/flask/wash of PBS without calcium or magnesium. Three ml of Trypsin-EDTA (0.05% Trypsin, 0.53 mM EDTA-4Na) was added to each flask, and the flasks were incubated at room temperature for approximately 5 minutes until the cells were rounded and detached from the surface of the flask(s). The cells were resuspended in 10 mL/flask of phenol red-free RPMI 1640
containing 10% fetal bovine serum and were pipetted up and down several times until a single cell suspension was formed. The resuspended cells were pooled and a 10 μL aliquot was removed and diluted at 1:10 in PBS. The diluted cells were counted using a hemacytometer to determine the total number of cells in the pool. The cells were transferred to sterile centrifuge tubes and pelleted at 1500 rpm in a Sorvall RC-3B refrigerated centrifuge at 4 °C for 5 minutes. The supernatant was aspirated and the cells were resuspended in cold, phenol red-free RPMI 1640 medium containing 50% FBS to a cell density of 2.5E+7 cells/ml. An equal volume of cold, 2x freezing medium (phenol red-free RPMI 1640 medium containing 50% FBS and 15% DMSO) was added slowly, dropwise to the resuspended cells with gentle mixing, resulting in a final cell density of 1.25E+7 cells/mL. The resuspended cells were placed on ice and aliquoted into sterile cryogenic vials. The vials were transferred to a Nalgene Cryo 1°C freezing container (Nalgene catalog # 5100-0001) containing 250 mL isopropyl alcohol. The sealed container was placed in a -80°C freezer overnight to freeze the cells at a cooling rate of 1°C/minute. The frozen cells were then transferred to a -150°C freezer for long-term storage.

**Benchtop Assay for Single Dose Confirmation of HTS Hits**

[0862] Early in the morning, a vial of frozen transfected cells was thawed, and the cells were resuspended in phenol red-free RPMI 1640 medium to a final cell density of 150,000 cells/mL. The resuspended cells were then plated in white, 96-well polystyrene tissue culture treated CulturPlates™ (Packard cat. # 6005180) at a volume of 100 μL of cell suspension/well (i.e. 15,000 cells/well). The plates were incubated at 37 °C inside a 5% CCV95% humidified air incubator for 6 hours or until the cells were attached and started to spread. Test compounds were then added to the wells (1 well/compound) and the plates were incubated at 37 °C overnight. After the overnight incubation, luciferase activity was measured using the Luc-Screen Luciferase Assay System (Tropix). Fifty μL of Luc-Screen buffer 1, warmed to room temperature, was added directly to the cells in the 96-well plates. Fifty μL of Luc-Screen buffer 2, warmed to room temperature, was then added, and the plates were incubated in the dark, at room temperature, for 10 minutes. The plates were transferred to a Packard Top Count Microplate Scintillation and Luminescence Counter (Packard), and the light emission was measured for 10 seconds after a 2 minute delay.
The luciferase activity data was transferred to a PC and analyzed using the SAS/Excel program as described above.

Analysis of Results

The luciferase data was analyzed using the SAS/Excel program. For the initial single dose experiment, if the compound treatment resulted in increased reporter activity and was specific to SFRP-I inhibition, then the results were reported as fold induction over SFRP-I control.

Compounds

A known inhibitor of GSK-3\(\beta\), a key enzyme involved in the Wnt signaling pathway, served as an internal control for measurement of the cellular response to Wnt signaling. The inhibition of GSK-3 results in stabilization of \(\beta\)-catenin, leading to up-regulation of LEF/TCF regulated reporter genes.

The data obtained from the experiments are shown in the table below.

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<th>Inhibition (%)</th>
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<th>EC(_{50}) ((\mu)M)</th>
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When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges specific embodiments therein are intended to be included.

The disclosures of each patent, patent application and publication cited or described in this document are hereby incorporated herein by reference, in its entirety.

Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments of the invention and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.
We claim:

1. A compound of formula I:

or a pharmaceutically acceptable salt thereof;

wherein:

- $R_1$ is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, heteroaryl, carbonyl, cyano, perfluoroalkyl, or perfluoroalkoxy;

- $R_2$ is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, arylthio, arylsulfonyl, heteroaryl, carbonyl, cyano, perfluoroalkyl, or perfluoroalkoxy, wherein any aryl or heteroaryl portion of $R_2$ may be optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, hydroxy, carboxy, alkoxyalkyl, alkylamino, dialkylamino, cyano, halo, alkylcarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonylamino, dialkylaminocarbonyl, aryaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, aminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl;

- $R_3$ is H, halo, alkyl, alkoxy, aryl, arylalkyl, or perfluoroalkyl;

- $R_4$ is halo, alkyl, cyano, cycloalkyl, aryalkyl, nitro, perfluoroalkyl, or perfluoroalkoxy;

- $R_5$ is H, alkyl, alkylamino, cycloalkyl, cycloalkylamino, alkoxy, alkoxyalkyl, aryl, arylalkyl, alkylamino, aminocarbonyl, aminalkyl, alkylaminocarbonylamino, heteroaryl, heteroarylamino, heterocycloalkyl, or heterocycloalkylamino, wherein any aryl, heteroaryl, or heterocycloalkyl portion of $R_5$ may be optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, oxo, alkoxyalkyl,
alkylamino, dialkylamino, alkylaminoalkylamino, dialkylaminoalkylamino, alkylaminodialkylamino, dialkylaminodialkylamino, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylamoalkyl, aminocarbonyl, alkylaminocarbonyl, alkylaminocarbonylamino, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, arylaminocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl; and

X is carbonyl, thiocarbonyl, sulfonyl, sulfoxide, alkyl, alkenyl or absent;

provided that R⁵ is other than alkoxy when R⁴ is nitro and X is carbonyl.

2. A compound according to claim 1,
   wherein R¹ is H.

3. A compound according to claim 1 or 2,
   \( R_2 \) is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, arylthio, arylsulfonyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or perfluoroalkoxy, wherein any aryl or heteroaryl portion of \( R_2 \) may be optionally substituted with 1 or 2 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, halo, hydroxy, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl.

4. A compound according to any one of claims 1 to 3,
   wherein said aryl portion of \( R_2 \) is optionally substituted with 1 or 2 substituents and wherein at least one said substituents is in the ortho position.

5. A compound according to any one of claims 1 to 4,
   wherein \( R_2 \) is phenyl, o-aminocarbonyl-phenyl, o-chloro-phenyl, o-fluoro-phenyl, o-cyano-phenyl, o-fluoro-p-fluoro-phenyl, o-perfluoromethoxy-phenyl, or o-perfluoromethoxy-o-fluoro-phenyl.

6. A compound according to claim 1 or 2,
wherein \( R_i \) is aryl optionally substituted with 1 to 5 substituents selected, independently at each occurrence, from the group consisting of alkyl, aryl, alkoxy, alkoxyalkyl, alkylamino, dialkylamino, cyano, halo, alkylcarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl.

7. A compound according to claim 1 or 2,
   wherein \( R_2 \) is bromo, isopropyl, phenyl, or phenylsulfonyle.

8. A compound according to any one of claims 1 to 7,
   wherein \( R_3 \) is H.

9. A compound according to any one of claims 1 to 8,
   wherein \( R_4 \) is perfluoroalkyl.

10. A compound according to claim 9,
    wherein \( R_4 \) is trifluoromethyl.

11. A compound according to any one of claims 1 to 10,
    wherein \( R_5 \) is H, aryl, heteroaryl, or heterocycloalkyl.

12. A compound according to any one of claims 1 to 11,
    wherein \( X \) is absent.

13. A compound according to any one of claims 1 to 11,
    wherein \( X \) is carbonyl.

14. A compound according to any one of claims 1 to 11,
    wherein \( X \) is sulfonyle.

15. A compound according to claim 1 or 2,
wherein:

\( R_2 \) is aryl optionally substituted with 1 to 2 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, halo, hydroxy, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl;

\( R_5 \) is H; and

\( X \) is absent.

16. A compound according to any one of claims 1 to 10,

wherein:

\( R_5 \) is heteroaryl or heterocycloalkyl, wherein any heteroaryl or heterocycloalkyl portion of \( R_s \) may be optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, alkoxyalkyl, alkylamino, dialkylamino, cyano, halo, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl; and

\( X \) is carbonyl.

17. A compound according to claim 16,

wherein:

\( R_5 \) is 6-chloropyridiny-3-yl, 6-trifluoromethylpyridin-3-yl, or (5S)-N-tetrt-butyl-2-oxo-pyrrolidin-5-yl-l-carboxamide.

18. A compound according to any one of claims 1 to 10.

wherein:

\( R_5 \) is aryl optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, alkoxyalkyl, alkylamino, dialkylamino, cyano, carboxy, halo, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl.
dialkylaminothiocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl; and

X is sulfonyl.

19. A compound according to any one of claims 1 to 10,

wherein:

R₅ is benzoic acid; and

X is sulfonyl.

20. A compound according to claim 16,

wherein:

Rₛ is heteroaryl or heterocycloalkyl, optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, alkoxyalkyl, dialkylamino, dialkylamino, cyano, halo, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl.

21. A compound selected from the group consisting of:

* 3-{[2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate;
* 4-{[5-bromo-2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidine-1-carboxylate;
* N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;
* 3-{[2-(trifluoromethyl)phenyl]sulfonyl}amino)piperidin-1-yl][sulfonyl]benzoic acid;
* 4-{[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl }amino)piperidine-1-carboxylate;
* 4-{[4-bromo-2-(trifluoromethoxy)phenyl]sulfonyl}amino)piperidine-1-carboxylate;
/er/-butyl 4-((2,5-bis(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate;

tert-buty\ 4-((2-chloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate;

/er/-butyl 4-((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate;

/er/-butyl 4-((2,3-dichlorophenyl)sulfonyl)amino)piperidine-1-carboxylate;

tert-buty\ 4-((2,4-dichlorophenyl)sulfonyl)amino)piperidine-1-carboxylate;

tert-buty\ 4-((2-methylphenyl)sulfonyl)amino)piperidine-1-carboxylate;

tert-buty\ 4-((2-cyanophenyl)sulfonyl)amino)piperidine-1-carboxylate;

tert-buty\ 4-((2-nitrophenyl)sulfonyl)amino)piperidine-1-carboxylate;

4-bromo-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;

4-bromo-N-piperidin-4-yl-2-(trifluoromethoxy)benzenesulfonamide;

N-piperidin-4-yl-2,5-bis(trifluoromethyl)benzenesulfonamide;

2-chloro-N-piperidin-4-yl-4-(trifluoromethyl)benzenesulfonamide;

2-chloro-N-piperidin-4-yl-5-(trifluoromethyl)benzenesulfonamide;

2,3-dichloro-N-piperidin-4-ylbenzenesulfonamide;

2,4-dichloro-N-piperidin-4-ylbenzenesulfonamide;

2-methyl-N-piperidin-4-ylbenzenesulfonamide;

2-cyano-N-piperidin-4-ylbenzenesulfonamide;

2-nitro-N-piperidin-4-ylbenzenesulfonamide;

2-[4-((2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]acacetamide;

3-[(4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl]benzoic acid

3-[(4-((4-bromo-2-(trifluoromethoxy)phenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl]benzoic acid

3-[(4-((2,5-bis(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl]benzoic acid

3-[(4-((2-chloro-4-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl]benzoic acid

3-[(4-((2-chloro-5-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl]benzoic acid

3-[(4-((2-nitrophenyl)sulfonyl)amino)piperidin-1-yl]sulfonyl]benzoic acid
4-bromo-\textit{N}-(1-[(3-cyanophenyl)sulfonyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide; 4-bromo-\textit{N}-(1-(3-cyanobenzoyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide; 4-bromo-\textit{N}-(1-(2-furoyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide; 4-bromo-\textit{N}-(1-(2,4-difluorobenzoyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide; 4-bromo-\textit{N}-(1-(3,4-difluorobenzoyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide; 4-bromo-\textit{N}-(1-(pyridin-2-ylcarbonyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide; 4-bromo-\textit{N}-(1-(pyridin-3-ylcarbonyl)piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide; 4-bromo-\textit{N}-(1-isonicotinoylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide; ^{\text{rt-butyl}}\,(2S)-2-[[4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate; ^{\text{r-er-butyl}}\,(2S)-2-[[4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-1-yl]carbonyl]-5-oxopyrrolidine-1-carboxylate; ^{\text{tert-butyl}}\,(2S)-2-[[4-((3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;
/e/-/-butyl (5S)-2-oxo-5-{4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidin-1-yl}carbonyl)pyrrolidine-1-carboxylate;  
4-bromo-\(N\)-1-([6-chloropyridin-3-yl]carbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;  
4-bromo-\(N\)-[1-(2-chloroisonicotinoyl)piperidin-4-yl]2-(trifluoromethyl)benzenesulfonamide;  
4-bromo-\(N\)-[1-((6-chloropyridin-3-yl)carbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;  
4-bromo-\(N\)-[1-(2-chloroisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;  
/er/-/-butyl 4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidine-1-carboxylate;  
\(N\)-piperidin-4-yl-3-(trifluoromethyl)benzyl-4-sulfonamide;  
\(tert\)-butyl 4-([4-(phenylsulfonyl)]2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate;  
4-(phenylsulfonyl)-\(N\)-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;  
\(tert\)-butyl 4-([4-bromo-(2-trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate;  
\(tert\)-butyl 4-([2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate;  
4-bromo-\(N\)-[1-(piperidin-4-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;  
\(tert\)-butyl 4-([4-bromo-(2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate;  
4-bromo-\(N\)-[1-(piperidin-4-ylcarbonyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;  
\(tert\)-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate;  
4-bromo-\(N\)-[1-(5-oxo-L-prolyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;  
\(tert\)-butyl 4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate;  
4-([4-bromo-(2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidine-1-carboxylate;  
3-([4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidin-1-yl]sulfonyl)benzoic acid  
3-([4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidin-1-yl]sulfonyl)benzoic acid
N-{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-(l-L-prolylpiperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-{l-(5-oxo-L-prolyl)piperidin-4-yl}-3-(trifluoromethyl)biphenyl-4-sulfonamide;

/er/-butyl 4-((4-cyano-2-(trifluoromethyl)phenyl)sulfonyl amino)piperidine-1-carboxylate;
4-cyano-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;
3-[[4-(4-(phenylsulfonyl)-2-(trifluoromethyl)phenyl)sulfonyl]amino]piperidin-l-yl)sulfonyl]benzoic acid
N-{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-4-(phenylsulfonyl)-2-(trifluoromethyl)benzenesulfonamide;
2-[4-((4-(phenylsulfonyl)-2-(trifluoromethyl)phenyl)sulfonyl)amino]piperidin-l-yl]acetamide;


/er/-butyl 4-((4-fluoro-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate;

ter/-butyl 4-((4-(dimethylamino)-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate;
4-(dimethylamino)-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;

ter/-butyl 4-(4-isopropyl-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidine-1-carboxylate;
4-isopropyl-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;

N-{1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-4-fluoro-2-(trifluoromethyl)benzenesulfonamide;

/er/-butyl (2S)-2-[[4-((4-fluoro-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-l-yl]carbonyl]pyrrolidine-1-carboxylate;
4-(phenylsulfonyl)-N-(l-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
4-fluoro-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;
3-[[4-(4-cyano-2-(trifluoromethyl)phenyl)sulfonyl]amino]piperidin-1-yl)sulfonyl]benzoic acid

N-[[6-chloropyridin-3-yl]carbonyl]piperidin-4-yl]-4-cyano-2-(trifluoromethyl)benzenesulfonamide;
4-cyano-IV-(L-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
4-[[1-([3-carboxyphenyl)sulfonyl]piperidin-4-yl]amino]sulfonyl]3-(trifluoromethyl)benzoic acid
N-L-(4-[[2-(dimethylamino)ethyl]amino]-2-fluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
N-L-(4-[[2-(dimethylamino)ethyl]methyl]amino]-3-fluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
N-L-(4-fluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
L-(4-bromobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-(dimethylamino) N-(L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
3-[[4-([4-isopropyl-2-(trifluoromethyl)phenyl)sulfonyl]amino]piperidin-1-yl]sulfonyl]benzoic acid
N-L-[1-([6-chloropyridin-3-yl]carbonyl]piperidin-4-yl]-4-isopropyl-2-(trifluoromethyl)benzenesulfonamide;
4-isopropyl-N-(L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
2-[[4-([4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino]piperidin-1-yl]acetamide;
ter-buty1 4-[[4-chloro-2-(trifluoromethyl)phenyl)sulfonyl]amino]piperidine-1-carboxylate;
3-[[4-([4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl]benzoic acid
4-fluoro-N-(L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
4-[[1-[(L-‘e’-butoxycarbonyl)-L-prolylpiperidin-4-yl]amino]sulfonyl]-3-(trifluoromethyl)benzoic acid
3-[[4-([4-(dimethylamino)-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl]benzoic acid
N-[[1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-4-(dimethylamino)-2-(trifluoromethyl)benzenesulfonamide;
\textsuperscript{1/-butyl (2S)-2-[[4-([4-(dimethylamino)-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;
4-chloro-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;
(2S)-2-[[4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino]piperidin-1-yl]carbonyl]N-([\textsuperscript{1/-butyl})pyrrolidine-1-carboxamide;
N-(L-[[3-(2H-tetrazol-5-yl)phenyl]sulfonyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-(L-[[3-(2H-tetrazol-5-yl)phenyl]sulfonyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
N-[[1-[(2H-tetrazol-5-yl)benzoyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
\textsuperscript{1/-butyl \textsuperscript{1/-butyl}}4-([4-methoxy-2-(trifluoromethyl)phenyl]sulfonyl]amino)piperidine-1-carboxylate;
4-methoxy-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;
3-[[4-([4-chloro-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl]benzoic acid
4-chloro-N-(L-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
\textsuperscript{1/-butyl (2S)-2-[[4-([4-chloro-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;
4-chloro-N-(L-L-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;
/er/-butyl (2S)-2-[[4-([5-[(3-cyanophenyl)sulfonyl]-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;

3-[[4-([4-methoxy-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl]benzoic acid

N-[[6-chloropyridin-3-yl]carbonyl]piperidin-4-yl]-4-methoxy-2-(trifluoromethyl)benzenesulfonamide;

/ert/-butyl (2S)-2-[[4-([4-methoxy-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;

4-methoxy-N-[[L-L-prolyIpiperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

4-bromo-N-[[L-(pyridin-3-ylmethyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

4-bromo-N-[[L-(pyridin-4-ylmethyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

4-bromo-N-[[L-(3-cyanobenzyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

2-/ert-butyl-N-piperidin-4-ylbenzenesulfonamide;

2,4-di-/ert-butyl-N-piperidin-4-ylbenzenesulfonamide;

/er/-butyl 4-(((4-phenoxy-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-1-carboxylate;

4-phenoxy-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;

4-bromo-N-[[1-(6-ethoxyopyridin-3-yl)carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

N-[[1-(6-ethoxyopyridin-3-yl)carbonyl]piperidin-4-yl]-4-isopropyl-2-(trifluoromethyl)benzenesulfonamide;

(2S)-2-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl]carbonyl]N-rer/-butyl-5-oxopyrrolidine-1-carboxamide;

2-isopropyl-N-piperidin-4-ylbenzenesulfonamide;

3-[[4-([4-phenoxy-2-(trifluoromethyl)phenyl]sulfonyl)amino]piperidin-1-yl]sulfonyl {benzoic acid
3-[(4-[(2,6-dichloro-1,3-benzodioxol-5-yl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[(4-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid
3-[[4-[[3-(trifluoromethyl)-1,4,5,6-tetrahydropyridin-1-yl]sulfonyl]amino]piperidin-1-yl]sulfonyl]benzoic acid
3-[[4-[[3-(trifluoromethyl)-1,3',4'-terphenyl-4-yl]sulfonyl]amino]piperidin-1-yl]sulfonyl]benzoic acid
3-[[4-[[3',5'-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino]piperidin-1-yl]sulfonyl]benzoic acid
3-[[4-[[4-(pyridin-3-yl)-2-(trifluoromethyl)phenyl]sulfonyl]amino]piperidin-1-yl]sulfonyl]benzoic acid
3-[[4-[[2',3'-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino]piperidin-1-yl]sulfonyl]benzoic acid
4-bromo-N-[1-[(6-chloropyridin-3-yl)methyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[1-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]-2-isopropylbenzenesulfonamide;
2-butyl-N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]benzenesulfonamide;
2,4-di-butyl-N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl]benzenesulfonamide;
5-bromo-4-isopropyl-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;
3-bromo-4-isopropyl-N-piperidin-4-yl-2-(trifluoromethyl)benzenesulfonamide;
tert-butyl 4-[[2'-methyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino]piperidine-1-carboxylate;
tert-butyl 4-({[2’-ethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate;
terf-butyl 4-({[2’-isopropyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate;
/e/7-butyl 4-({[2’-fluoro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate;
/er/-butyl 4-({[2’-acetyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate;
te/7-butyl 4-({[2’-ethoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate;
fer/-butyl 4-({[2’-propoxy-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate;
fe/7-butyl 4-({[2’-(methoxymethyl)-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate;
/er/-butyl 4-({[2’,6’-dimethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate;
/er/-/butyl 4-({[2’,5’-dichloro-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl}amino)piperidine-1-carboxylate;
4-bromo-N-[1-(4-chlorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-{1-[4-(4-chlorophenyl)sulfonyl]piperidin-4-yl}-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[1-(4-fluorobenzoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-2-(trifluoromethyl)-N-[1-(4-cyanobenzoyl)piperidin-4-yl]-benzenesulfonamide;
4-bromo-2-(trifluoromethyl)-N-[1-[(4-(trifluoromethoxy)benzoyl)piperidin-4-yl]benzenesulfonamide;
4-bromo-2-(trifluoromethyl)-N-(1-[(6-(trifluoromethyl)pyridin-3-yl)carbonyl]piperidin-4-yl)benzenesulfonamide,
4-bromo-N-[1-(2-chloro-6-methylisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[1-(2-chloro-6-methoxyisonicotinoyl)piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-[1-[(2,5-dichloropyridin-3-yl)carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;
4-bromo-N-{1-[(6-pyrrolidin-1-yl)pyridin-3-yl)carbonyl]piperidin-4-yl}-2-(trifluoromethyl)benzenesulfonamide;
2'-methyl- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2'-ethyl- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2'-isopropyl- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2'-fluoro- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2'-acetyl- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2'-ethoxy- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-piperidin-4-yl-2'-prooxy-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2'-(methoxymethyl)- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2',6'-dimethyl- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
2',5'-dichloro- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin^-yl]J^-methyl-S-(trifluoromethyl)biphenyl-4-sulfonamide;
N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin^-yl]J^-ethyl-S-(trifluoromethyl)biphenyl-4-sulfonamide;
N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin^-yl]J^-isopropyl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin^-yl]J^-fluoro-S-(trifluoromethyl)biphenyl-4-sulfonamide;
2'-acetyl- N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin^-yl]J^-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-[1-[(6-chloropyridin-3-yl)carbonyl]piperidin^-yl]J^-ethoxy-3-(trifluoromethyl)biphenyl-4-sulfonamide;
\( N\)-[1-{(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl-propoxy-S-(trifluoromethyl)biphenyl-4-sulfonamide,

\( N\)-[1-{(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl-2'-(methoxymethyl)-3-(trifluoromethyl)biphenyl-4-sulfonamide;

\( N\)-[1-{(6-chloropyridin-S-yl]carbonyl]piperidin-4-yl}^{\circ}-dimethyl-S-(trifluoromethyl)biphenyl-4-sulfonamide;

2\(^{\text{S,S}}\)-dichloro- \( N\)-[1-{(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}-3-(trifluoromethyl)biphenyl-4-sulfonamide;

**tert-butyl** 4-([2'-carbamoyl-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidine-1-carboxylate;


3-{4-([2'-methyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid;

3-{4-([2'-ethyl-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl]amino)piperidin-1-yl]sulfonyl]benzoic acid;

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4'-[(piperidin-4-ylamino)sulfonyl]-3'-(trifluoromethyl)biphenyl-2-carboxamide;

4'-[({l-[(6-chloropyridin-3-yl)carbonyl]piperidin-4-yl}amino)sulfonyl]-3'-(trifluoromethyl)biphenyl-2-carboxamide;

4-bromo-N-(l-[(6-(dimethylamino)pyridin-3-yl)carbonyl]piperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide;

N-(l-[(6-(dimethylamino)pyridin-3-yl)carbonyl]piperidin-4-yl)-3-(trifluoromethyl)biphenyl-4-sulfonamide;

4-bromo-N-1-[4-(dimethylamino)benzoyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

N-1-[4-(dimethylamino)benzoyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;

N-1-[2-chloropyridin-3-yl]carbonyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;

N-1-[2-(dimethylamino)pyridin-3-yl]carbonyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;

N-1-[2-(dimethylamino)pyridin-3-yl]carbonyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;

4-bromo-N-1-[3-(dimethylamino)benzoyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

N-1-[3-(dimethylamino)benzoyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;

2'-chlooro- \( \mathcal{N} \)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;

2'-methoxy- \( \mathcal{N} \)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;

2'-fluoro-6'-methoxy- \( \mathcal{N} \)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;

\( \mathcal{N} \)-piperidin-4-yl-2'-(trifluoromethoxy)-3-(trifluoromethyl)biphenyl-4-sulfonamide;

\( \mathcal{N} \)-piperidin-4-yl-3-(trifluoromethyl)-1,r,2',1"'-te \( \phi \) henyl-4-sulfonamide;

2'-phenoxy- \( \mathcal{N} \)-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-{4’-[(piperidin-4-ylamino)sulfonyl]-3’-(trifluoromethyl)biphenyl-2-y1}acetamide;

2’-hydroxy- N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;

4’-[(piperidin-4-ylamino)sulfonyl]-3’-(trifluoromethyl)biphenyl-2-carboxylic acid

N-piperidin-4-yl-4-(2-thienyl)-2-(trifluoromethyl)benzenesulfonamide;

/er/-butyl 4-((2’-chloro-3-(trifluoromethyl)biphenyl-4-y1)sulfonyl)amino)piperidine-l-carboxylate;

terl-butyl 4-((2’-methoxy-3-(trifluoromethyl)biphenyl-4-y1)sulfonyl)amino)piperidine-l-carboxylate;

tert-butyl 4-((2’-fluoro-6’-methoxy-3-(trifluoromethyl)biphenyl-4-y1)sulfonyl)amino)piperidine-l-carboxylate;

tør/-butyl 4-((2’-fluoro-6’-methoxy-3-(trifluoromethyl)biphenyl-4-y1)sulfonyl)amino)piperidine-l-carboxylate;

/er/-butyl 4-((2’-acetamido-3-(trifluoromethyl)biphenyl-4-y1)sulfonyl)amino)piperidine-l-carboxylate;

terf.-butyl 4-((2’-hydroxy-3-(trifluoromethyl)biphenyl-4-y1)sulfonyl)amino)piperidine-l-carboxylate;

4’-([(l-[(/er/-butoxycarbonyl)piperidin-4-yl]amino)sulfonyl]-3’-(trifluoromethyl)biphenyl-2-carboxylic acid

tert-butyl 4-((4-(2-thienyl)-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidine-l-carboxylate;

tert-butyl (4-((4-bromo-2-(trifluoromethyl)phenyl)sulfonyl)amino)piperidin-l-ylcarbonyl)phenyl)methylcarbamate

tert-butyl methyl(4-((4-((3-(trifluoromethyl)biphenyl-4-y1)sulfonyl)amino)piperidin-l-yl)carbonyl)phenyl)carbamate

4-bromo- N- [l-4-(methylamino)benzoyl]piperidin-4-yl] -2-(trifluoromethyl)benzenesulfonamide;
N- { 1-[4-(methylamino)benzoyl]piperidin-4-yl }-3-(trifluoromethyl)benzyl-4-sulfonamide,

tert-butyI (2R)-2- {[4-( {4-bromo-2-(trifluoromethyl)phenyl}sulfonyl } amino)piperidin-1-yl]carbonyl }pyrrolidine-1-carboxylate;

4-bromo-JV-(1-D-prolylpiperidin-4-yl)-2-(trifluoromethyl)benzenesulfonamide,

(2R)-2- {[4-({4-bromo-2-(trifluoromethyl)phenyl}sulfonyl} amino)piperidin-1-yl]carbonyl }-N-ter/-butylpyrrolidine-1-carboxamide;

tert-butyI (2- {[4-({4-bromo-2-(trifluoromethyl)phenyl}sulfonyl} amino)piperidin-1-yl]carbonyl }phenyl)carbamate
tert-butyI (3- {[4-({4-bromo-2-(trifluoromethyl)phenyl}sulfonyl} amino)piperidin-1-yl]carbonyl }phenyl)carbamate
tert-butyI (4- {[4-({4-bromo-2-(trifluoromethyl)phenyl}sulfonyl} amino)piperidin-1-yl]carbonyl }phenyl)carbamate
tert-butyI (2- {[4->({3-(trifluoromethyl)biphenyl-4-yl}sulfonyl} amino)piperidine-1-carboxylate;

N-piperidin-4-yl-4-(IH-pyrrol-2-yl)-2-(trifluoromethyl)benzenesulfonamide;
N-[l-(2-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide;
N-[l-(3-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide;
N-[l-(4-aminobenzoyl)piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide;
N-[l-(2-aminobenzoyl)piperidin-4-yl]-3-(trifluoromethyl)benzyl-4-sulfonamide;
217

$N\{l-(3\text{-aminobenzoyl})\text{piperidin-4-yl}\}-3\text{-}(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide},$

$N\{l-(4\text{-aminobenzoyl})\text{piperidin-4-yl}\}-3\text{-}(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide};$

4-bromo-$N\{1\{-2\{[(\text{tert-butylcarbamoyl})\text{amino}]\text{benzoyl}\}l\text{piperidin-4-yl}\}-2\text{-}$(trifluoromethyl)benzenesulfonamide;

4-bromo-$N\{1\{-3\{[(\text{ethylycarbamoyl})\text{amino}]\text{benzoyl}\}l\text{piperidin-4-yl}\}-2\text{-}$(trifluoromethyl)benzenesulfonamide;

4-bromo-$N\{1\{-4\{[(\text{ethylycarbamoyl})\text{amino}]\text{benzoyl}\}l\text{piperidin-4-yl}\}-2\text{-}$(trifluoromethyl)benzenesulfonamide;

$N\{1\{-2\{[(\text{tert-butylcarbamoyl})\text{amino}]\text{benzoyl}\}l\text{piperidin-4-yl}\}-3\text{-}$(trifluoromethyl)benzenesulfonamide;

$N\{1\{-3\{[(\text{tert-butylcarbamoyl})\text{amino}]\text{benzoyl}\}l\text{piperidin-4-yl}\}-3\text{-}$(trifluoromethyl)benzenesulfonamide;

$N\{1\{-4\{[(\text{ethylycarbamoyl})\text{amino}]\text{benzoyl}\}l\text{piperidin-4-yl}\}-3\text{-}$(trifluoromethyl)benzenesulfonamide;

$N\{1\{-[(\text{6-chloropyridin-3-yl})\text{carbonyl}]l\text{piperidin-4-yl}\}^\wedge\text{H-pyrrol-yl}\}^\wedge\text{-(trifluoromethyl)benzenesulfonamide};$

$N\{1\{-[(\text{acetyl}l\text{piperidin-4-yl})-4\{-1\text{H-pyrrol-2-yl}\}-2\text{-}$(trifluoromethyl)benzenesulfonamide;

2'-chloro-$N\{1\{-[(\text{6-chloropyridin-3-yl})\text{carbonyl}]l\text{piperidin-4-yl}\}-3\text{-}$(trifluoromethyl)benzenesulfonamide;

$N\{1\{-[(\text{6-chloropyridin-3-yl})\text{carbonyl}]l\text{piperidin-4-yl}\}-2\text{-}'\text{methoxy}3\text{-}$(trifluoromethyl)benzenesulfonamide;

$N\{1\{-[(\text{6-chloropyridin-3-yl})\text{carbonyl}]l\text{piperidin-4-yl}\}-2\text{-}'\text{fluoro-o'}\text{methoxy-S-}$(trifluoromethyl)benzenesulfonamide;

$N\{1\{-[(\text{6-chloropyridin-3-yl})\text{carbonyl}]l\text{piperidin-4-yl}\}-2\text{-'}\text{(trifluoromethoxy)}3\text{-}$(trifluoromethyl)benzenesulfonamide;

$N\{1\{-[(\text{6-chloropyridin-3-yl})\text{carbonyl}]l\text{piperidin-4-yl}\}-3\text{-'}\text{(trifluoromethyl)-}l,2',r\text{terphenyl-4-sulfonamide};$

$N\{1\{-[(\text{6-chloropyridin}^\wedge\text{yl})\text{carbonyl}l\text{piperidin}^\wedge\text{yl}^\wedge\text{phenoxy-S-}$(trifluoromethyl)benzenesulfonamide;
$\text{N-}\{4'-\{(\text{L-}[(6\text{-chloropyridin-3-yl})\text{carbonyl}]\text{piperidin-4-yl})\text{amino}\text{sulfonyl}\}\text{-3'}-(\text{trifluoromethyl})\text{biphenyl-2-yl})\text{acetamide};$

$\text{N-}\{1-[(6\text{-chloropyridinO-}y\text{tycarbonyl}]\text{piperidin}^\text{\$\$}\text{-y}^\text{\$\$}-\text{hydroxy-S-}
(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide};$

$4'-\{(\{\{6\text{-ch'o\$\$oPyridin-3-yl})\text{carbonyl}]\text{piperidin-4-yl})\text{amino}\text{sulfonyl}\}\text{-3'}-
(\text{trifluoromethyl})\text{biphenyl-2-carboxylic acid}$

$\text{N-}\{1-[(6\text{-chloropyridin-3-yl})\text{carbonyl}]\text{piperidin-4-yl}]\text{-4-(2-thienyl)-2-}
(\text{trifluoromethyl})\text{benzenesulfonamide;}

$\text{tert-butyl } 4-(\{2'-\text{cyano-3-}(\text{trifluoromethyl})\text{biphenyl-4-
yl)sulfonfonyl\} \text{amino} \text{piperidine-1-carboxylate;}

2'-\text{cyano-N-piperidin-4-yl-3-(trifluoromethyl)biphenyl-4-sulfonamide;}

$\text{N-}\{1-[(6\text{-chloropyridin-3-yl})\text{carbonyl}]\text{piperidin-4-yl}]\text{-2'-cyano-3-}
(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide;}

4-(1\text{-acetyl-1H-pyrrol-2-yl})- \text{N-}\{1-[(6\text{-chloropyridin-3-yl})\text{carbonyl}]\text{piperidin-4-
yl}]\text{-2-(trifluoromethyl)benzenesulfonamide;}

$\text{tert-butyl } 2-[4-(\{4\text{-bromo-2-}
(\text{trifluoromethyl})\text{phenyl}sulfonfonyl\} \text{amino} \text{piperidine-1-y1}]\text{-2-oxoethyl} \text{carbamate}$

4-bromo-N-(1\text{-glycypiperidin-4-yl})-2-(trifluoromethyl)benzenesulfonamide;

$\text{N-(1-}\text{acetyl)piperidin-4-yl}]\text{-4-(1\text{-acetyl-1H-pyrrol-2-yl})-2-}
(\text{trifluoromethyl})\text{benzenesulfonamide;}

$\text{tert-butyl } 2\text{-oxo-2-4-(\{3-(trifluoromethyl)biphenyl-4-
yl)sulfonfonyl\} \text{amino} \text{piperidine-1-yl}]\text{ethyl} \text{carbamate}$

N-(1\text{-glycypiperidin-4-yl])\text{-3-(trifluoromethyl)biphenyl-4-sulfonamide;}

4-bromo-N-\{1\text{-}\text{N-(ter/-butylcarbamoyl)glycyl}]\text{piperidin-4-yl}]\text{-2-}
(\text{trifluoromethyl})\text{benzenesulfonamide;}

$\text{N-}\{1\text{-}\text{N-(ter/-butylcarbamoyl)glycyl}]\text{piperidin-4-yl}]\text{-3-}
(\text{trifluoromethyl})\text{biphenyl-4-sulfonamide;}

4-(\{4-(\{4\text{-bromo-2-(trifluoromethyl)phenyl}sulfonfonyl\} \text{amino} \text{piperidin-1-
ylcarbonyl}\})\text{-N-ter/-butylpiperidine-1-carboxamide;}

4-(\{4-(\{4\text{-bromo-2-(trifluoromethyl)phenyl}sulfonfonyl\} \text{amino} \text{piperidin-1-
ylcarbonyl}\})\text{-N-ter/-butylpiperidine-1-carbothioamide;}

(e-/γ-buty)l 2-[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl]-1,1-dimethyl-2-oxoethy1]carbamate;

(See-l-buty)l 1,1-dimethyl-2-oxo-2-[4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidin-1-yl]ethyl]carbamate;

N-[l-(2-methylalanyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;

3-[[4-([2'-cyano-3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidin-1-yl]sulfonyl]benzoic acid;

(2S)-N-te/l-buty1-2-[4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxamide;

4-bromo-N-[l-[N-(3/-/-butylcarbamoyl)-2-methylalanyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

N-[l-[N-(3/-/-butylcarbamoyl)-2-methylalanyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;

N-[l-[(6-aminopyridin-3-yl)carbonyl]piperidin-4-yl]-4-bromo-2-(trifluoromethyl)benzenesulfonamide;

tert-buty1 (3S)-3-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;

tert-buty1 (3R)-3-[[4-([4-bromo-2-(trifluoromethyl)phenyl]sulfonyl)amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;

4-bromo-N-[l-[(3S)-pyrrolidin-3-yl]carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

4-bromo-N-[l-[(3R)-pyrrolidin-3-yl]carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

tert-buty1 (3S)-3-[[4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;

tert-buty1 (3R)-3-[[4-([3-(trifluoromethyl)biphenyl-4-yl]sulfonyl)amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxylate;

N-[l-[33-34]-pyrrolidin-3-yl]carbonyl]piperidin-4-yl]-3-(trifluoromethyl)benzenesulfonamide;
N-{1-[(3R)-pyrrolidin-3-ylcarbonyl]piperidin-4-yl}-3-(trifluoromethyl)biphenyl-4-sulfonamide;

(2S)-N-tert-butyl-2-{[4-((2'-cyano-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl)amino]piperidin-1-yl}carbonyl]-5-oxopyrrolidine-1-carboxamide;

(2S)-N-tert-butyl-2-{[4-([4'-fluoro-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]carbonyl}-S-oxopyrrolidine-1-carboxamide;

(2S)-N-tert-butyl-2-{[4-([2',4'-difluoro-3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]carbonyl}-5-oxopyrrolidine-1-carboxamide;

(2S)-2-[[4-([2]3-bis(trifluoromethyl)biphenyl-4-yl)sulfonyl]araino)piperidin-1-yl]carbonyl]-N-tert-butyl-5-oxopyrrolidine-1-carboxamide;

2'-cyano-3-(trifluoromethyl)-N-([6-(trifluoromethyl)pyridin-3-yl]carbonyl)piperidin-4-yl)biphenyl-4-sulfonamide;

(35)-3-[[4-([4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]carbonyl]-N-fc77-butylpyrrolidine-1-carboxamide;

(3i?)-3-[[4-([4-bromo-2-(trifluoromethyl)phenyl)sulfonyl]amino)piperidin-1-yl]carbonyl]-N-tert-butylpyrrolidine-1-carboxamide;

(35)-N-tert-butyl-3-[[4-([3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxamide;

(3R)-N-tert-butyl-3-[[4-([3-(trifluoromethyl)biphenyl-4-yl)sulfonyl]amino)piperidin-1-yl]carbonyl]pyrrolidine-1-carboxamide;

N-[1-(pyrimidin-5-ylcarbonyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;

N-[1-(pyridazin-4-ylcarbonyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;

N-[1-(pyrazin-2-ylcarbonyl)piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;

4-bromo-N-[1-[[3S]-1-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

4-bromo-N-[1-[[3/S]-1-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl]piperidin-4-yl]-2-(trifluoromethyl)benzenesulfonamide;

N-[1-[[35]-1-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl]piperidin-4-yl]-3-(trifluoromethyl)biphenyl-4-sulfonamide;
N-[(3/2)-1-(2,2-dimethylpropanoyl)pyrrolidin-3-yl]carbonyl)piperidin-4-
yl)-3-(trifluoromethyl) biphenyl-4-sulfonamide; and
pharmaceutically acceptable salts thereof.

22. A compound according to claim 1,
wherein said pharmaceutically acceptable salt is a hydrochloride salt.

23. A composition, comprising:
   a. at least one compound of formula I:

   or a pharmaceutically acceptable salt thereof;
   wherein:
   
   R₁ is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy,  
   arylalkyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or perfluoroalkoxy;

   R₂ is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy,  
   arylalkyl, arythio, arylsulfonyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or  
   perfluoroalkoxy, wherein any aryl or heteroaryl portion of R₂ may be optionally  
   substituted with 1 to 5 substituents, selected independently at each occurrence  
   from the group consisting of alkyl, aryl, alkoxy, alkoxy, carboxy, alkoxylkyl, alkylamino,  
   dialkylamino, cyano, halo, alkylcarbonyl, aminocarboxyl, alkylaminocarboxyl,  
   alkylcarbonylamino, dialkylaminocarboxyl, arylaminocarboxyl,  
   alkylaminothiocarboxyl, dialkylaminothiocarboxyl, arylaminothiocarboxyl,  
   cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl,  
   perfluoroalkoxy, and perfluoroalkylcarbonyl;

   R₃ is H, halo, alkyl, alkoxy, aryl, arylalkyl, or perfluoroalkyl;

   R₄ is halo, alkyl, cyano, cycloalkyl, arylalkyl, nitro, perfluoroalkyl, or  
   perfluoroalkoxy;
R.5 is H, alkyl, alkylamino, cycloalkyl, cycloalkylamino, alkoxy, alkoxyalkyl, aryl, arylalkyl, arylamino, aminocarbonyl, aminoalkyl, alkylaminocarbonylaminoalkyl, heteroaryl, heteroarylamino, heterocycloalkyl, or heterocycloalkylamino, wherein any aryl, heteroaryl, or heterocycloalkyl portion of R5 may be optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, oxo, alkoxyalkyl, alkylamino, dialkylamino, alkylaminoalkylamino, heteroaryl, heteroarylamino, heterocycloalkyl, or heterocycloalkylamino, where

24. Use of a compound or composition of any one of the previous claims for the treatment of osteoporosis, arthritis, chronic obstructive pulmonary disease, cartilage defects, bone fracture, leiomyoma, acute myeloid leukemia, wound healing, prostate cancer, autoimmune inflammatory disorder, or combination thereof.

25. Use of a compound or composition of any one of the previous claims in the manufacture of a medicament for the treatment of osteoporosis, arthritis, chronic obstructive pulmonary disease, cartilage defects, bone fracture, leiomyoma, acute myeloid leukemia, wound healing, prostate cancer, autoimmune inflammatory disorder, or combination thereof.

26. Use of a compound as in claim 24 or 25, wherein the treatment is for osteoporosis or arthritis.

27. A process for the preparation of a compound of formula I:
or a pharmaceutically acceptable salt thereof;
wherein:

R₁ is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or perfluoroalkoxy;

R₂ is H, halo, alkyl, alkoxy, alkylamino, alkylthio, dialkylamino, aryl, aryloxy, arylalkyl, arylothio, arylsulfonyl, heteroaryl, carboxyl, cyano, perfluoroalkyl, or perfluoroalkoxy, wherein any aryl or heteroaryl portion of R₂ may be optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, cyano, alkoxyalkyl, alkylamino, dialkylamino, cyano, halo, alkylcarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonylamino, dialkylaminocarbonyl, aryaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, aryaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl;

R₃ is H, halo, alkyl, alkoxy, aryl, aryalkyl, or perfluoroalkyl;

R₄ is halo, alkyl, cyano, cycloalkyl, arylalkyl, nitro, perfluoroalkyl, or perfluoroalkoxy;

R₅ is H, alkyl, alkylamino, cycloalkyl, cycloalkylamino, alkoxy, alkoxyalkyl, aryl, arylalkyl, alkylamino, aminocarbonyl, aminoalkyl, alkylaminocarbonylaminoalkyl, heteroaryl, heteroarylamino, heterocycloalkyl, or heterocycloalkylamino, wherein any aryl, heteroaryl, or heterocycloalkyl portion of R₅ may be optionally substituted with 1 to 5 substituents, selected independently at each occurrence from the group consisting of alkyl, aryl, alkoxy, oxo, alkoxyalkyl, alkylamino, dialkylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylaminodialkylamino, dialkylaminodialkylamino, cyano, carboxy, halo, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, alkoxycarbonylamino,
alkoxycarbonylaminoalkyl, aminocarbonyl, alkylaminocarbonyl, alkylaminocarbonylamino, dialkylaminocarbonyl, arylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, arylaminothiocarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, perfluoroalkyl, perfluoroalkoxy, and perfluoroalkylcarbonyl; and

$X$ is carbonyl, thiocarbonyl, sulfonyl, sulfoxide, alkyl, alkenyl or absent;

the process comprising:

reacting a compound of formula IA:

$$\text{IA;}$$

with a compound of formula IB:

$$\text{IB;}$$

wherein,

if $W$ is $X$-$R$$_5$, the compound of formula I is formed; or

if $W$ is a protecting group, the compound of formula IC is formed and the process further comprises the steps of:

deprolecting the compound of formula IC.

$$\text{IC;}$$

to form a compound of formula ED:

$$\text{ED;}$$

reacting the compound of formula ID with $R$$_S$-$X$-$G$$_A$;
wherein $G_A$ is an activating group,
thereby forming the compound of formula I.

28. The process of claim 27, wherein the activating group is selected from the group consisting of halo, tosylate, mesylate, triflate, an ester, epoxide or aldehyde.

29. The process of claim 27, wherein the protecting group is selected from the group consisting of BOC, benzyl, acetyl, PMB, alkyl, Fmoc, Cbz, or trifluoroacetyl, tosyl and triphenylmethyl.
## INTERNATIONAL SEARCH REPORT

**International application No:**

PCT/US2007/084285

### A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D211/58 C07D401/06 C07D407/06 A61K31/445 A61P11/06 A61P19/00 A61P35/00 C07D401/12 C07D401/14

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

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>DATABASE CHEMCATS&lt;br&gt;Chemical Abstract on line; CAS registry numbers 847473-74-9 and 693820-47-2&lt;br&gt;7 February 2006 (2006-02-07), XP002473487&lt;br&gt;abstract</td>
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<td>CARULLO, FRANCESCA ET AL: &quot;Parallel Protocol for the Selective Methylation and Alkylation of Primary Amines&quot;&lt;br&gt;JOURNAL OF COMBINATORIAL CHEMISTRY, 8(6), 834-840 CODEN: JCCHF; ISSN: 1520-4766, 9 August 2006 (2006-08-09), XP002473485&lt;br&gt;page 838; compound 39</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

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**Date of the actual completion of the International search:**

19 March 2008

**Date of mailing of the international search report:**

07/04/2008

**Name and mailing address of the ISA:**

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-0240, Tx. 31 651 epc nl, Fax: (+31-70) 340-3016

Authorized officer

Marzi, Elena
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<td>DE PAULIS, T. ET AL: &quot;Potential antipsychotic agents. 6. Synthesis and antagonistic properties of substituted N-(1-benzyl-4-piperidinyl)salicyl amides and related compounds. QSAR based design of more active members&quot; EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, 25(6), 507-17 CODEN: EJMCA5; ISSN: 0223-5234, 1990, XP002473486 page 511; compound 40</td>
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**INTERNATIONAL SEARCH REPORT**

**Box No. II**  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   
   see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

**Box No. IH**  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

**Remark on Protest**

- [ ] The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.
- [ ] The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- [ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/21 0 (continuation of first sheet (2)) (April 2005)
Although claims 24 and 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
**INTERNATIONAL SEARCH REPORT**

Information on patent family members

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