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Pharmaceutically Active Sulfonamide Derivatives Bearing Both Lipophilic and Ionisable Moieties as Inhibitors of Protein JunKinases

Field of the invention

The present invention is related to sulfonamide derivatives having a lipophilic moiety and which are substantially soluble. Said sulfonamide derivatives are notably for use as pharmaceutically active compounds. Also, the present invention is related to pharmaceutical formulations containing such sulfonamide derivatives. In particular, the present invention is related to sulfonamide derivatives that are useful in the treatment and/or prevention of disorders of the immune and the neuronal system. Specifically, the sulfonamide derivatives of the present invention display a substantial modulatory, notably an inhibitory activity of the JNK (Jun-Kinase) function or pathways respectively.

Background of the invention

Apoptosis denotes the complex contortions of the membrane and organelles of a cell as it undergoes the process of programmed cell death. During said process, the cell activates an intrinsic suicide program and systematically destroys itself. The following series of events can be observed:

- The cell surface begins to bleb and expresses pro-phagocytic signals. The whole apoptotic cell then fragments into membrane-bound vesicles that are rapidly and neatly disposed of by phagocytosis, so that there is minimal damage to the surrounding tissue.
- The cell then separates from its neighbors.

The nucleus also goes through a characteristic pattern of morphological changes as it commits genetic suicide, the chromatin condenses and is specifically cleaved to fragments of DNA.

Neuronal cell death plays an important role in ensuring that the nervous system develops normally. It appears that the death of developing neurons depends on the size of the target that they innervate: cells with fewer synaptic partners are more likely to die than those that have formed multiple synapses. This may reflect a process, which balances the relative number of pre- to postsynaptic neurons in the developing nervous system.

Although neuronal cell death was assumed to be apoptotic, it was only recently that neurons in developing rodent brain were conclusively shown to undergo apoptosis as classified by morphology and DNA fragmentation. As cell death during development is clearly not a pathological process, it makes sense that cells actually cease to exist.

Neuronal death occurs via either apoptotic or necrotic processes following traumatic nerve injury or during neurodegenerative diseases. Multiple components are emerging as key players having a role in driving neuronal programmed cell death. Amongst the components leading to neuronal apoptosis are members of the SAPK/JNK being a sub-family of MAP Kinases (MAPKs).

Mammalian cells respond to some extracellular stimuli by activating signaling cascades which are mediated by various mitogen-activated protein kinases (MAPKs). Despite the differences in their response to upstream stimuli, the MAP kinase cascades are organized in a similar fashion, consisting of MAP kinase kinase kinases (MAPKKK or MEKK), MAP kinase kinases (MAPKK or MKK) and MAP kinases (MAPK). MAP kinases are a broad family of kinases which includes c-Jun N-Terminal kinases (JNKs), also known as "stress-activated protein kinases" (SAPKs), as well as extracellular signal regulated kinases (ERKs) and p38 MAP kinases. Each of these three MAP kinases sub-families is involved in at least three different but parallel pathways conveying the information triggered by external stimuli. The JNK signaling pathway is activated by exposure of cells to environmental stress -such as chemical toxins, radiation, hypoxia and osmotic shock- as well as by treatment of cells with growth factors or pro-inflammatory cytokines -such as tumour necrosis factor alpha (TNF-α) or interleukin-1 beta (IL-1β).

Two MAP kinase kinases (known as MKKs or MAPKKs), i.e. MKK4 (known also as JNKK1) and MKK7 (known also as JNKK2), activate JNK by a dual phosphorylation of specific threonine and tyrosine residues located within a Thr-Pro-Tyr motif on the activation loop on the enzyme, in response to cytokines and stress signals. Even further upstream in the signaling cascade, MKK4 is known to be activated itself also by a MAP kinase kinase kinase, MEKK1 through phosphorylation at serine and threonine residues.

Once activated, JNK binds to the N-terminal region of transcription factor targets and phosphorylates the transcriptional activation domains resulting in the up-regulation of

expression of various gene products, which can lead to apoptosis, inflammatory responses or oncogenic processes **(1-5).**

MAPKs (mitogen-activated protein kinases) are serine/threonine kinases that are activated by dual phosphorylation on threonine and tyrosine residues. In mammalian cells, there are at least three separate but parallel pathways that convey information generated by extra-cellular stimuli to the MAPKs. Said pathways consist of kinase cascades leading to activation of the ERKs (extracellular regulated kinases), the JNKs (c-Jun N-terminal kinases), and the p38/CSBP kinases. While both the JNK and p38 pathways are involved in relaying stress-type extramolecular signals, the ERK pathway is primarily responsible for transducing mitogenic/differentiation signals to the cell nucleus.

SAPK cascades represent a sub-family of the mitogen-activating protein kinase family, that are activated by different external stimuli including DNA damage following UV irradiation, TNF-α, IL-1β, ceramide, cellular stress, and reactive oxygen species and have distinct substrate specificities. Signal transduction via MKK4/JNK of MKK3/p38 results in the phosphorylation of inducible transcription factors, c-Jun and ATF2, which then act as either homodimers or heterodimers to initiate transcription of down-stream effectors.

c-Jun is a protein that is forming homodimers and heterodimers (with e.g. c-Fos) to produce the transactivating complex AP-which is required for the activation of many genes (e.g. matrix metalloproteinases) involved in the inflammatory response. The JNKs were discovered when it was found that several different stimuli such as UV light and TNF-α stimulated phosphorylation of c-Jun on specific serine residues in the N-terminus of the protein.

Three distinct JNK enzymes have been identified as products of the genes JNK1, JNK2 and JNK3 and ten different isoforms of JNK have been identified **(3, 6, 7).** JNK1 and -2 are ubiquitously expressed in human tissues, whereas JNK3 is selectively expressed in the brain, heart and testes **(7, 8, 9, 10).** Each isoform binds to the substrates with different affinities, suggesting, *in vivo*, a substrate specific regulation of the signaling pathways by the different JNK isoforms.

In a recent publication of Xie X et al, (*Structure* **1998**, *6 (8)*; 983-991) it has been suggested that activation of stress-activated signal transduction pathways are required for neuronal apoptosis induced by NGF withdrawal in rat PC-12 and superior cervical ganglia (SCG) sympathetic neuronal cells. Inhibition of specific kinases, namely MAP kinase kinase 3 (MKK3) and MAP kinase kinase 4 (MKK4), or c-Jun (part of the MKK-4 cascade) may be sufficient to block apoptosis (see also Kumagae Y et al, in *Brain Res Mol Brain Res*, **1999**, *67(1)*, 10-17 and Yang DD et al in *Nature*, **1997**, *389 (6653)*; 865-870). Within a few hours of NGF deprivation in SCG neurones, c-Jun becomes highly phosphorylated and protein levels increase. Similarly in rat PC-12 cells deprived of NGF, JNK and p38 undergo sustained activation while ERKs are inhibited. Consistent with this JNK3 KO mice are resistant to excitotoxicity induced apoptosis in the hippocampus and more importantly they display greatly reduced epileptic like seizures in response to excitotoxicity as compared to normal animals (*Nature* **1997**, *389*, 865-870). More recently, it has been reported that the JNK signalling pathway is implicated in cell proliferation and could play an important role in autoimmune diseases (*Immunity*, **1998**, *9*, 575-585; *Current Biology*, **1999**, *3*, 116-125) which are mediated by T-cell activation and proliferation.

Naive (precursor) $CD4^+$ helper T (Th) cells recognise specific MHC-peptide complexes on antigen-presenting cells (APC) via the T-cell receptor (TCR) complex. In addition to the TCT-mediated signal, a co-stimulatory signal is provided at least partially by the ligation of CD28 expressed on T-cells with B7 proteins on APC. The combination of these two signals induces T-cell clonal expression.

After 4-5 days of proliferation, precursor of $CD4^+$ T cells differentiate into armed effector Th cells that mediate the functions of the immune system. During the differentiation process, substantial reprogramming of gene expression occurs.

Two subsets of effector Th cells have been defined on the basis of their distinct cytokine secretion pattern and their immuno-modulatory effects: Th1 cells produce IFNγ and LT (TNF-β), which are required for cell-mediated inflammatory reactions; Th2 cells secrete IL-4, IL-5, IL-6, IL-10 and IL-13, which mediate B cell activation and differentiation. These cells play a central role in the immune response. The JNK MAP Kinase pathway

is induced in Th1 but not in Th2 effector cells upon antigen stimulation. Furthermore, the differentiation of precursor $CD4^+$ T cells into effector Th1 but not Th2 cells is impaired in JNK2-deficient mice. Therefore, in recent years it has been realised that the JNK kinase pathway plays an important role in the balance of Th1 and Th2 immune response through JNK2.

Some transcription factors known to be JNK substrates are the Jun proteins (c-jun, JunB and Jun D), the related transcription factors ATF2 and ATFa, Ets transcription factors such as Elk-1 and Sap-1, the tumor suppressor p53 and a cell death domain protein (DENN).

Activation of the JNK pathway has been documented in a number of disease processes, thus providing a rationale for targeting this pathway for drug discovery. In addition, molecular genetic approaches have validated the pathogenic role of this pathway in several diseases.

For example, auto-immune and inflammatory diseases derive from the inappropriate activation of the immune system. Activated immune cells express many genes encoding inflammatory molecules, including cytokines, growth factors, cell surface receptors, cell adhesion molecules and degradative enzymes. Many of these genes are known to be regulated by the JNK pathway, through the activation of the transcription factors c-Jun and ATF-2.

The inhibition of JNK activation in bacterial lipopolysaccharide-stimulated macrophages, effectively modulates the production of the key pro-inflammatory cytokine, TNFα **(11).**

The inhibition of JNK activation decreases the transcription factor activation responsible of the inducible expression of matrix metalloproteinases (MMPs) **(12),** which are known to be responsible of the promotion of cartilage and bone erosion in rheumatoid arthritis and of generalized tissue destruction in other auto-immune diseases.

The JNK cascade is also activated in T cells by antigen stimulation and CD28 receptor co-stimulation **(13)** and regulates the production of the IL-2 promoter **(14).** Inappropri-

ate activation of T lymphocytes initiates and perpetuates many auto-immune diseases, including asthma, inflammatory bowel syndrome and multiple sclerosis.

In neurons vulnerable to damage from Alzheimer's disease and in CA1 neurons of patients with acute hypoxia (**15**), JNK3 protein is highly expressed. The JNK3 gene was also found to be expressed in the damaged regions of the brains of Alzheimer's patients (**16**). In addition, neurons from JNK3 KO mice were found to become resistant to kainic acid induced neuronal apoptosis compared to neurons from wild-type mice (**8**).

Based on these findings, the JNK signaling pathway and especially that of JNK2 and JNK3, is thought to be implicated in apoptosis-driven neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, epilepsy and seizures, Huntington's disease, traumatic brain injuries as well as ischemic and hemorrhaging strokes.

Cardiovascular diseases, such as atherosclerosis and restenosis result from defective regulation of growth of the blood vessel wall. The JNK pathway is activated by atherogenic stimuli and regulates local cytokine and growth factor production in vascular cells (**17, 18**) inducing pro-atherosclerotic gene (**19**).

Ischemia alone or coupled with reperfusion in the heart, liver, kidney or brain results in cell death and scar formation, which can ultimately lead to congestive heart failure, hepatic disorders, renal failure or cerebral dysfunction. The JNK pathway is activated by ischemia and reperfusion in the heart (**20**), leading to the activation of JNK-responsive genes and leukcocyte-mediated tissue damage. JNK activation is also observed in kidney (**21**) or liver (**22**) following ischemia and reperfusion. The down-regulation of JNKs has been proven to improve renal function and long-term outcome during nephritic and ischemic renal failure (**23**).

Cancer is characterized by uncontrolled growth, proliferation and migration of cells. In early lung cancer, expression of c-jun is altered and may mediate growth factor signaling in non-small cell lung cancer (**24**). In addition to regulating c-jun production and activity, JNK activation can regulate phosphorylation of p53, and thus can modulate cell cycle progression (**25**). Moreover, the role of JNK activation in HTLV-1 (human T cell leukemia virus type 1) mediated tumorgenesis (**26**) suggests the potential use of JNK

inhibitors in cancer treatment (27). Selective inhibition of JNK activation by a naturally occuring JNK inhibitory protein, called JNK-interacting-protein-1 (JIP1), blocks cellular transformation (28). Thus, JNK inhibitors may block transformation and tumor cell growth.

With the objective of inhibiting the JNK kinase pathway, WO/9849188 teaches the use of a human polypeptide, i.e. JNK-interacting protein 1 (JIP-1), which is a biological product and which has also been assayed for overcoming apoptosis related disorders.

Although such human polypeptides have been confirmed to have an inhibitory effect onto the JNK kinase pathway, a whole variety of drawbacks are associated with their use :

- Active bio-peptides or bio-proteins are only obtained by means of rather comprehensive and expensive bio-synthesis which consequently frequently renders the resulting products fairly cost-intensive.
- The peptides are known to display poor membrane penetration and may not cross the blood brain membrane,
- The principal drawback to the use of peptide inhibitors or antagonists is the problem of low oral bioavailability resulting from intestinal degradation. Hence, they must be administered parenterally and finally,
- peptide inhibitors or antagonists are frequently viewed by the host body as intruding material to be eliminated, thus setting off an auto-immune response.

The high relevance of the JNK pathway in some widely spread diseases stresses the need to develop inhibitors, preferentially selective, of JNKs.

It is therefore an objective of the present invention to provide molecules which are suitable for the treatment of a variety of diseases, in particular of neuronal or the autoimmune system related disorders, cancer, ischemic conditions and cardiovascular diseases.

It is notably an objective of the present invention to provide chemical compounds which are able to modulate, preferably to down-regulate or to inhibit the JNK (Jun kinase) pathway so to be useful in method of treating diseases which involve the JNK pathway.

Moreover, it is an objective of the present invention to provide methods for preparing said chemical compounds. It is furthermore an objective of the present invention to provide a new category of pharmaceutical formulations for the treatment of diseases, in particular those mediated by the JNK function.

It is finally an objective of the present invention to provide a method for the treatment and/or prevention of diseases that are caused by disorders of the autoimmune and/or the neuronal system.

Description of the invention

The aforementioned objectives have been met according to the independent claims. Preferred embodiments are set out within the dependent claims which are incorporated herewith.

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

"C_1-C_6-alkyl" refers to monovalent alkyl groups having 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-hexyl and the like.

"Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g. phenyl) or multiple condensed rings (e.g. naphthyl). Preferred aryl include phenyl, naphthyl, phenantrenyl and the like.

"C_1-C_6-alkyl aryl" refers to C_1-C_6-alkyl groups having an aryl substituent, including benzyl, phenethyl and the like.

"Heteroaryl" refers to a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,1,3,4-triazinyl, 1,2,3-triazinyl,

benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnnolinyl, napthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl or benzoquinolyl.

"C_1-C_6-alkyl heteroaryl" refers to C_1-C_6-alkyl groups having a heteroaryl substituent, including 2-furylmethyl, 2-thienylmethyl, 2-(1H-indol-3-yl)ethyl and the like.

"Alkenyl" refers to alkenyl groups preferably having from 2 to 6 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Preferable alkenyl groups include ethenyl (-CH=CH_2), n-2-propenyl (allyl, -CH_2CH=CH_2) and the like.

"Alkynyl" refers to alkynyl groups preferably having from 2 to 6 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH_2C≡CH), and the like.

"Acyl" refers to the group –C(O)R where R includes "C_1-C_6-alkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"Acyloxy" refers to the group –OC(O)R where R includes "C_1-C_6-alkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"Alkoxy" refers to the group –O-R where R includes "C_1-C_6-alkyl" or "aryl" or "heteroaryl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl". Preferred alkoxy groups include by way of example, methoxy, ethoxy, phenoxy and the like.

"Alkoxycarbonyl" refers to the group –C(O)OR where R includes "C_1-C_6-alkyl" or "aryl" or "heteroaryl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"Aminocarbonyl" refers to the group –C(O)NRR' where each R, R' includes independently hydrogen or C_1-C_6-alkyl or aryl or heteroaryl or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"Acylamino" refers to the group –NR(CO)R' where each R, R' is independently hydrogen or "C_1-C_6-alkyl" or "aryl" or "heteroaryl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"Halogen" refers to fluoro, chloro, bromo and iodo atoms.

"Sulfonyl" refers to group "–SO_2-R" wherein R is selected from H, "aryl", "heteroaryl", "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens e.g. an –SO_2-CF_3 group, "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"Sulfoxy" refers to a group "–S(O)-R" wherein R is selected from H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens e.g. an –SO-CF_3 group, "aryl", "heteroaryl" , "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"Thioalkoxy" refers to groups –S-R where R includes "C_1-C_6-alkyl" or "aryl" or "heteroaryl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl". Preferred thioalkoxy groups include thiomethoxy, thioethoxy, and the like.

"Substituted or unsubstituted" : Unless otherwise constrained by the definition of the individual substituent, the above set out groups, like "alkyl", "alkenyl", "alkynyl", "aryl" and "heteroaryl" etc. groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of "C_1-C_6-alkyl", "C_1-C_6-alkyl aryl", "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", primary, secondary or tertiary amino groups or quarter-nary ammonium moieties, "acyl", "acyloxy", "acylamino", "aminocarbonyl", "alkoxycarbonyl", "aryl", "heteroaryl", carboxyl, cyano, halogen, hydroxy, mercapto, nitro, sulfoxy, sulfonyl, alkoxy, thioalkoxy, trihalomethyl and the like. Alternatively said substitution could also comprise situations where neighboring substituents have undergone ring closure, notably when viccinal functional substituents are involved, thus forming e.g. lactams, lactons, cyclic anhydrides, but also acetals, thioacetals, aminals formed by ring closure for instance in an effort to obtain a protective group.

"Pharmaceutically acceptable salts or complexes" refers to salts or complexes of the below-identified compounds of formula I that retain the desired biological activity. Examples of such salts include, but are not restricted to acid addition salts formed with in-

organic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene sulfonic acid, naphthalene disulfonic acid, and polygalacturonic acid. Said compounds can also be administered as pharmaceutically acceptable quaternary salts known by a person skilled in the art, which specifically include the quarternary ammonium salt of the formula $-NR,R',R''^{+}Z^{-}$, wherein R, R', R" is independently hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, cinnamoate, mandeloate, and diphenylacetate).

"Pharmaceutically active derivative" refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the activity disclosed herein.

"Ionisable moiety" refers to functional groups, wherein its characteristic electron distribution confers to said moiety its capacity to be transformed into an ionic or ionised group, or in other words into a salt. Preferred ionisable moieties are basic groups like amines that are protonated thus yielding a salt.

"Essentially soluble" means that the compounds of the present invention display a good solubility in aqueous solvents. A preferred threshold is at about 50 µg/mL solvent, more preferably of at least 100 µg/mL solvent.

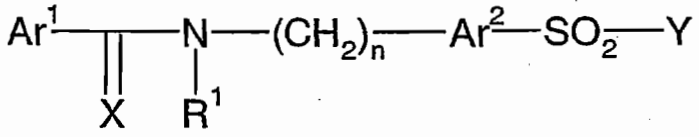
"Lipophilic chain" refers to groups which have a pronounced attraction to hydrophobic groups, substituents or compounds, notably to lipids or fatty compounds or moieties. They notably include optionally substituted C_4-C_{18}-alkyl groups or a substituted or unsubstituted alkyl-aryl group.

"Hydrophilic group" refers to functional groups which have a pronounced attraction to hydrophilic or polar groups, substituents or compounds or fatty compounds or moieties.

They notably include carboxylates, hydroxides, sulfates or sulfonates or amines or ammonium salts.

"Enantiomeric excess" (ee) refers to the products that are obtained by an essentially enantiomeric synthesis or a synthesis comprising an enantioselective step, whereby a surplus of one enantiomer in the order of at least about 52% ee is yielded. In the absence of an enantiomeric synthesis, racemic products are usually obtained that do however also have the inventive set out activity as JunK 2 and/or 3 inhibitors.

One aspect of the present invention consists in sulfonamide derivatives according to formula I :



I

Ar^1 and Ar^2 are independently from each other aryl or heteroaryl groups.
X is O or S, preferably O.
R^1 is hydrogen or a C_1-C_6-alkyl group, preferably H, or R^1 forms a 5-6—membered saturated or non-saturated ring with Ar^1.
n is an integer from 0 to 5, preferably between 1-3 and most preferred 1.

Y within the above formula I is a 4-12-membered saturated cyclic or bicyclic alkyl containing a nitrogen, which forms a bond with the sulfonyl group of formula I. Said 4-12-membered saturated cyclic or bicyclic alkyl is substituted with at least one ionisable moiety carrying a lipophilic chain.

The above mentioned ionisable moiety within L^1 confers an improved solubility to the molecules of formula I, compared to sulfonamide compounds which do not have such moiety.

Particularly potent compounds of formula I in respect of the inhibition of JNKs, in particular of JNK 2 and/or 3 are those where L^1 also comprises a lipophilic moiety. Such lipophilic groups are believed to enter into a cavity of the enzyme to be inhibited.

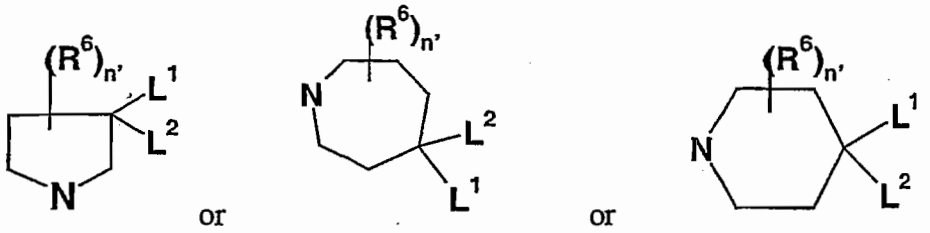
The present invention also includes the geometrical isomers, the optically active forms, enantiomers, diastereomers of compounds according to formula I, as well as their racemates and also pharmaceutically acceptable salts as well as the pharmaceutically active derivatives of the sulfonamide derivatives of formula I.

Preferred Ar^1 and Ar^2 in formula I are those that are independently selected from the group comprising or consisting of phenyl, thienyl, furanyl, pyrrol, pyridyl, optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halo, hydroxy, nitro, sulfonyl, sulfoxy, acyloxy, C_1-C_6- thioalkoxy. The most preferred Ar^1 is a substituted phenyl including halogenophenyl (e.g. 4-chlorophenyl), nitrophenyl, hydroxyphenyl, alkoxy phenyl, pyridyl, 3,4,-dihydroxyphenyl, thioxo-dihydropyridine or its tautomer, pyrazole while the most preferred Ar^2 is an unsubstituted or substituted thienyl or furanyl group.

Preferably, such substituents attached to said thienyl or furanyl group are hydrophilic groups which are groups conferring a better solubility to the molecules of formula I. They include notably carboxylic groups, carboxylates, carboxamides, OH, or OH carrying alkyl groups, hydrazido carbonyl groups, sulfates or sulfonates or amines or ammonium salts. Hydrophilic substituents on Ar^2 are of particular interest in order to further improve the solubility of the molecules of formula I.

Where Ar^1 is a 4-chlorophenyl, nitrophenyl, hydroxyphenyl, alkoxy phenyl, pyridyl, 3,4,-dihydroxyphenyl, thioxo-dihydropyridine or its tautomer, pyrazole group, X is preferably O, R^1 is hydrogen, n is 1 and Ar^2 is thienyl or furanyl.

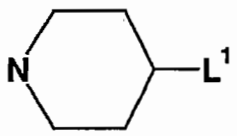
A particularly preferred embodiment of the present invention is related to the sulfonamide derivatives, wherein Y is a pyrrolidine, an azepan or a piperidine moiety of the below formulae.



In said formulae, R^6 is selected from the group comprising or consisting of hydrogen, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_1-C_6-alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo (=O), sulfoxy, acyloxy, thioalkoxy and where R^6 is not hydrogen, n' is an integer from 0 to 4, preferably 1 or 2, whereby at least one of L^1 and/or L^2 is an ionisable moiety to which a lipophilic chain is attached.

In a more preferred embodiment of the sulfonamide derivatives according to formula I, Y is a pyrrolidine, an azepan or a piperidine moiety as described above, wherein R^6 is H, L^2 is H, L^1 is $-NR^{3'}R^3$; where at least one of $R^{3'}$ and R^3 is not a hydrogen, but a substituent selected from the group consisting of straight or branched C_4-C_{18}-alkyl, aryl-C_1-C_{18}-alkyl, heteroaryl-C_2-C_{18}-alkyl, C_1-C_{14}-alkyl substituted with a C_3-C_{12}-cycloalkyl or -bicyclo or -tricyloalkyl, and whereby said alkyl chain may contain 1-3 O or S atoms.

More preferred L^1 is $-NHR^3$; where R^3 is a straight or branched C_4-C_{12}-alkyl, preferably a C_6-C_{12}-alkyl, optionally substituted with a cyclohexyl group or R^3 is a benzyl moiety. The most preferred sulfonamide derivatives according to the present invention are those wherein, wherein Y is a piperidine group



and wherein L^1 is $-NHR^3$; where R^3 is a straight or branched C_6-C_{12}-alkyl, preferably a C_8-C_{12}-alkyl, or R^3 is a benzyl moiety.

Specific examples of compounds of formula I include the following :

4-chloro-N-[(5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-Methoxy-N-{[5-({4-[(4-trifluoromethylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-[(5-{[4-(1,3-thiazol-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(heptylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-[(5-{[4-(pentylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-[(5-{[4-(butylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(dodecylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-{[5-({4-[(2-cyclohexylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[(cyclohexylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-({5-[(4-{[(1R)-1-cyclohexylethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

4-chloro-N-{[5-({4-[(2-propoxyethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(1-adamantylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({4-[(2-pyridin-2-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[(2-piperidin-1-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[(2-ethylhexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-({5-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-[(5-{[4-(octylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(heptylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
3-methoxy-N-[(5-{[4-(octylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
3-methoxy-N-[(5-{[4-(pentylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
N-[(5-{[4-(butylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
N-[(5-{[4-(dodecylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
N-{[5-({4-[(2-cyclohexylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-({5-[(4-{[(1R)-1-cyclohexylethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

3-methoxy-N-{[5-({4-[(2-propoxyethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(1-adamantylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[(3,3-diethoxypropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(3-morpholin-4-ylpropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-methoxy-N-{[5-({4-[(2-pyridin-2-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(2-piperidin-1-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(2-ethylhexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-({5-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
N-[(5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
N-[(5-{[4-(heptylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
3-methoxy-N-[(5-{[4-(octylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-methoxy-N-[(5-{[4-(pentylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
N-[(5-{[4-(butylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

N-[(5-{[4-(dodecylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
N-{[5-({4-[(2-cyclohexylethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-({5-[(4-{[(1R)-1-cyclohexylethyl]amino}azepan-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

3-methoxy-N-{[5-({4-[(2-propoxyethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(cyclohexylmethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[(1-adamantylmethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(3-morpholin-4-ylpropyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-methoxy-N-{[5-({4-[(2-pyridin-2-ylethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(2-piperidin-1-ylethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({4-[(2-ethylhexyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-({5-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}azepan-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
4-chloro-N-[(5-{[4-(heptylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(octylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(pentylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(butylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

4-chloro-N-[(5-{[4-(dodecylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-{[5-({4-[(2-cyclohexylethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

4-chloro-N-{[5-({4-[(2-propoxyethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[(2-ethylhexyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-[(5-{[4-(hexylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(hexylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
3-methoxy-N-[(5-{[4-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-methoxy-N-({5-[(4-{[2-(4-methylphenyl)ethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

3-methoxy-N-({5-[(4-{[(1S,2R)-2-phenylcyclopropyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

3-methoxy-N-{[5-({4-[(1-naphthylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(2-phenylpropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-({5-[(4-{[2-(4-hydroxyphenyl)ethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(3-phenylpropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(2,3-dihydroxypropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[(2-hydroxyethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-[(5-{[4-(nonylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-methoxy-N-[(5-{[4-(decylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
3-methoxy-N-[(5-{[4-(ethylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
N-{[5-({4-[(2-[1,1'-biphenyl]-4-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[([1,1'-biphenyl]-3-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(2-thien-2-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-[(5-{[4-({4-[(trifluoromethyl)sulfonyl]benzyl}amino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-methoxy-N-{[5-({4-[(quinolin-4-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[([1,1'-biphenyl]-4-ylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide

4-chloro-N-{[5-({4-[(2-{[(trifluoromethyl)sulfonyl]amino}ethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide

4-chloro-N-[(5-{[4-(propylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide
4-chloro-N-[(5-{[4-({4-[(trifluoromethyl)sulfonyl]benzyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-{[5-({4-[(3,4-dihydroxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
methyl [{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetate
tert-butyl [{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetate
[{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetic acid
N-[(5-{[3-(heptylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
3-methoxy-N-[(5-{[3-(octylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
3-methoxy-N-[(5-{[3-(pentylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
N-[(5-{[3-(butylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
N-[(5-{[3-(dodecylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
N-{[5-({3-[(2-cyclohexylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-({5-[(3-{[(1R)-1-cyclohexylethyl]amino}pyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide

N-{[5-({3-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

3-methoxy-N-{[5-({3-[(2-propoxyethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({3-[(cyclohexylmethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({3-[(1-adamantylmethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({3-[(3-morpholin-4-ylpropyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-methoxy-N-{[5-({3-[(2-pyridin-2-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({3-[(2-piperidin-1-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({3-[(2-ethylhexyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-[(5-{[3-(hexylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
4-chloro-N-[(5-{[3-(heptylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-[(5-{[3-(hexylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-[(5-{[3-(pentylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
N-[(5-{[3-(butylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
4-chloro-N-{[5-({3-[(2-cyclohexylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({3-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

4-chloro-N-({5-[(3-{[(1-hydroxycyclohexyl)methyl]amino}pyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-{[5-({3-[(1-adamantylmethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({3-[(3-morpholin-4-ylpropyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({3-[(2-pyridin-2-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({3-[(2-piperidin-1-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({3-[(2-ethylhexyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-[(5-{[3-(octylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

methyl (2S)-1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-(hexylamino)-2-pyrrolidinecarboxylate
3-methoxy-N-{[5-({4-[(pentylamino)methyl]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[2-(butylamino)ethyl]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[(4-butylanilino)methyl]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
4-chloro-N-{[5-({4-[hexyl(methyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[(cyclohexylmethyl)(hexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({4-[benzyl(hexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({4-[hexyl(pyridin-3-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[hexyl(pyridin-4-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[hexyl(pyridin-2-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({4-[butyl(hexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({4-[hexyl(3-phenylpropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[hexyl(2-phenylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[[(5-bromo-2-furyl)methyl](hexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide
3-methoxy-N-({5-[(4-{methyl[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide

4-chloro-N-{[5-({4-[(3-chlorobenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

3-methoxy-N-{[5-({4-[(3-methylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(4-propylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-({5-[(4-{[3-(trifluoromethyl)benzyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

3-methoxy-N-({5-[(4-{[4-(trifluoromethoxy)benzyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-({5-[(4-{[4-(difluoromethoxy)benzyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(2,3,4,5,6-pentamethylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-methoxy-N-{[5-({4-[(4-propoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(4-butoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(4-methoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(pyridin-4-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(pyridin-2-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(pyridin-3-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(4-tert-butylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[(3-ethoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(4-phenoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-[(5-{[4-({4-[(trifluoromethyl)sulfanyl]benzyl}amino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-methoxy-N-({5-[(4-{[4-(methylsulfonyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
N-({5-[(4-{[3,5-bis(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

N-({5-[(4-{[2,5-bis(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

N-({5-[(4-{[4-(ethylsulfanyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

3-methoxy-N-[(5-{[4-({3-[(trifluoromethyl)sulfanyl]benzyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

N-({5-[(4-{[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

N-{[5-({4-[(4-iodobenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
N-({5-[(4-{[4-(benzyloxy)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

N-{[5-({4-[(mesitylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide

N-{[5-({4-[(4-chlorobenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
N-{[5-({4-[(4-ethylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(4-pentylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
3-methoxy-N-[(5-{[4-({1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

3-methoxy-N-{[5-({4-[(4-methylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
N-{[5-({4-[(4-butylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
N-{[5-({4-[(4-isopropylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide

N-{[5-({4-[(4-isobutylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
N-({5-[(4-{[(1-hydroxy-1lambda~5~-pyridin-4-yl)methyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

N-{[5-({4-[(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide

N-{[5-({4-[(2,3-dihydro-1-benzofuran-5-ylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide

4-chloro-N-{[5-({4-[(4-propylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
4-chloro-N-({5-[(4-{[4-(trifluoromethoxy)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
4-chloro-N-({5-[(4-{[4-(difluoromethoxy)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
4-chloro-N-{[5-({4-[(4-propoxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
N-{[5-({4-[(4-butoxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({4-[(4-quinolinylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
N-{[5-({4-[(4-tert-butylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({4-[(4-phenoxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
4-chloro-N-[(5-{[4-({4-[(trifluoromethyl)sulfanyl]benzyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
3-methoxy-N-({5-[(4-{[2-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide

3-methoxy-N-[(5-{[4-({[6-(trifluoromethyl)-3-pyridinyl]methyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

N-[(5-{[4-(benzylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-3-methoxybenzamide
3-methoxy-N-[(5-{[4-({1-[4-(trifluoromethyl)phenyl]propyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

3-methoxy-N-[(5-{[4-({1-methyl-1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-[(5-{[4-({1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-[(5-{[4-({1-methyl-1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-[(5-{[2-({[4-(trifluoromethyl)benzyl]amino}methyl)-1-pyrrolidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-[(5-{[(3R)-3-({[4-(trifluoromethyl)benzyl]amino}methyl)pyrrolidinyl]sulfonyl}-2-thienyl)methyl]benzamide
4-chloro-N-({5-[(3-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
4-chloro-N-{[5-({3-[(hexylamino)methyl]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
4-chloro-N-({5-[(3-{[4-(trifluoromethyl)benzyl]amino}-1-pyrrolidinyl)sulfonyl]-2-thienyl}methyl)benzamide
4-chloro-N-{[5-({(3R)-3-[(hexylamino)methyl]pyrrolidinyl}sulfonyl)-2-thienyl]methyl}benzamide

4-chloro-N-[(5-{[3-({[4-(trifluoromethyl)benzyl]amino}methyl)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

2-oxo-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-1,2-dihydro-3-pyridinecarboxamide

N-[(5-{[4-(hexylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-oxo-1,2-dihydro-3-pyridinecarboxamide
N-[(5-{[4-(hexylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-hydroxybenzamide
2-hydroxy-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
N-[(5-{[4-(hexylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-thioxo-1,2-dihydro-3-pyridinecarboxamide

2-thioxo-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-1,2-dihydro-3-pyridinecarboxamide

N-[(5-{[4-(butylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-oxo-1,2-dihydro-3-pyridinecarboxamide
N-({5-[(4-{ethyl[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

4-chloro-N-[(5-{[4-({imino[4-(trifluoromethyl)phenyl]methyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-(hexylamino)proline

ethyl 2-{[4-(hexylamino)piperidin-1-yl]sulfonyl}-5-{[(3-methoxybenzoyl)amino]methyl}thiophene-3-carboxylate
N-{[5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}-4-(trimethylsilyl)thien-2-yl]methyl}-3-methoxybenzamide
N-({5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}-4-[hydroxy(phenyl)methyl]thien-2-yl}methyl)-3-methoxybenzamide

5-[(3-Methoxy-benzoylamino)-methyl]-2-[4-(4-trifluoromethyl-benzylamino)-piperidine-1-sulfonyl]-thiophene-3-carboxylic acid ethyl ester
N-[(4-chloro-5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

The compounds of formula I are suitable for use in treating disorders of the immune system and neuronal system of mammals, notably of human beings. Such neuronal system disorders include for example neurodegenerative diseases e.g. Alzheimer's disease, Huntington's disease, Parkinson's disease, retinal diseases, spinal cord injury, multiple sclerosis, head trauma, epilepsy and seizures, ischemic and hemorragic brain strokes. Immune system disorders include for example asthma, transplant rejection, inflammatory processes such as inflammatory bowel disease (IBD), cartilage and bone erosion disorders, rheumatoid arthritis, septic shock.

The compounds according to formula I are also suitable for use in treating cancers, such as breast, colorectal, pancreatic, prostate, testicular, ovarian, lung, liver and kidney cancers.

In another embodiment, the compounds according to formula I may be used for treating cardiovascular diseases including atherosclerosis, restenosis, stroke, ischemia, e.g. cerebral ischemia, myocordial infarction.

In another embodiment, the compounds according to formula I may be used for treating various ischemic conditions including heart and kidney failures, hepatic disorders and brain reperfusion injuries.

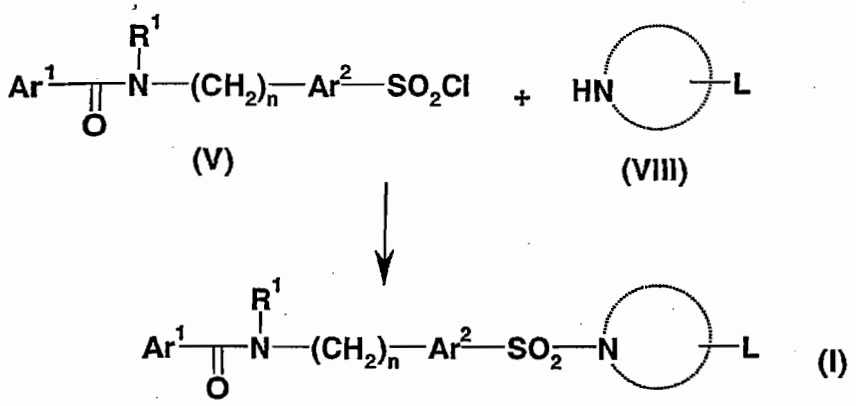
Preferably, the compounds according to formula I, alone or in the form of a pharmaceutical composition, are useful for the modulation of the JNK pathway, more specifically for treatment or prevention of disorders associated with expression or activity of JNK, notably of JNK2 and -3. Said modulation usually preferably involves the inhibition of the JNK pathways, notably of the JNK2 and/or -3. Such an abnormal expression or activity of JNK may be triggered by numerous stimuli (e.g. stress, septic shock, oxidative stress, cytokines) and may cause a cascade of processes, leading to, for example, uncontrolled apoptosis, inflammatory responses or oncogenic processes. These phenomena are frequently involved in various disorders including the above enumerated disorders and disease states. Hence, the compounds according to the invention may be used for the treatment of disorders by modulating the JNK function or signaling pathways. The modulation of the JNK function or pathways may involve its activation, but preferably it involves the down-regulation up to inhibition of the JNK pathways, notably of JNK1 and/or -2 and/or JNK3. The compounds of the invention may be employed alone or in combination with further pharmaceutical agents, e.g. with a further JNK modulator.

Still a further object of the present invention is a process for preparing the novel sulfonamide derivatives according to formula I which have been set out above. The sulfonamide derivatives of this invention may be prepared from readily available starting materials using the following general methods and procedures.

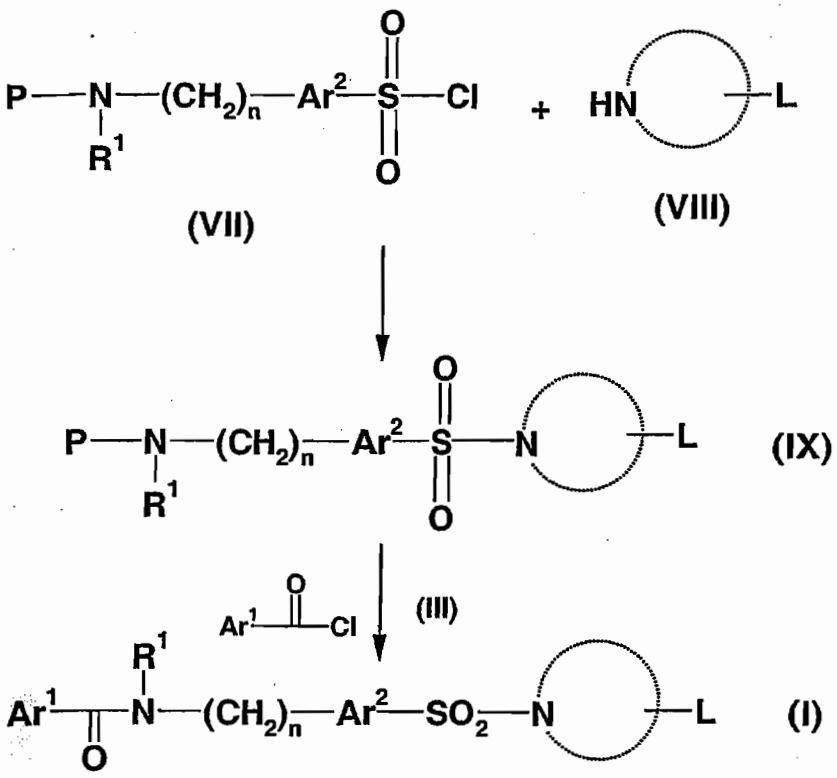
It will be appreciated that where typical or preferred experimental conditions (i.e., reaction temperatures, time, moles of reagents, solvents, etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimisation procedures.

The compounds of formula I may be obtained by either of the approaches set out in Scheme 1 or 2:

Scheme 1



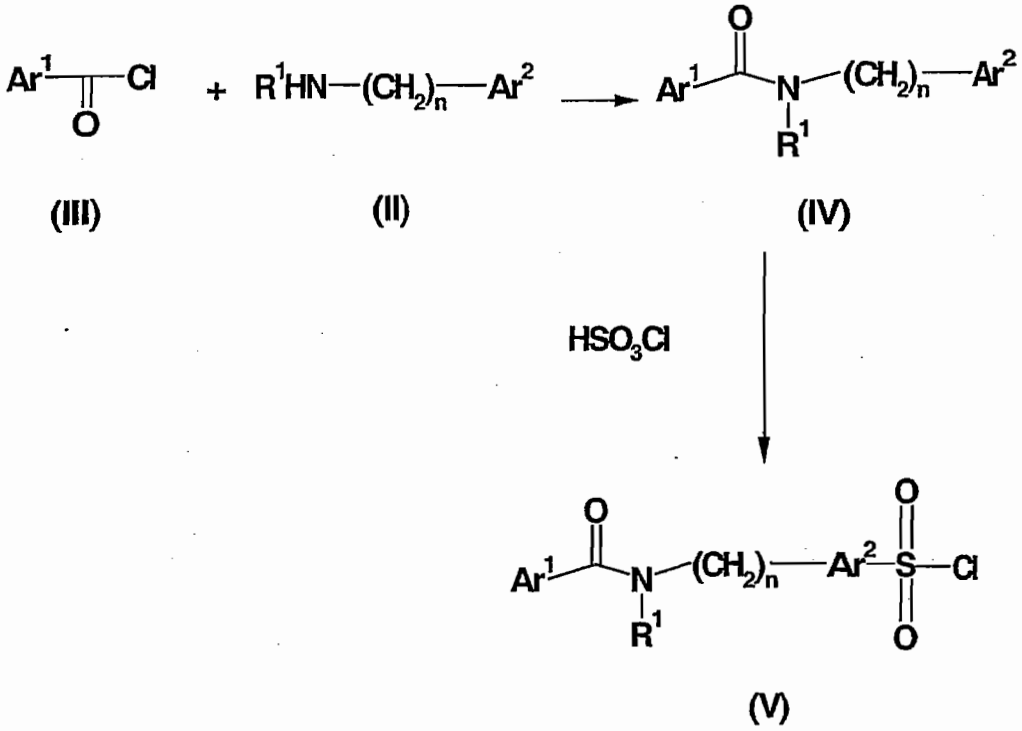
Scheme 2



Thereby, Ar^1, Ar^2, R^1, L and n are as above defined, P is a suitable protective group (R^1 is preferably not a hydrogen, preferably a protective group).

Sulfonyl chlorides of formula (V), as used in Scheme 1, may be prepared according to a procedure set out in Scheme 3 :

Scheme 3 :



Thereby, Ar^1, Ar^2, R^1 and n are as above defined.

Amines of formula II are either known compounds or may be prepared from known compounds by conventional procedures. Preferred amines as starting materials include thien-2-yl-methylamine, furan-2-yl-methylamine, pyrrolyl-2-yl-methylamine, pyridyl-2-yl-methylamine, thien-2-yl-ethylamine, furan-2-yl-ethylamine, pyridyl-2-yl-ethylamine, thien-2-yl-propylamine, furan-2-yl-propylamine, pyridyl-2-yl-propylamine and the like.

The acyl chlorides of formula III are also commercially available or previously described compounds. Preferred acyl chlorides include halogenobenzoylchlorides, e.g. 4-chlorobenzoyl chloride, 4-fluorobenzoyl chloride or trifluoromethylbenzoyl chloride, alkoxybenzoylchloride, pyridylcarbonylchloride and the like. Acyl halides (III) may also be prepared by reacting the corresponding carboxylic acid with an inorganic acid halide, such as thionyl chloride, phosphorus trichloride or oxalyl chloride under conventional conditions. Generally, such reaction is performed upon using about 1 to 5 molar equivalents of the acyl halide or oxalyl chloride, either in pure form or in an inert

solvent, such as carbon tetrachloride, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours. A catalyst, as *N,N*-dimethylform-amide, may also be used in this reaction.

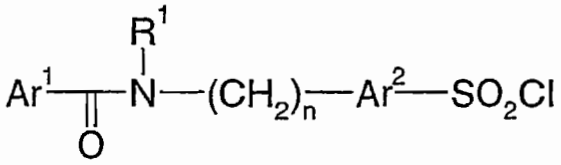
When an acyl halide (III) is employed in the coupling reaction set out in Scheme 3, it is typically reacted with amine (II) in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, an excess of amine II may be used to scavenge the acid generated during the reaction.

Alternatively, the carboxylic acid of compound (III) can be employed in the coupling reaction. The carboxylic acids and derivatives (III) are usually commercially available reagents or can be prepared by conventional procedures.

The coupling reaction of carboxylic acid of formula III (i.e. the acyl chloride) with the amine (II) is typically performed while using any conventional coupling reagent including, for example, carbodiimides such as dicyclohexylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide and other promoting agents, such as *N,N*-carbonyl-diimidazole or PyBOP. This reaction can be conducted with or without the use of well known additives such as *N*-hydroxysuccinimide, 1-hydroxybenzotriazole, etc. which are known to facilitate the coupling of carboxylic acids and amines.

The coupling reaction using either acyl halide (III) or its carboxylic acid is preferably conducted at a temperature of from about 0°C to about 6°C for about 1 to about 24 hours. Typically, the reaction is conducted in an inert aprotic polar solvent such as N,N-dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like using about 1 to about 5 molar equivalents of the amine based on the carboxylic acid or its acid halide. Upon completion of the reaction, the carboxamide (IV) is recovered by conventional methods including precipitation, chromatography, filtration, distillation and the like.

The sulfonyl chorides of formula V necessary for the preparation of the final products of formula I, notably those being sulfonylpiperidines or -pyrrolidines or –azepans, are prepared using conventional sulfonating methods applied on the carboxamides (IV):



(V)

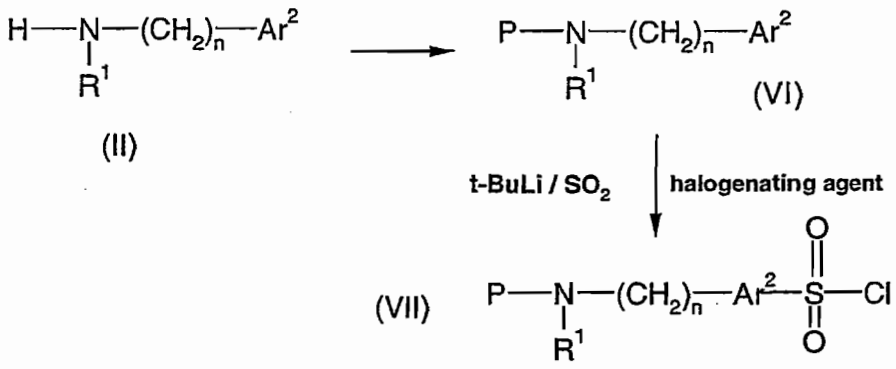
A preferred sulfonating reagent for use in this reaction (as set out in scheme 3) is chlorosulfonic acid (HSO_3-Cl). Typically, the sulfonation reaction is performed by treating the carboxamide of formula (IV) with about 5 to about 10 molar equivalent of the sulfonating reagent in an inert solvent, such as dichloromethane, at a temperature ranging from about –70°C to about 50°C. Preferably, the addition of chlorosulfonic acid takes place at –70°C and leads to the formation of the intermediate sulfonic acid. Increasing the temperature to 20°C allows the formation of the sulfonyl chloride of formula V. Compounds of formula I with X = S are accessible from the corresponding arylamides (with X = O), e.g. benzamides, through standard functional group inter-conversion methods well known to the person skilled in the art, e.g., by treatment with Lawesson's reagent or others (Pedersen, B. S. et al.; *Bull. Soc. Chim. Belg.* **1978**, *87*, 223).

An alternative approach for the preparation of compounds of formula I is set out in Scheme 2 above and involves the following steps :

- Protection of the amine function of compounds of formula II;
- Chlorosulfonylation of the aromatic group (Ar^2 in compounds VI), thus yielding compounds of formula VII;
- Formation of the sulfonamide function (yielding compounds IX);
- Removal of the protecting group P (Deprotection) within compounds IX;
- Acylation of the above generated free amine to provide compounds (I);

Thereby, the sulfonyl chloride precursor (VII) may be prepared by the following steps :

Scheme 4



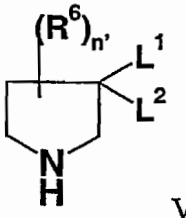
Amines of formula II are protected with a suitable protecting group for an amine moiety to provide intermediate of formula VI wherein P denotes the protecting group. Numerous protecting groups P of the amine function as well as their introduction and removal, are well described in T.W. Greene and G.M. Wuts, Protecting groups in Organic Synthesis, Third Edition, Wiley, New York, 1998, and references cited therein. Preferred are protecting groups that are acids and bases stable and can be further removed by using metal transition complexes such as palladium complexes, for example the allylcarbamate group (Alloc) or the N,N'-bisallyl group. Another preferred protecting group is the maleimide group which is stable in a all range of experimental conditions.

The introduction of said groups may be performed by reacting the corresponding bisallylcarbonate anhydride or allylbromide or maleic anhydride in the presence of a base such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like in an aprotic solvent such as N,N-dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like at a temperature ranging from about 0°C to about 80°C.

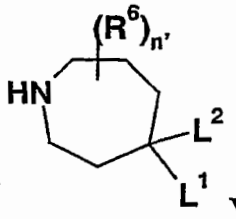
Compounds of formula VI in Scheme 4 are then sulfonated using a conventional, very mild sulfonating procedure that allows the obtention of sulfonyl chloride of formula VII. Typically, protected amines VI are treated with a base such as n-butyllithium or tert-butyl-lithium under an inert atmosphere, in a polar aprotic solvent such as tetrahydrofuran, ether or dioxane at a temperature ranging from –70°C to 0°C during a time ranging from 15 minutes to 4 hours. The so formed anion is then treated with SO_2Cl_2 or

most preferably SO_2 by bubbling the gas into the reaction mixture at a temperature ranging from –70°C to 20°C during a time ranging from 5 minutes to 1 hour. The sulfinate obtained is then transformed "*in situ*" to the sulfonyl chloride of formula VII by contacting with *N*-chlorosuccinimide or other suitable chlorinating agents including $POCl_3$, SO_2Cl_2, $COCl_2$, at a temperature ranging from 0°C to 70°C.

Following either of Schemes 1 and 2, the sulfonamide derivatives of formula I may be obtained by reacting sulfonyl chlorides V or VII with a cyclic or bicyclic amine (VIII), i.e. an alkyl containing a nitrogen according to the above definition. Preferred cyclic amines (VIII) include pyrrolidine or azepan or piperidine derivatives of the general formula (VIII'') or (VIII') or (VIII''').

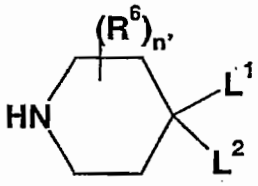


VIII'' or



VIII'

or



VIII'''

whereby $(R^6)_n$, L^1 and L^2 are as above defined.

The amines of formula VIII''' or VIII'' or VIII' are either commercially available compounds or compounds that may be prepared by known procedures.

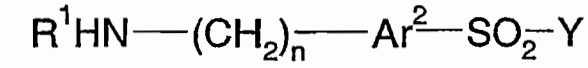
The coupling reaction of sulfonyl chlorides (V) and (VII) with the amines VIII to provide sulfonamides of formula I is performed by contacting the sulfonyl chlorides with an amine of formula VIII in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is preferably conducted in a solvent such as N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile typically at a temperature from about 0° to about 100°C.

According to a preferred embodiment, the sulfonamide derivatives of formula I are prepared by reacting a sulfonyl chloride V or VII, with a piperidine of formula VIII'''.

Piperidines of formula VIII''' are either commercially available or they may be prepared by known procedures. Such conventional methods known by one skilled in the art are described by way of examples in *J. Pharm. Sci.* **1972**, *61*, 1316; *J. Heterocyclic. Chem.*, **1986**, *23*, 73; *Tetrahedron Lett.*, **1996**, *37*, 1297, US 5106983, WO/9113872 and WO/9606609.

The piperidino sulfonamides of formula I may be prepared by contacting the sulfonyl chlorides (V) and /or (VII) with a piperidine of formula VIII''' in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is preferably conducted in solvents such as N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

The specific sulfonamides of formula XIV - where R^1 is hydrogen - are readily prepared from the protcted sulfonyl chlorides VII, by contacting said sulfonyl chlorides VII with an amine of formula VIII in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is preferably conducted in solvents such as N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C. The use of sulfonyl chloride of type VII leads to amines that have to be deprotected using well known methods by one skilled in the art to afford amine of general formula XIV



XIV

wherein R^1, Ar^2, Y and n are as above defined.

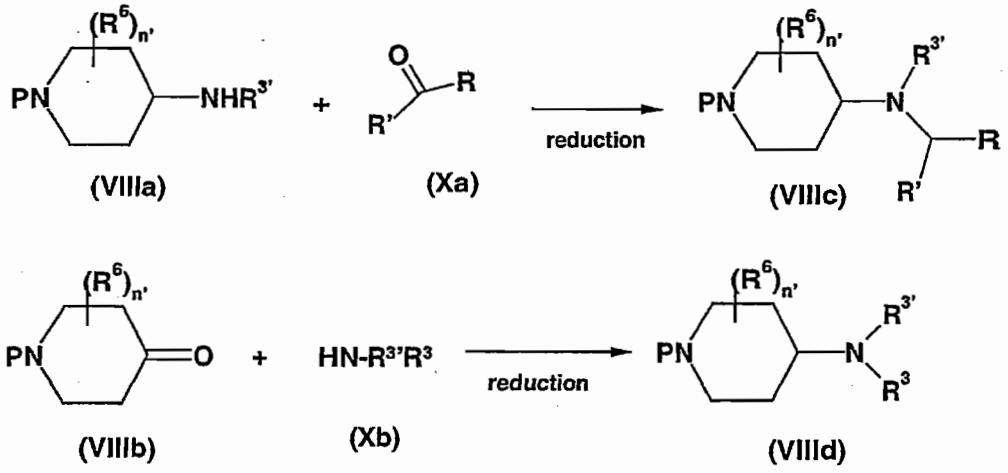
Derivatives of type XIV are then acylated according to described methods for the preparation of amides by condensation of amines with acid chlorides or carboxylic acids in the preferred conditions described above leading to compounds of general formula I

A specific approach for preparing piperidino sulfonamides of formula I (Y is a piperidine VIII'''), wherein L^1 is a moiety $-NHR^3$, involves either

- the reaction of an amino-piperidine (VIIIa) with an aldehyde (Xa), or
- the reaction of a piperidine-4-one (VIIIb) with an amine (Xb);

and is specified in Scheme 5 :

Scheme 5



R^3, $R^{3'}$, R^6 are as above defined, R' is H or an alkyl group, R is an aryl, preferably a phenyl group and P is a protective group. The aminated piperidines (VIIIc) and (VIIId) may then be reacted with the sulfonyl chlorides V or VII to provide the sulfonamides of formula I or formula IX respectively.

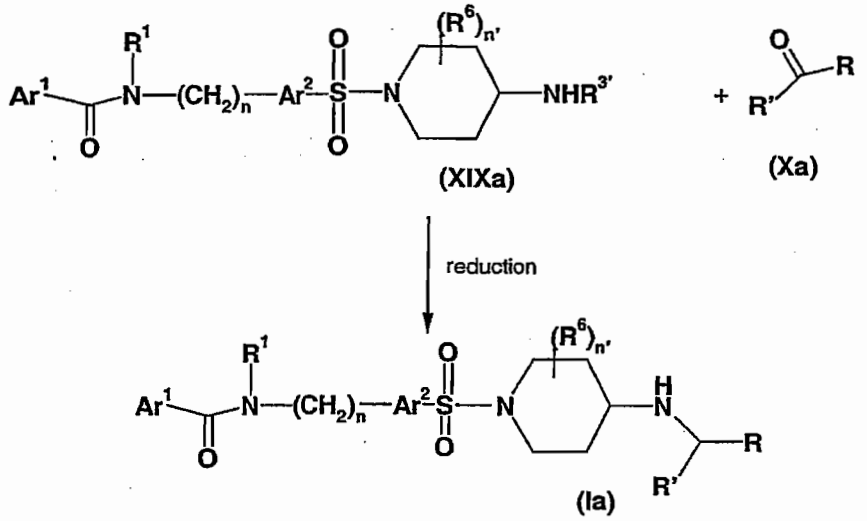
Carbonyl compounds (Xa) are commercially available and include unsubstituted or substituted benzaldehydes (like e.g. benzaldehyde or 4-trifluoromethylbenzaldyde, etc.), unsubstituted or substituted ketones (like e.g. acetophenone or 4-trifluoroacetophenone, etc.), unsubstituted or substituted aliphatic aldehydes or ketones (like e.g. hexanal, 2-propoxyacetaldehyde or heptane-2-one, etc.)

Amines (Xb) are commercially available and include unsubstituted or substituted primary alkylamines (like e.g. hexylamine, 2-pyridine-2-ethylamine etc.), as well as unsubstituted or substituted secondary alkylamines (like, e.g. N-methylhexylamine, etc.)

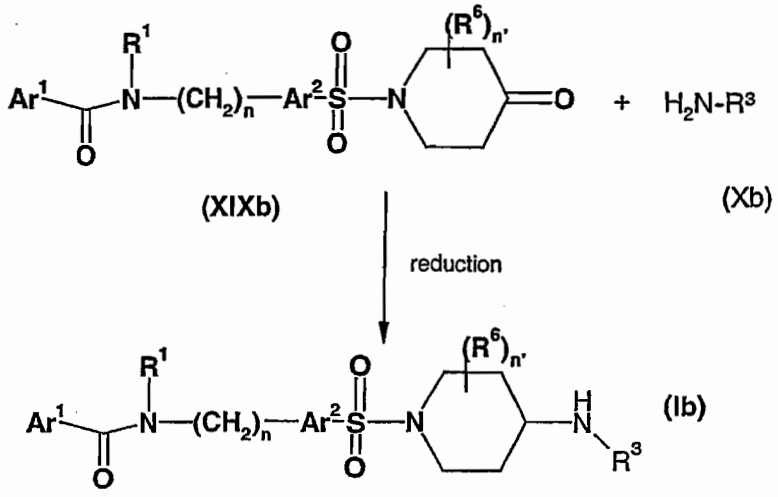
4-Oxo-piperidine and azepane-4-one are commercially available.

A more preferred approach for preparing sulfonamides of formula I wherein Y is a piperidine moiety (VIIIc) and (VIIId) are obtained by following Scheme 6 and 7:

Scheme 6



Scheme 7

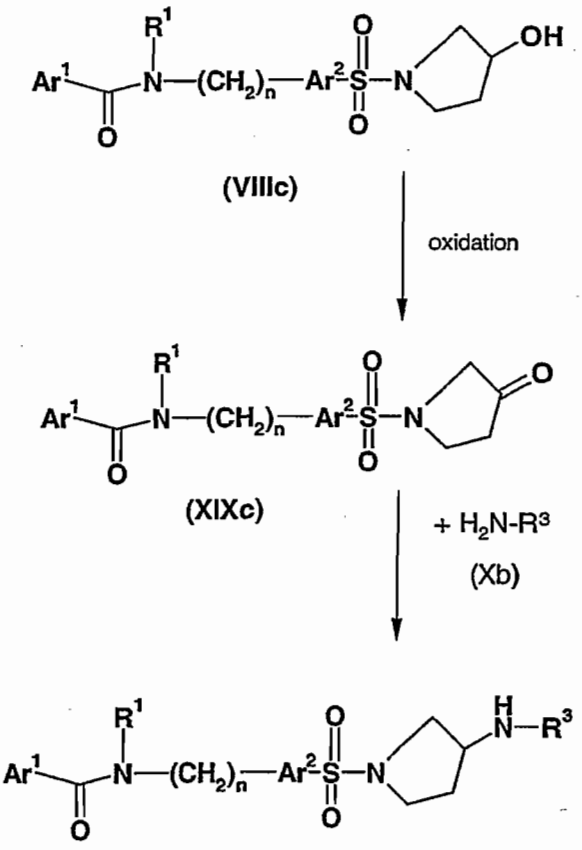


A specific approach for preparing pyrrolidine sulfonamides of formula I (i.e. where Y is a pyrrolidine VIII''), with L^1 being a moiety $-NHR^3$, involves the steps of

- providing a hydroxypyrrolidine (VIIIf);
- subjecting said hydroxypyrrolidine (VIIIf) to an oxidation to yield the corresponding ketone (VIIIg) and
- to reductively aminate the ketone (VIIIg) to yield the sulfonamide (Ic)

Said approach is specified in Scheme 8 :

Scheme 8 :

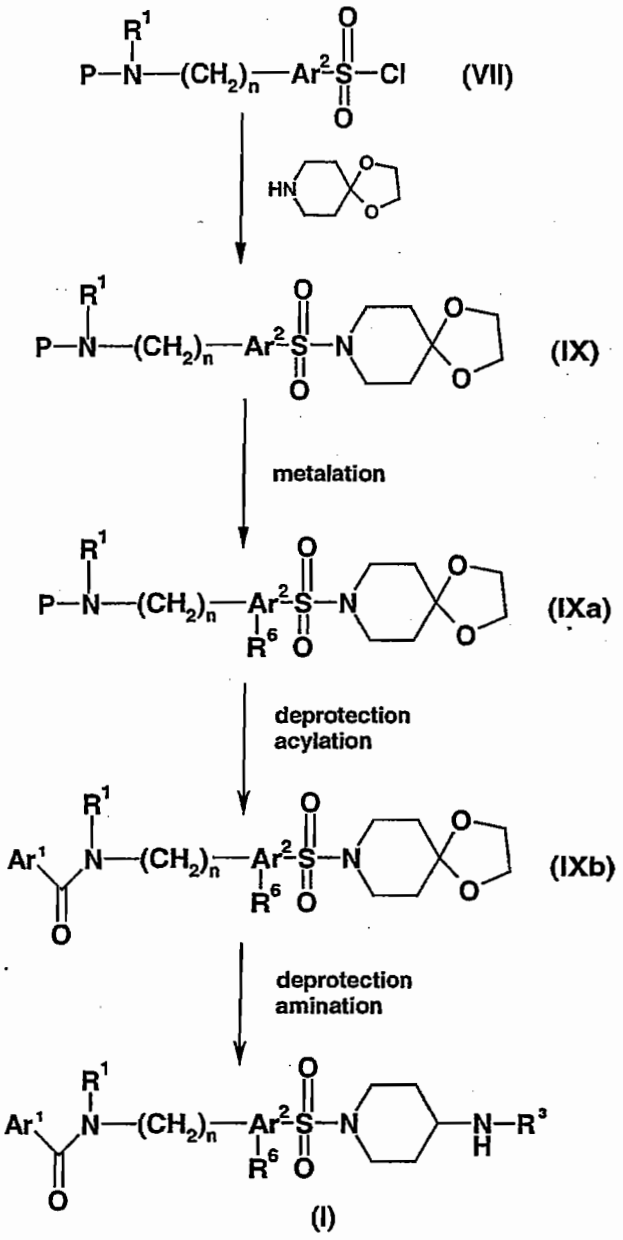


The oxidative step may be performed using oxidative agents like $C_2O_2Cl_2$/DMSO or Chromium(VI)derivatives or periodinane derivatives as described by Dess and Martin (40).

A specific approach for preparing sulfonamides of formula I where Ar^2 is substituted with R^6 involves the steps of:

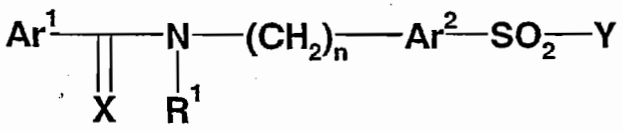
- providing the sulfonyl choride (VII) with a protecting group P;
- reacting the sulfonyl choride (VII) with an amine (VIII), e.g. a protected piperidin-4-one thus providing a sulfonamide (IX)
- subjecting said sulfonamide (IX) to a metalation of Ar^2 (e.g. by using BuLi) to yield the corresponding substituted sulfonamide (IXa), with R^6 being a carboxylic group, carboxylate, carboxamide, OH, or OH carrying alkyl group, hydrazido carbonyl groups, sulfate or sulfonate or amine or ammonium salts,
- removing protecting group P of said sulfonamide (IXa) and acylating the sulfonamide to yield compounds of formula (IXb),
- deprotecting said sulfonamide (IXb) and to reductively aminate the corresponding ketone to yield compounds of formula I.

Scheme 9:



If the above set out general synthetic methods are not applicable for the obtention of compounds of formula I, suitable methods of preparation known by a person skilled in the art should be used. For example, when Ar^2 is phenyl, one should start from commercially available 4-cyanophenyl sulfonyl chloride and applies conventional methods known by a person skilled in the art to reach sulfonamide derivatives of formula I.

A further aspect of the present invention is related to sulfonamide compounds (XIX)



(XIX)

in particular for use as intermediate compounds in the preparation of sulfonamides of formula (I).

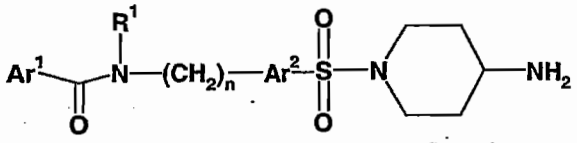
wherein Ar^1 and Ar^2 are independently from each other aryl or heteroaryl,

X is O or S;

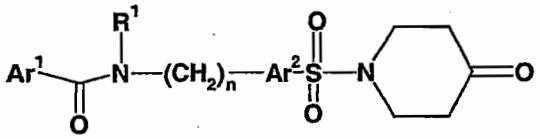
R^1 is hydrogen or a C_1-C_6-alkyl group,

n is an integer from 0 to 5, and

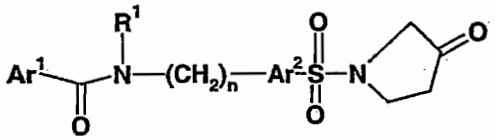
Y is a pyrrolidine-3-one, a piperidine 4-one, pyrrolidine-3-amine or a piperidine 4-amine, or their ammonium salts.



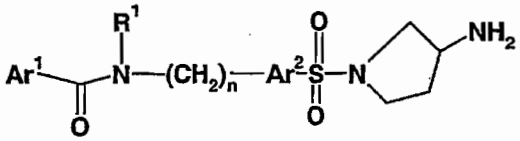
(XIXa)



(XIXb)



(XIXc)



(XIXd)

A final aspect of the present invention is related to the use of the compounds according to formula I for the modulation of the JNK function, or signaling pathways, the use of said compounds for the preparation of pharmaceutical compositions for the modulation

of the JNK pathway as well as the formulations containing the active compounds according to formula I. Said modulation of the JNK pathway is viewed as a suitable approach of treatment for various disorders. When employed as pharmaceuticals, the sulfonamide derivatives of the present invention are typically administered in the form of a pharmaceutical composition. Hence, pharmaceutical compositions comprising a compound of formula I and a pharmaceutically acceptable carrier, diluent or excipient therefore are also within the scope of the present invention. A person skilled in the art is aware of a whole variety of such carrier, diluent or excipient compounds suitable to formulate a pharmaceutical composition. Also, the present invention provides compounds for use as a medicament. In particular, the invention provides the compounds of formula I for use as JNK inhibitor, notably JNK 2 and/or 3, for the treatment of disorders of the immune as well as the neuronal system of mammals, notably of humans, either alone or in combination with other medicaments.

The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous use). Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

When employed as pharmaceuticals, the sulfonamides derivatives of this invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual com-

pound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of these inventions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds are preferably formulated as either injectable or oral compositions. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the sulfonamide compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or non-aqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As above mentioned, the sulfonamide compound of formula I in such compositions is typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 8 of *Remington's Pharmaceutical Sciences*, 17th Edition, 1985, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein be reference. The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can also be found in the incorporated materials in *Remington's Pharmaceutical Sciences*.

In the following the present invention shall be illustrated by means of some examples which are not construed to be viewed as limiting the scope of the invention. The HPLC, NMR and MS data provided in the examples described below were obtained as followed. The following abbreviations are hereinafter used in the accompanying examples: min (min-ute), hr (hour), g (gram), mmol (millimole), m.p. (melting point), eq (equivalents), mL (milliliter), µL (microliters), mL (milliliters), ACN (Acetonitrile), Boc (butoxycarbonyl), $CDCl_3$ (deuterated chloroform), cHex (Cyclohexanes), DCM (Dichloromethane), DECP (Diethylcyanophosphonate), DIEA (Diisopropylethylamine), DIC (Diisopropyl carbodiimide), DMAP (4- Dimethylaminopyridine) DMF (Dimethylformamide), DMSO (Dimethylsulfoxide), DMSO-d_6 (deuterated dimethylsul-foxide), EDC (1-(3-Dimethyl-amino-propyl)-3-ethylcarbodiimide), EtOAc (Ethyl acetate), Et_2O (Diethyl ether), Fmoc (9-fluorenylmethoxycarbonyl), HOBt (1-Hydroxybenzotriazole), K_2CO_3 (potassium carbonate), NaH (Sodium hydride), $NaHCO_3$ (Sodium bicarbonate), nBuLi (n-Butyllithium), TBTU (*O*-Benzotriazolyl-*N*,*N*,*N*',*N*'-tetramethyluronium-tetrafluoroborate), TEA (Triethyl amine), TFA (Trifluoro-acetic acid), THF (Tetrahydrofuran), TMOF (trimethylorthoformate), $MgSO_4$ (Magnesium sulfate), PetEther (Petroleum ether), rt (room temperature).

Examples

Example 1 (Protocole E; see Schemes 1, 3 & 6)

Preparation of 3-Methoxy-*N*-{[5-({4-[(4-trifluoromethylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide (1)

{[(3-methoxybenzoyl)amino]methyl}thiophene-2-sulfonyl chloride **(1a)**

To a solution of 2-Aminomethylthiophene (10.6ml, 103mmol) and pyridine (9.1ml, 104mmol) in 100ml chloroform was added at 0°C a solution of 3-methoxybenzoyl-chloride (19.2g, 103mmol) in CH_2Cl_2. The reaction was allowed to warm to rt. during 1h and stirred for additional 3h. Water was added while 3-methoxy-*N*-(thien-2-ylmethyl)benzamide, **(1b)** (10.1g) precipitated. The solid was filtered of and washed with water. The remaining organic layer was washed with brine, dried over MgSO4 and evaporated to dryness to afford additional **(1b)** (15.2g). The overall yield was 25.3 g (99.9%). **(1b)** was used for the next step without further purification.

Chlorosulfonic acid (5.62ml, 84mmol) was dissolved in 20ml CH_2Cl_2 and added to a solution of **(1b)** (11.0g, 42mmol) in 100ml CH_2Cl_2 under vigorous stirring. A gummy solid was formed and the reaction mixture was stirred for 3h. The reaction was quenched with ice, and ice cold NaHCO3 solution was added to reach pH8.5. The aqueous layer was washed twice with CH_2Cl_2. Tetrabutylammoniumhydroxide (40% in water) (32ml, 50mmol) was added to the aqueous layer, while a solid was formed. The precipitate was extracted into CH_2Cl_2 and the aqueous layer was washed 3x with CH_2Cl_2. The combined organic layers were dried over MgSO4 and evaporated to dryness to afford a slightly colored foam of Tetrabutylammonium 5-{[(3-methoxybenzoyl)-amino]methyl}thiophene-2-sulfonate **(1c)** (24g, 97%). NMR spectra indicated pure compound, which was used for the following chlorination step.

To a solution of **(1c)** (2.0g, 3.4mmol) in 50ml CH_2Cl_2 was added triphosgene (800mg, 2.7mmol, 2.3eq.), dissolved in 10ml CH_2Cl_2. To this reaction mixture DMF (0.1ml, 1.4mmol) was added dropwise during 10', while gas evolution could be observed. The gases were trapped at the outlet of the reaction flask in a 2N NaOH solution. The reaction mixture was stirred for 3h, and the crude was directly filtered through silica gel using EtOAc/hexane 1:2 as eluent. An orange solid could be isolated which was recrystallised from cyclohexane/ CH_2Cl_2. **(1a)** (730mg, 60%) was obtained as colorless needles. ^{1}H NMR ($CDCl_3$) δ 8.83 (t, J = 1.5 Hz, 1H), 8.35 (t, J = 7.5Hz, 1H), 7.76 (t, J = 4.1 Hz, 1H), 7.70-7.58 (m, 3H), 7.52-7.40 (m, 2H), 7.05 (t, J = 3.8 Hz, 1H).

1-[(5-{[(3-Methoxybenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-ammonium trifluoroacetate (**1d**)

To a solution of 5-({[1-(3-Methoxybenzoyl]-amino}-methyl)-thiophene-2-sulfonyl chloride (**1a**) (8g, 23 mmol) and DIEA (8.7 ml, 50.9 mmol) in 100 ml CH_2Cl_2 was added a solution of 4-Boc-amino-piperidine (5.5g, 27.7 mmol) in 50ml CH_2Cl_2. The reaction mixture was stirred for 4h. Excess of amines were removed by extraction with HCl (1N). The dried organic layer was evaporated to dryness. Recrystallization provided 8.3g (71%) of pure *tert*-butyl 1-[(5-{[(3-Methoxybenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-ylcarbamate, (**1e**). ^{1}H NMR showed pure product , which was deprotected according to standard protocols using TFA. The deprotected crude product was precipitated with Diethylether to provide 8.43g (82%) of (**1d**): H^1 NMR (DMSO-*d6*) δ9.29 (t, J = 5.8 Hz, 1H), 7.88 (m, 3H), 7.48-7.36 (m, 4H), 7.17 (d, J = 3.7 Hz, 1H), 7.11 (d, J = 6.8 Hz, 1H), 4.66 (d, J = 5.6 Hz, 2H), 3.79 (s, 3H), 3.61 (d, J = 11.7 Hz, 2H), 3.09 (m, 1H), 2.43 (t, J = 11.1 Hz, 2H), 1.96 (d, J = 11.1 Hz, 2H), 1.54 (dd, J = 11.9, 3.7 Hz, 2H), M/Z APCI: 410.1 (M+1), 408.2 (M-1).

3-Methoxy-*N*-{[5-({4-[(4-trifluoromethylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide (**1**)

(**1d**) (50mg, 0.1 mmol) was dissolved in 2 ml DCM and neutralized with DIEA (18µl, 0.1mmol) to pH 7. To this solution was added 4-Trifluoromethylbenzaldehyde (18mg, 0.11 mmol), and the reaction was stirred for 30', followed by the addition of acetic acid (6ul, 0.1 mmol) and Sodium triacetoxyborohydride (28mg, 0.14 mmol). The reaction was stirred at r.t. for 4h, diluted with ethylether and quenched with NaOH (1N) to reach pH 9. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to dryness. The crude was purified by flash chromatography to obtain 51 mg of pure (**1**) (91%) as a colorless solid: mp.of HCl salt: 235-236°C, H^1 NMR (DMSO-d^6) δ9.29 (t, J = 5.8Hz, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.65-7.40 (m, 6H), 7.19 (d, J = 3.8 Hz, 1H), 7.15 (dd, J = 7.9, 1.5 Hz, 1H), 4.70 (d, J = 5.6 Hz, 2H), 3.83 (s, 3H), 3.77 (d, b, 2H), 3.41 (d, b, 2H), 2.61-2.40 (m, 3H), 1.93 (m, 2H), 1.42 (m, 2H), M/Z APCI: 568.6 (M+1), 566.6 (M-1).

Alternatively **1** can be synthesised in a parallel solution phase approach:

(**1d**) (50mg, 0.1 mmol) was suspended in 2 ml DCE using parallel synthesizer Quest®210. The suspension was neutralized with DIEA (18µl, 0.1mmol) to pH 7, while (**1c**) is dissolved. To this solution was added 4-Trifluoromethylbenzaldehyde in 100µl DMF (18mg, 0.11 mmol), and the reaction was stirred for 30' under Ar, followed by the addition of acetic acid (6ul, 0.1 mmol) and Sodium triacetoxyborohydride (28mg, 0.14 mmol). The reaction was stirred at r.t. overnight, diluted with DCE and quenched with $NaHCO_3$ (sat.) to reach pH 9. The organic layer was washed with brine, dried over $MgSO_4$ and filtered into scintilation vials. 50 mg of polymer bound benzaldehyde and 20 mg of Aminomethyl Merryfield resin were added and shaken overnight. The solution was filtered off, polymers were rinsed twice with solvent and the combined organic layers were evaporated to dryness at medium temperature for 1h using a Savant Speed Vac® Plus vacuum centrifuge.

The procedure afforded in a parallel array pure (**1**), as a colourless powder, which was upon treatment with HCl in Diethylether transformed into its HCl salt.

The below listed compounds (designated as Example No.) were prepared in a similar way by following the above set out protocole and using the corresponding starting compounds (HPLC conditions: C8 Symmetry a- MeCN, 0.09%TFA, 0 to 100% (10min), b: MeCN, 0.09%TFA, 0 to 100% (8 min); Mass spectrum APCI).

Example No.	Compound Name	rt_HPLC	Purity (%)	Gradient_HPLC	Mass_M+1	Mass_M
2	4-chloro-N-{[5-({4-[(3-chlorobenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	4.83	99.0	a	538	536
3	3-methoxy-N-[(5-{[4-({4-[(trifluoromethyl)sulfanyl]benzyl}amino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.55	99.9	a	600	598
4	3-methoxy-N-{[5-({4-[(4-phenoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	4.59	97.9	a	592	590
5	3-methoxy-N-{[5-({4-[(3-methylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.89	95.3	a	514	512
6	3-methoxy-N-{[5-({4-[(4-propylbenzyl)amino]piperidin-1-	4.48	99.0	a	542	540

	yl}sulfonyl)thien-2-yl]methyl}benzamide					
7	3-methoxy-N-({5-[(4-{[3-(trifluoromethyl)benzyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	4.27	99.9	a	568	566
8	3-methoxy-N-({5-[(4-{[4-(trifluoromethoxy)benzyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	4.53	99.9	a	584	582
9	N-({5-[(4-{[4-(difluoromethoxy)benzyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	4.09	98.0	a	566	564
10	3-methoxy-N-{[5-({4-[(2,3,4,5,6-pentamethylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	4.65	98.0	a	570	568
11	3-methoxy-N-{[5-({4-[(4-propoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	4.35	98.0	a	558	556
12	N-{[5-({4-[(4-butoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.65	99.9	a	572	570
13	3-methoxy-N-{[5-({4-[(4-methoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.73	98.0	a	530	528
14	3-methoxy-N-{[5-({4-[(pyridin-4-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	2.72	99.9	a	501	499
15	3-methoxy-N-{[5-({4-[(pyridin-2-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.27	99.2	a	501	499
16	3-methoxy-N-{[5-({4-[(pyridin-3-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	2.79	99.9	a	501	499
17	N-{[5-({4-[(4-tert-butylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.64	99.7	a	556	554
18	N-{[5-({4-[(3-ethoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.01	97.3	a	544	542
19	3-methoxy-N-({5-[(4-{[4-(methylsulfonyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide	3.37	96.0	a	578	576
20	N-({5-[(4-{[3,5-bis(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide	4.76	91.0	a	636	634
21	N-({5-[(4-{[2,5-bis(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide	4.46	95.0	a	636	634

22	N-({5-[(4-{[4-(ethylsulfanyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide	4.25	88.0	a	560	558
23	3-methoxy-N-[(5-{[4-({3-[(trifluoromethyl)sulfanyl]benzyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide	4.48	96.0	a	600	598
24	N-({5-[(4-{[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide	4.22	95.0	a	580	578
25	N-{[5-({4-[(4-iodobenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide	4.11	89.0	a	626	624
26	N-({5-[(4-{[4-(benzyloxy)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide	4.67	90.0	a	606	604
27	N-{[5-({4-[(mesitylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide	4.22	96.0	a	542	540
28	N-{[5-({4-[(4-chlorobenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide	3.95	97.0	a	534	532
29	N-{[5-({4-[(4-ethylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide	4.08	82.0	a	528	526
30	3-methoxy-N-{[5-({4-[(4-pentylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide	5.08	100.0	a	570	568
31	3-methoxy-N-[(5-{[4-({1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide	4.43	100.0	a	582	580
32	3-methoxy-N-{[5-({4-[(4-methylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide	3.86	75.0	a	514	512
33	N-{[5-({4-[(4-butylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide	4.79	91.0	a	556	554
34	N-{[5-({4-[(4-isopropylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide	4.41	91.0	a	542	540
35	N-{[5-({4-[(4-isobutylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide	4.77	74.0	a	556	554
36	N-({5-[(4-{[(1-hydroxy-1lambda~5~-pyridin-4-yl)methyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide	2.89	100.0	a	517	515
37	N-{[5-({4-[(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide	3.75	85.0	a	558	556
38	N-{[5-({4-[(2,3-dihydro-1-benzofuran-5-ylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide	3.73	87.0	a	542	540

39	4-chloro-N-{[5-({4-[(4-propylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide	4.75	92.0	a	546	544
40	4-chloro-N-({5-[(4-{[4-(trifluoromethoxy)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide	4.63	97.0	a	588	586
41	4-chloro-N-({5-[(4-{[4-(difluoromethoxy)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide	4.63	97.0	a	588	586
42	4-chloro-N-{[5-({4-[(4-propoxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide	4.57	96.0	a	562	560
43	N-{[5-({4-[(4-butoxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-4-chlorobenzamide	4.91	91.0	a	576	574
44	4-chloro-N-{[5-({4-[(4-quinolinylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide	3.27	99.0	a	555	553
45	N-{[5-({4-[(4-tert-butylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-4-chlorobenzamide	4.85	90.0	a	560	558
46	4-chloro-N-{[5-({4-[(4-phenoxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide	4.82	90.0	a	596	594
47	4-chloro-N-[(5-{[4-({4-[(trifluoromethyl)sulfanyl]benzyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide	4.77	90.0	a	604	602
48	4-chloro-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide	4.76	100.0	a	572	570
49	3-methoxy-N-({5-[(4-{[2-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide	3.97	90.0	a	604	602
50	3-methoxy-N-[(5-{[4-({[6-(trifluoromethyl)-3-pyridinyl]methyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide	3.75	85.0	a	569	567
51	N-[(5-{[4-(benzylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-3-methoxybenzamide	3.58	88.0	a	500	498
52	3-methoxy-N-[(5-{[4-({1-[4-(trifluoromethyl)phenyl]propyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide	4.79	88.0	a	596	594
53	3-methoxy-N-[(5-{[4-({1-methyl-1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide	3.89	99.0	a	596	594

54	4-chloro-N-[(5-{[4-({1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide	3.78	98.0	b	586	584
55	4-chloro-N-[(5-{[4-({1-methyl-1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide	3.80	99.0	b	601	559
56	4-chloro-N-[(5-{[2-({[4-(trifluoromethyl)benzyl]amino}methyl)-1-pyrrolidinyl]sulfonyl}-2-thienyl)methyl]benzamide	4.44	95.0	10	556	554
57	4-chloro-N-[(5-{[(3R)-3-({[4-(trifluoromethyl)benzyl]amino}methyl)pyrrolidinyl]sulfonyl}-2-thienyl)methyl]benzamide	3.70	94.0	b	572	570
58	4-chloro-N-({5-[(3-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide	3.76	92.0	b	572	570
59	4-chloro-N-{[5-({3-[(hexylamino)methyl]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide	3.75	100.0	b	512	510
60	4-chloro-N-({5-[(3-{[4-(trifluoromethyl)benzyl]amino}-1-pyrrolidinyl)sulfonyl]-2-thienyl}methyl)benzamide	3.78	99.9	a	558	556
61	4-chloro-N-{[5-({(3R)-3-[(hexylamino)methyl]pyrrolidinyl}sulfonyl)-2-thienyl]methyl}benzamide	3.59	82.0	b	498	496
62	4-chloro-N-[(5-{[3-({[4-(trifluoromethyl)benzyl]amino}methyl)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide	3.86	100.0	b	586	584

Example 63 (Protocole A; see Schemes 1, 3 & 7:

Preparation of 4-chloro-N-[(5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]benzamide

4-Chloro-*N*-thiophen-2-ylmethyl-benzamide **(63a)**

A solution of 4-chlorobenzoyl chloride (0.114 mol) in 50 ml dry CH_2Cl_2 was added over 30 min to a stirred solution of 2-aminomethyl-thiophene (0.137 mol) and $^iPr_2NEt$ (0.25 mol) in CH_2Cl_2 (200 ml) at 0°C. A white solid was formed and the reaction was allowed to warm to room temperature over 1 h. The mixture was diluted with 200 ml of CH_2Cl_2, washed twice with HCl aq. (0.1N) and dried over $MgSO_4$. Evaporation of the solvents afforded 28 g (98%) of the title benzamide as a white solid: m.p. 153-54°C, ^1H NMR ($CDCl_3$) δ 7.9 (d, J = 8.67 Hz, 2H), 7.58 (d, J = 8.67 Hz, 2H), 7.44 (dd, J = 3.77,

1.13 Hz, 1H), 7.22 (d, J = 5.27 Hz, 1H), 7.16 (dd, J = 3.39, 5.27 Hz, 1H), 6.62 (br d, 1H), 4.98 (d, J = 5.65 Hz, 2H).

5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl chloride **(63b)**

Chlorosulfonic acid (20.1 ml, 198 mmol) in CH_2Cl_2 (80 ml) was added dropwise to a solution of **(63a)** (10 g, 40 mmol) in CH_2Cl_2 (500 ml) at –80°C. The mixture was allowed to reach room temperature in 5h.. The reaction mixture was poured on ice and quickly extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to dryness which afforded 8.8 g (63%) of desired sulfonyl chloride **(63b)**; mp 133-35°C, ^{1}H NMR (DMSO-*d6*) δ 9.21 (t, J = 6.4 Hz, 1H), 7.87 (d, J = 8.67 Hz, 2H), 7.53 (d, J = 8.67 Hz, 2H), 6.91 (d, J = 3.39 Hz, 1H), 6.77 (d, J = 3.39 Hz, 1H), 4.53 (d, J = 3.77 Hz, 2H).

4-Chloro-*N*-({5-[(4-oxopiperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide **(63c)**

A solution of 5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl chloride **(1b)** (5.0g, 14mmol) in 100ml chloroform and a solution of 4-piperidinone hydrochloride monohydrate (4.3g, 28mmol) in 21ml of NaOH (2N) were stirred vigorously for 15h. The reaction was quenched with HCl (2N) and the organic layer was extracted twice with HCl (2N) and twice with brine. The dried organic phase affords after evaporation of chloroform 5.8g (99.5%) of **(63c)** as a colourless solid: ^{1}H NMR ($CDCl_3$) δ7.67 (d, J = 8.7 Hz, 2H), 7.42-7.38 (m, 3H), 6.99 (d, J = 3.8 Hz, 1H), 6.53 (t, J = 5.3 Hz, 1H), 4.74 (d, J = 6.0 Hz, 2H), 3.37 (d, J = 6.2 Hz, 4H), 2.50 (d, J = 6.2 Hz, 4H).

4-Chloro-N-[(5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide **(63)**

A mixture of N-sulfonyl piperidone **(63c)** (3.01 g, 7.28 mmol), n-hexylamine (1.06 ml, 8.01 mmol), freshly powdered $NaBH(OAc)_3$ (3.1 g, 14.6 mmol), anhydrous 1,2-dichloroethane (150 ml), and THF (100 ml) was stirred for 80 min at 23°C. The mixture was concentrated on a rotary evaporator (T_{bath} = 57°C), dissolved in EtOAc (500 ml), washed (brine:K_2CO_3 sat, 4:1; 250 ml) and evaporated to give 4.1 g of crude material. The residue was dissolved in 50 ml hot acetone, adsorbed on silica gel, evaporated,

loaded on a chromatography column (silica gel, diameter = 5.5 cm), and eluted (MeOH:CH_2Cl_2 7:150). The chromatography was repeated to give 2.95 g (81%) of the title secondary amine as a white solid: ^{1}H NMR (DMSO-*d6*) 9.37 (t, *J* = 5.8 Hz, 1H), 7.90 (dt, *J* = 8.7, 2.2 Hz, 2H), 7.51 (dt, *J* = 8.5, 2.2 Hz, 2H), 7.16 (d, *J* = 3.8 Hz, 1H), 4.65 (d, *J* = 5.8 Hz, 2H), 3.39 (dm, *J* = 11.9 Hz, 2H), 3.60–3.00 (br. s, 1H), 2.49 (ddd, *J* = 11.5, 9.8, 1.7 Hz, 2H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.44–2.38 (buried m, 1H), 1.82 (dm, *J* = 10.0 Hz, 2H), 1.38–1.14 (m, 10H), 0.83 (t, *J* = 6.7 Hz). ^{13}C NMR (DMSO-*d6*) 165.33 (C=O), 150.46 (thiophene, C2), 136.41 (chlorobenzamide, C1), 133.86 (thiophene, C5), 132.42 (thiophene, C3), 132.37 (chlorobenzamide, C4, 129.22 (chlorobenzamide, C2 & C6), 128.52 (chlorobenzamide, C3 & C5), 126.27 (thiophene, C4), 52.53 (piperidine, C4), 46.07 (hexyl), 44.41 (piperidine, C2 & C6), 38.09 (thienyl-CH_2), 31.21 (piperidine, C3 & C5), 30.66 (hexyl), 29.49 (hexyl), 26.48 (hexyl), 22.06 (hexyl), 13.91 (hexyl).). M/Z APCI : 498 (M+1), 496 (M–1). Anal. HPLC: R.t = 5.00 min (method a).$C_{23}H_{32}ClN_3O_3S_2$ Calc.: C: 55.46%. H: 6.48%. N: 8.44%. Found: C: 54.19%, H: 6.52%, N: 8.22%.

Alternatively (**63**) can be synthesised in a parallel solution phase approach:
(**63c**) (20mg, 0.05 mmol) was dissolved in 2 ml THF using parallel synthesizer Quest®210. To this solution was added N-hexylamine in DCE (5.6mg, 0.06 mmol), and the reaction was stirred for 30' under Ar, followed by the addition of acetic acid (6ul, 0.1 mmol) and Sodium triacetoxyborohydride (28mg, 0.14 mmol). The reaction was stirred at r.t. for 4h, diluted with DCE and quenched with $NaHCO_3$ (sat.) to reach pH 8.5. The organic layer was washed with brine, dried over $MgSO_4$ and filtered into scintillation vials. To each vial was added MP-TsOH (3eq.) and shaken overnight. The solution was filtered off and the polymer was rinsed extensively with DCE. To the polymer was than added 3 times 1ml NH_3 in EtOH and shaken each for 10min. The polymer was washed and the combined ethanolic solution was evaporated to dryness at medium temperature for 1h using a Savant Speed Vac® Plus vacuum centrifuge.
The procedure afforded in a parallel array pure (**63**), as a colourless powder, which was upon treatment with HCl in Diethylether transformed into its HCl salt.

The below listed compounds (designated as Example No.) were prepared in a similar way by following the above set out protocole and using the corresponding starting compounds :

Example No.	Compound Name	Rt HPLC	Purity (%)	Gradient HPLC	Mass_ M+1	Mass M
64	3-methoxy-N-[(5-{[4-({4-[(trifluoro-methyl)sulfonyl]benzyl}-amino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.84	97.6	a	632	630
65	3-methoxy-N-{[5-({4-[(quinolin-4-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.02	99.9	a	551	549
66	4-chloro-N-[(5-{[4-(heptylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.27	100.0	a	512	510
67	4-chloro-N-[(5-{[4-(pentylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.72	95.5	a	484	482
68	4-chloro-N-[(5-{[4-(butylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.41	100.0	a	470	468
69	4-chloro-N-[(5-{[4-(dodecylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.59	100.0	a	582	580
70	4-chloro-N-{[5-({4-[(2-cyclohexy-lethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	5.25	95.0	a	524	522
71	4-chloro-N-{[5-({4-[(cyclohexyl-methyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	4.87	100.0	a	510	508
72	4-chloro-N-({5-[(4-{[(1R)-1-cyclohexy-lethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	5.03	100.0	a	524	522
73	N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	4.64	96.4	a	508	506

74	4-chloro-N-{[5-({4-[(2-propoxyethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	4.53	100.0	a	500	498
75	N-{[5-({4-[(1-adamantylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	5.53	100.0	a	563	561
76	4-chloro-N-{[5-({4-[(2-pyridin-2-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.75	99.4	a	519	517
77	4-chloro-N-{[5-({4-[(2-piperidin-1-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.76	98.5	a	525	523
78	4-chloro-N-{[5-({4-[(2-ethylhexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	5.41	99.3	a	526	524
79	4-chloro-N-[(5-{[4-(octylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.57	100.0	a	526	524
80	N-[(5-{[4-(heptylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	5.03	92.0	a	508	506
81	3-methoxy-N-[(5-{[4-(octylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.30	79.5	a	522	520
82	3-methoxy-N-[(5-{[4-(pentylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.37	93.0	a	480	478
83	N-[(5-{[4-(butylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.07	93.3	a	466	464
84	N-[(5-{[4-(dodecylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	6.39	86.7	a	578	576
85	3-methoxy-N-[(5-{[4-(nonylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.63	100.0	a	536	534
86	3-methoxy-N-[(5-{[4-(decylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.90	99.9	a	550	548

87	N-[(5-{[4-(ethylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	2.60	99.9	a	438	436
88	N-{[5-({4-[(2-cyclohexylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.91	92.0	a	520	518
89	N-({5-[(4-{[(1R)-1-cyclohexylethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	4.67	93.0	a	520	518
90	N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.29	95.4	a	504	502
91	3-methoxy-N-{[5-({4-[(2-propoxyethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	4.16	91.3	a	496	494
92	N-{[5-({4-[(1-adamantylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	5.04	100.0	a	558	556
93	N-{[5-({4-[(3,3-diethoxypropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	3.87	89.0	a	512	510
94	3-methoxy-N-{[5-({4-[(3-morpholin-4-ylpropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.30	91.2	a	537	535
95	3-methoxy-N-{[5-({4-[(2-pyridin-2-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.37	94.0	a	515	513
96	3-methoxy-N-{[5-({4-[(2-piperidin-1-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.40	89.7	a	521	519
97	N-{[5-({4-[(2-ethylhexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	5.10	98.4	a	522	520
98	N-[(5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.65	92.9	a	494	492

99	3-methoxy-N-[(5-{[4-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.07	100.0	a	582	580
100	3-methoxy-N-({5-[(4-{[2-(4-methylphenyl)ethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	3.73	100.0	a	528	526
101	3-methoxy-N-({5-[(4-{[(1S,2R)-2-phenylcyclopropyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	3.62	100.0	a	526	524
102	3-methoxy-N-{[5-({4-[(1-naphthylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.66	94.9	a	550	548
103	3-methoxy-N-{[5-({4-[(2-phenylpropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.56	100.0	a	528	526
104	N-({5-[(4-{[2-(4-hydroxyphenyl)ethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	3.02	100.0	a	530	528
105	3-methoxy-N-{[5-({4-[(3-phenylpropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.68	100.0	a	528	526
106	N-{[5-({4-[(2,3-dihydroxypropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	2.42	100.0	a	484	482
107	N-{[5-({4-[(2-hydroxyethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	2.47	58.6	a	454	0
108	N-{[5-({4-[(2-[1,1'-biphenyl]-4-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.48	96.7	a	590	588
109	N-{[5-({4-[([1,1'-biphenyl]-3-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.24	92.6	a	576	574
110	3-methoxy-N-{[5-({4-[(2-thien-2-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.78	92.1	a	520	518

111	4-chloro-N-[(5-{[4-(1,3-thiazol-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.27	93.7	a	497	495
112	4-chloro-N-({5-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	3.66	92.7	a	522	520
113	N-({5-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	3.30	66.2	a	518	516
114	N-{[5-({4-[([1,1'-biphenyl]-4-ylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide	4.51	85.0	a	576	574
115	4-chloro-N-{[5-({4-[(2-{[(trifluoromethyl)sulfonyl]amino}ethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide	4.32	98.0	a	589	587
116	4-chloro-N-[(5-{[4-(propylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide	3.75	100.0	a	457	455
117	4-chloro-N-[(5-{[4-({4-[(trifluoromethyl)sulfonyl]benzyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide	3.77	99.0	b	637	635
118	4-chloro-N-{[5-({4-[(3,4-dihydroxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide	2.91	86.0	b	536	534
119	methyl [{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetate	3.72	97.0	b	570	568
120	tert-butyl [{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetate	4.18	99.0	b	612	610
121	[{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetic acid	3.60	96.0	b	556	554

Example 122 (Protocole L; see Schemes 2 & 7):

Preparation of Ethyl 2-{[4-(hexylamino)piperidin-1-yl]sulfonyl}-5-{[(3-methoxy-benzoyl)amino]methyl}thiophene-3-carboxylate (122)

Diallyl-thiophen-2-ylmethylamine (122a)

A solution of 2-aminomethyl-thiophene (51.4 g, 956 mmol) and *i*-Pr_2NEt (140 g, 1081 mmol) in CH_2Cl_2 (1 l) was placed in a 3-l flask equipped with a condenser and an efficient magnetic agitation. Allyl bromide (115.7 g, 454 mmol) was added, whereupon the moderately exothermic reaction spontaneously reached the reflux temperature after 2 h. The mixture was stirred overnight (16 h), washed ($NaHCO_3$ sat.; brine), dried ($MgSO_4$), and concentrated. The resulting oil was filtered over silica gel (EtOAc:hexane 1:4). The filtrate was concentrated and the filtration was repeated to afford 70.3 g (80%) of the title diallylamine as a brown-yellow oil, clean by NMR: ^1H NMR ($CDCl_3$) δ7.25 (br. d, J = 5.9 Hz, 1H), 6.98 (br. dd, J = 5.1, 2.8 Hz, 1H), 6.94–6.92 (m, 1H), 5.99–5.86 (m, 2H), 5.29–5.18 (m, 4H), 3.85 (s, 2H), 3.16 (dd, J = 6.3, 0.9 Hz, 4H).

5-Diallylaminomethyl-thiophene-2-sulfonyl chloride (122b)

A solution of the allyl-protected thiophene (122a) (6.2 g, 32.1 mmol) in Et_2O was cooled to – 70°C by means of an acetone/dry ice bath. A solution of *t*-BuLi in pentane (21.38 ml, 1.5M, 32.1 mmol) was added over 2 min whereupon the internal temperature momentarily rose to –50°C and the mixture turned orange. After 10 min., SO_2 was bubbled for 2 min, which led to the immediate formation of a thick precipitate. The reaction was allowed to reach 0°C, and a suspension of NCS (4.63 g, 32.1 mmol) in THF (20 ml) was added, whereupon the slurry turned purple. After 45 min at r.t., the mixture was filtered over SiO_2, eluting with EtOAc. Evaporation, dilution with EtOAc:hexane 1:5 and filtration over SiO_2 gave 5.0 g (53%) of the title sulfonyl chloride (122b) as a pale brown oil which was used without further purification.

N,N-Diallyl-*N*-{[5-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)thien-2-yl]methyl}amine (122c)

Procedure A (from the isolated sulfonyl chloride (122b)). A solution of (122b) (5.84 g, 20 mmol) in $CHCl_3$ was cooled to 0°C, and treated with 1,4-dioxa-8-

azaspiro[4,5]decane (2.8 ml, 22 mmol) and Et_3N (4.2 ml, 30 mmol), and warmed to 23 °C for 10 min. Dilution with EtOAc (100 ml), standard work-up ($NaHCO_3$ sat.; brine; $MgSO_4$) and chromatography (EtOAc:cyclohexane 1:2) gave 7.57 g (95%) of the title sulfonamide as a colourless oil.

Procedure B (from **(122a)**, without isolation of the sulfonyl chloride **(122b)**. A solution of the allyl-protected thiophene **(1a)** (29.1 g, 150 mmol) in Et_2O (440 g, 617 ml) was placed in a 1-l three-necked flask (thermometer; argon; septum or SO_2 inlet) and cooled to – 74°C by means of an acetone/dry ice bath. A solution of *t*-BuLi in pentane (100 ml, 1.5M, 150 mmol) was added over 5 min whereupon the internal temperature momentarily rose to –64°C and the mixture turned pink. After 20 min., SO_2 (20 g, 312 mmol) was bubbled over 15 min. The SO_2 consumption was best monitored by placing the SO_2 bottle on a scale during the reaction The reaction mixture, which had turned to a thick, white wax was allowed to warm to room temperature over 2h. A suspension of NCS (30 g, 226 mmol) was added, and stirring was continued overnight, whereupon the slurry turned purple. The mixture was filtered (fritted glass), and the precipitate was carefully washed with CH_2Cl_2 (2 x 300 ml). The combined organic layers were cooled to 0°C under Ar, and treated with a solution of 1,4-dioxa-8-azaspiro[4,5]decane (27.8 g, 194 mmol) and triethylamine (19.7 g, 194 mmol) in CH_2Cl_2 (200 ml). After 1 h, the mixture was washed ($NaHCO_3$ sat.; brine), dried ($MgSO_4$), and concentrated to afford 53 g (83%) of the title sulfonamide as yellow oil: ^{1}H NMR ($CDCl_3$) δ7.36 (d, J = 3.8 Hz, 1H), 6.90 (br. d, J = 3.4 Hz, 1H), 5.92–5.79 (m, 2H), 5.33–5.16 (m, 4H), 3.93 (s, 4H), 3.78 (s, 2H), 3.21 (t, 5.7 Hz, 4H), 3.13 (d, 6.2 Hz, 4H), 1.81 (t, 5.7 Hz, 4H).

Ethyl 5-[(diallylamino)methyl]-2-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)thiophene-3-carboxylate **(122d)**

A solution of the sulfonamide **(122c)** (3.36 g, 8.43 mmol) in THF (120 ml) was cooled to –78°C and treated with *t*-BuLi (7.0 ml, 1.5M in hexane, 10.5 ml). After 5 min, the mixture was canulated into a cooled (–100°C; acetone/liquid N_2) solution of ethyl chloroformate (6.45 ml, 67.5 mmol) in THF (60 ml). The reaction mixture was allowed to warm to –30°C over 2h, and then to 23°C overnight. The mixture was concentrated on a rotary evaporator and diluted with EtOAc (250 ml). Standard work-up (H_2O; brine;

$MgSO_4$) and two chromatographies (EtOAc:cyclohexane 1:4) afforded 1.48 (37%) of the title ethyl ester: ^{1}H NMR (DMSO-*d6*) δ 7.36 (d, 1H), 5.98–5.82 (m, 2H), 5.32–5.17 (m, 4H), 4.33 (q, J = 7.1 Hz, 2H), 3.92 (s, 4H), 3.85 (s, 2H), 3.32 (dd, $J \approx$ 6.0, 5.0 Hz, 4H), 3.17 (d, J = 6.0 Hz, 4H), 1.74 dd, $J \approx$ 6.0, 5.0 Hz, 4H), 1.33 (t, J = 7.2 Hz, 3H).

Ethyl 2-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)-5-{[(3-methoxybenzoyl)amino]-methyl}thiophene-3-carboxylate **(122e)**

A solution of the ethyl ester (**122d**) (1.47 g, 3.12 mmol) and NDMBA (1.07 g, 6.87 mmol) in CH_2Cl_2 (30 ml) was degassed by bubbling argon and sonicating. Then, $Pd(PPh_3)_4$ (216 mg, 0.187 mmol) was added and the mixture was stirred at 23°C. After 2h, the mixture was cooled to –50°C, treated with Et_3N (525 ul, 3.76 mmol) and 3-(methoxy)-benzoyl chloride (300ul, 2.13 mmol), and warmed to r.t. over 30 min. Dilution with EtOAc, standard work-up (H_2O; $NaHCO_3$ sat.; brine; $MgSO_4$) and chromatography (EtOAc:cyclohexane 1:1) afforded 1.0 g (61%) of the title 3-methoxybenzamide: ^{1}H NMR (DMSO-*d6*) 9.29 (t, J = 5.8 Hz, 1H), 7.49–7.34 (m, 4H), 7.12 (ddd, J = 7.9, 2.6, 1.0 Hz, 1H), 4.66 (d, J = 5.7 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 3.84 (s, 4H), 3.80 (s, 3H), 3.24 (dd, $J \approx$ 6.0, 5.0 Hz, 4H), 1.67 (dd, $J \approx$ 6.0, 5.0 Hz, 4H), 1.26 (t, J = 7.0 Hz, 3H). M/Z APCI: 525 (M + 1), 523 (M–1).

Ethyl 5-{[(3-methoxybenzoyl)amino]methyl}-2-[(4-oxopiperidin-1-yl)sulfonyl]-thiophene-3-carboxylate **(122f)**

A solution of the spiroketal (**122e**) (500 mg, 0.953 mmol) in acetone (5 ml) was treated with HCl 1N (2.5 ml) for 18 h at 48°C. Dilution with EtOAc and standard work-up (H_2O; $NaHCO_3$ sat.; brine; $MgSO_4$) gave 425 mg of a 9:1 mixture of the desired title ketone (83%) and of unreacted starting material (9%) (single spot by TLC). ^{1}H NMR ($CDCl_3$) 7.37–7.35 (m, 1H), 7.33–7.29 (m, 3H), 7.05 (ddd, J = 7.7, 2.6, 1.7 Hz, 1H), 6.81 (t, J = 5.8 Hz, 1H), 4.74 (d, J = 6.1 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.70 (t, J = 6.1 Hz, 4H), 2.52 (t, J = 6.2 Hz, 4H), 1.34 (t, J = 7.1 Hz, 3H). M/Z APCI: 481 (M + 1), 479 (M–1).

Ethyl 5-{[(3-methoxybenzoyl)amino]methyl}-2-{[4-(hexylamino)piperidin-1-yl]-sulfonyl}thiophene-3-carboxylate **(122)**

A solution of the ketone (**122f**) (86 mg, 0.18 mmol),n-hexylamine (26 ul, 0.20 mmol), and $NaBH(OAc)_3$ (75 mg, 0.36 mmol) in 1,2-dichloroethane (3 ml) was stirred for 3h at r.t:. Dilution with EtOAc, standard work-up ($NaHCO_3$ sat.; brine; $MgSO_4$) afforded 85 mg (84%) of the desired compound **122** as a white foam.

The below listed compounds (designated as Example No.) were prepared in a similar way by following the above set out protocole and using the corresponding starting compounds.

Example No	Compound Name	Rt HPLC	Purity (%)	Gradient HPLC	Mass M+1	Mass_M
123	N-{[5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}-4-(trimethylsilyl)thien-2-yl]methyl}-3-methoxybenzamide	5.27	93.6	a	566	564
124	N-({5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}-4-[hydroxy(phenyl)methyl]thien-2-yl}methyl)-3-methoxybenzamide	4.73	61.0	a	600	598
125	N-[(4-chloro-5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.56	84.5	a	528	526
126	5-[(3-Methoxy-benzoylamino)-methyl]-2-[4-(4-trifluoromethyl-benzylamino)-piperidine-1-sulfonyl]-thiophene-3-carboxylic acid ethyl ester	4.66	93	a	640	638

Example 127 (Protocole N; see Schemes 1 & 7)

Preparation of N-[(5-{[4-(heptylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxy-benzamide (**127**)

The corresponding 3-Methoxy-*N*-({5-[(4-oxoazepan-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide (**127a**), was prepared according to Example 63 and could be isolated as colourless powder in quantitative yield (693 mg). M/Z APCI: 423.5 (M+1), 421 (M–1).). Anal. HPLC: R.t = 4.97 min (method a).

(**127**) was prepared according to the protocol example 63 and was isolated as colourless solid in 47% yield (12mg). ^{1}H NMR (DMSO-d^6) 9.25 (t, J = 5.8 Hz, 1H), 7.46-7.35 (m, 4H), 7.10 (m, 2H), 4.65 (d, J = 6.0 Hz, 2H), 3.79 (s, 3H), 3.29–3.20 (m, 2H), 3.12 (m,

2H), 2.58 (m, 1H), 2.49 (m, 2H), 1.75 (m, 2H), 1.44-1.22 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H). M/Z APCI: 522.5 (M+1), 520 (M–1).).

Alternatively, **(127)** can be synthesised in a parallel solution phase approach according to the synthesis described for **(63).**

The following compounds (designated as Example No.) were prepared in a parallel fashion according to the above set out protocole.

Example No	Compound Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
128	3-methoxy-N-[(5-{[4-(octylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.38	100.0	a	536	534
129	3-methoxy-N-[(5-{[4-(pentylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.45	100.0	a	494	492
130	N-[(5-{[4-(butylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.14	100.0	a	480	478
131	N-[(5-{[4-(dodecylamino)azepan-1-yl]sulfonyl}-thien-2-yl)methyl]-3-methoxybenzamide	6.44	100.0	a	592	590
132	N-{[5-({4-[(2-cyclohexylethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxy-benzamide	5.01	95.4	a	534	532
133	N-({5-[(4-{[(1R)-1-cyclohexylethyl]-amino}azepan-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxy-benzamide	4.76	100.0	a	534	532
134	N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.83	100.0	a	518	516
135	3-methoxy-N-{[5-({4-[(2-propoxyethyl)amino]-azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	4.22	100.0	a	510	508
136	N-{[5-({4-[(cyclohexylmethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxy-benzamide	4.62	100.0	a	520	518
137	N-{[5-({4-[(1-adamantylmethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxy-benzamide	5.11	100.0	a	572	570
138	3-methoxy-N-{[5-({4-[(3-morpholin-4-ylpropyl)-amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	3.55	100.0	a	551	549
139	3-methoxy-N-{[5-({4-[(2-pyridin-2-ylethyl)amino]-azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.38	100.0	a	529	527
140	3-methoxy-N-{[5-({4-[(2-piperidin-1-ylethyl)-amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	3.44	100.0	a	535	533
141	N-{[5-({4-[(2-ethylhexyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxy-benzamide	5.20	100.0	a	536	534
142	N-({5-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}-	3.32	100.0	a	532	530

	azepan-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide					
143	4-chloro-N-[(5-{[4-(heptylamino)azepan-1-yl]-sulfonyl}thien-2-yl)methyl]benzamide	5.37	100.0	a	526	524
144	4-chloro-N-[(5-{[4-(octylamino)azepan-1-yl]-sulfonyl}thien-2-yl)methyl]benzamide	5.63	100.0	a	540	538
145	4-chloro-N-[(5-{[4-(pentylamino)azepan-1-yl]-sulfonyl}thien-2-yl)methyl]benzamide	4.78	100.0	a	498	496
146	N-[(5-{[4-(butylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.49	10'0	a	484	482
147	4-chloro-N-[(5-{[4-(dodecylamino)azepan-1-yl]-sulfonyl}thien-2-yl)methyl]benzamide	6.66	100.0	a	596	594
148	4-chloro-N-{[5-({4-[(2-cyclohexylethyl)amino]-azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	5.28	95.2	a	538	0
149	N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	4.71	100.0	a	522	520
150	4-chloro-N-{[5-({4-[(2-propoxyethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	4.57	100.0	a	514	512
151	4-chloro-N-{[5-({4-[(2-ethylhexyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	5.44	100.0	a	540	538
152	4-chloro-N-[(5-{[4-(hexylamino)azepan-1-yl]-sulfonyl}thien-2-yl)methyl]benzamide	5.04	100.0	a	512	510
153	3-methoxy-N-[(5-{[4-(hexylamino)azepan-1-yl]-sulfonyl}thien-2-yl)methyl]benzamide	4.77	100.0	a		

Example 154(Protocole D)

Preparation of 4-Chloro-*N*-{[5-({4-[hexyl(pyridin-2-ylmethyl)amino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide **(154)**

A solution of **63** (19.6 mg, 0.039 mmol) and pyridine 2-carbaldehyde (20 ul, 0.210 mmol) in THF (2.5 ml) was treated with $NaBH(OAc)_3$ (90 mg, 0.425 mmol) under argon at reflux over 16h. The mixture was cooled to r.t. and the excess aldehyde was removed with aminomethyl polystyrene resin (160 mg, 0.308 mmol, pre-suspended in 4 ml CH_2Cl_2) for 10 min at 23°C. Dilution with CH_2Cl_2 (10 ml), filtration over cotton-wool, and standard work-up (H_2O; brine; $MgSO_4$) afforded 17.8 mg (77%) of the title tertiary amine as a pale yellow oil.). M/Z APCI : 589 (M+1), 587 (M–1). Anal. HPLC: R.t = 5.00 min (method a, 96% optical purity (254 nM)).

In this protocol, pyridine-2-carbaldehyde could be replaced with other aldehydes, which include (but are not limited to): pyridine-3-carbaldehyde, pyridine-4-carbaldehyde, benzaldehyde, cycohexanecarbaldeyde.

The following compounds were prepared in a parallel fashion according to the above set out protocole (HPLC conditions: C8 Symmetry a- MeCN, 0.09%TFA, 0 to 100% (10min); b MeCN, 0.09%TFA, 0 to 100% (8min); Mass spectrum APCI).

Example No.	Compound Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
155	4-chloro-N-{[5-({4-[(cyclohexylmethyl)(hexyl)-amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.87	64.3	a	594	592
156	N-{[5-({4-[benzyl(hexyl)amino]piperidin-1-yl}-sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	5.53	87.0	a	588	586
157	4-chloro-N-{[5-({4-[hexyl(pyridin-3-ylmethyl)-amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	4.56	77.5	a	589	587
158	4-chloro-N-{[5-({4-[hexyl(pyridin-4-ylmethyl)-amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	4.11	91.3	a	589	587
159	N-{[5-({4-[[(5-bromo-2-furyl)methyl](hexyl)-amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	5.29	90.7	a	658	656
160	N-{[5-({4-[butyl(hexyl)amino]piperidin-1-yl}-sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	5.18	94.4	a	554	552
161	4-chloro-N-{[5-({4-[hexyl(3-phenylpropyl)amino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.61	94.3	a	616	614
162	4-chloro-N-{[5-({4-[hexyl(2-phenylethyl)amino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.47	94.4	a	602	600
163	4-chloro-N-{[5-({4-[hexyl(methyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	5.04	96.2	a	512	510

Example 164 (Protocole B; see Schemes 1 & 8)

Preparation of 4-chloro-N-[(5-{[3-(pentylamino)pyrrolidin-1-yl]-sulfonyl}thien-2-yl)methyl]benzamide **(164)**

4-chloro-*N*-[(5-{[(3*R*)-3-hydroxypyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide, **(164a)**

To a suspension of R-3-pyrrolidinol hydrochloride (530mg, 4.29 mmol) and DIEA (0.75ml, 14.3mmol) in CH_2Cl_2/DMF 1:1 was added a solution of 5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl chloride **(63b)** (1.0g, 2.86 mmol). At the end of addition the suspension disappeared. The reaction mixture was

stirred overnight. 100ml EtOAc were added and the excess of amine was extracted with HCl (1N), followed by washings with brine. The organic layers were dried over $MgSO_4$ and evaporated to dryness to provide (**164a**) (1.14 g, 99.9%) as a colourless foam: H^1 NMR (DMSO *d6*) δ9.34 (t, J = 5.8 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 3.8 Hz, 1H), 7.55 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 3.8 Hz, 1H), 4.95 (d, J = 3.4 Hz, 1H), 4.65 (d, J = 5.6 Hz, 2H), 4.16 (m, 1H), 3.40-3.20 (m, 5H), 3.00 (m, 1H), 3.35-3.23 (m, 3H), 1.80-1.60 (m, 2H), M/Z APCI: 401.2 (M+1), 398.9 (M-1).

4-chloro-N-({5-[(3-oxopyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide, (**164b**)

At –80°C oxalylchloride (36mg, 0.28mmol) was dissolved in dry CH_2Cl_2, while DMSO (50ul, 0.6 mmol) were added slowly. The solution was stirred under Ar for 15minutes. (**164a**) (100mg, 0.25mmol) was dissolved in 2ml CH_2Cl_2, and this solution was added dropwise to the above reaction mixture at –80°C. The reaction was stirred for 15' at low temperature, before DIEA (0.21ml, 1.25mmol) was added. The reaction was stirred at –80°C for 30 minutes and allowed to warm to rt. during 2h. A white solid was formed, the reaction was quenched with water and extracted with CH_2Cl_2 several times. The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The crude was purified by flash chromatography on silica gel using EtOAc/cyclohexane 2:1 as eluent. (**164b**) (80mg, 80%) was obtained as a colourless solid.: H^1 NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 3.8 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 3.8 Hz, 1H), 6.59 (t, J = 5.8, 1H), 4.80 (d, J = 6.0 Hz, 2H), 3.58 (t, J = 7.5 Hz, 2H), 3.50 (s, 3H), 2.54 (t, J = 7.5, 2H), 3.35-3.23 (m, 3H), 2.95 (m, 2H), 1.94 (m, 2H), 1.86 (m, 2H), 1.70-1.50 (m, 5H), 1.30-1.20 (m, 8H), 0.87 (t, J = 6.8, 3H), M/Z APCI 399.0 (M+1), 397.2 (M-1)

4-chloro-N-[(5-{[3-(pentylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide (**164**)

(**164b**) was prepared according to example 63 and was isolated as colourless solid in 84% yield (15mg). M/Z APCI: 522.5 (M+1), 520 (M–1).). Anal. HPLC: R.t = 4.62 min (method a).

Alternatively, (**164**) can be synthesised in a parallel solution phase approach according to the synthesis described for compound **(63).**

The following compounds (designated as Example No.) were prepared in a similar fashion according to the above set out protocole (HPLC conditions: C8 Symmetry a-MeCN, 0.09%TFA, 0 to 100% (10min); b MeCN, 0.09%TFA, 0 to 100% (8min); Mass spectrum APCI).

Example No.	Compound Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
165	N-[(5-{[3-(heptylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.94	88.3	a	494	492
166	3-methoxy-N-[(5-{[3-(octylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.24	100.0	a	508	506
167	3-methoxy-N-[(5-{[3-(pentylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.28	100.0	a	466	464
168	N-[(5-{[3-(butylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	3.97	100.0	a	452	450
169	N-[(5-{[3-(dodecylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	6.34	100.0	a	564	562
170	N-{[5-({3-[(2-cyclohexylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.89	96.5	a	506	504
171	N-({5-[(3-{[(1R)-1-cyclohexylethyl]amino}pyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	4.59	100.0	a	506	504
172	N-{[5-({3-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.23	100.0	a	490	488
173	3-methoxy-N-{[5-({3-[(2-propoxyethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	4.10	100.0	a	482	480
174	N-{[5-({3-[(cyclohexyl-methyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.49	100.0	a	492	490

175	N-{[5-({3-[(1-adamantylmethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.99	100.0	a	544	542
176	3-methoxy-N-{[5-({3-[(3-morpholin-4-ylpropyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.20	100.0	a	523	521
177	3-methoxy-N-{[5-({3-[(2-pyridin-2-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.31	100.0	a	501	499
178	3-methoxy-N-{[5-({3-[(2-piperidin-1-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.32	100.0	a	507	505
179	N-{[5-({3-[(2-ethylhexyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	5.04	100.0	a	508	506
180	N-[(5-{[3-(hexylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.60	95.2	a	480	478
181	4-chloro-N-[(5-{[3-(heptylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.27	96.4	a	498	496
182	4-chloro-N-[(5-{[3-(hexylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.54	100.0	a	512	510
183	4-chloro-N-[(5-{[3-(pentylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.62	95.2	a	470	468
184	N-[(5-{[3-(butylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.36	100.0	a	456	454
185	4-chloro-N-{[5-({3-[(2-cyclohexylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	5.16	96.8	a	510	508
186	N-{[5-({3-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	4.56	85.0	a	494	492
187	4-chloro-N-({5-[(3-{[(1-hydroxycyclohexyl)methyl]amino}pyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	4.80	100.0	a	496	494

188	N-{[5-({3-[(1-adamantylmethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	5.25	100.0	a	548	546
189	4-chloro-N-{[5-({3-[(3-morpholin-4-ylpropyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.59	100.0	a	527	525
190	4-chloro-N-{[5-({3-[(2-pyridin-2-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.68	91.9	a	505	503
191	4-chloro-N-{[5-({3-[(2-piperidin-1-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	3.69	100.0	a	511	509
192	4-chloro-N-{[5-({3-[(2-ethylhexyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	5.36	100.0	a	512	510
193	4-chloro-N-[(5-{[3-(octylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.96	91.6	a	484	482
194	methyl (2S)-1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-(hexylamino)-2-pyrrolidinecarboxylate	3.69	94.0	a	542	540

Example 195 (Protocole C; see Schemee 1 & 2)

Preparation of 3-methoxy-N-{[5-({4-[(pentylamino)methyl]piperidin-1-yl}sulfonyl)-thien-2-yl]methyl}benzamide **(195)**

N-[(5-{[4-(hydroxymethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxy-benzamide, **(195a)**

To a solution of 4-hydroxymethyl-piperidine (499mg, 4.33 mmol) and DIEA (1.5ml, 8.67mmol) in 15 ml CH_2Cl_2 was added slowly a solution of 5-({[1-(3-methoxy-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl chloride (1.0g, 2.89mmol) in CH_2Cl_2/ DMF. The reaction mixture was stirred for overnight. 100ml of EtOAc were added and the excess of amines were removed by extraction with HCl (1N). The dried organic layer was evaporated to dryness to provide 1.25 g (99.9%) of pure **(135a)** as a colour-less foam: H^1 NMR (DMSO *d6*) δ 9.26 (t, J = 5.8 Hz, 1H), 7.55-7.25 (m, 4H), 7.16 (d, J

= 3.8 Hz, 1H), 7.11 (d, J = 9.4 Hz, 1H), 4.66 (d, J = 6.0 Hz, 2H), 4.48 (m, 1H), 3.80 (s, 3H), 3.59 (d, J = 11.7, 2H), 3.31 (b, m, 1H), 3.20 (d, J = 6.0 Hz, 2H), 2.27 (t, J = 11.0 Hz, 2H), 1.72 (d, J = 11.0 Hz, m, 2H), 1.40-1.0 (m, 4H), M/Z APCI: 425.3 (M+1).

3-methoxy-*N*-{[5-({4-[(pentylamino)methyl]piperidin-1-yl}sulfonyl)thien-2-yl]-methyl}benzamide, **(195)**

(195a) (200mg, 0.47mmol) and Triphenylphosphine (247mg, 0.94mmol) were dissolved in dry DMF. To this solution was added at 0°C in small portions N-bromosuccinimide (167mg, 0.94mmol) as a solid. Each portion was added after the yellow color in the solution disappeared. At the end of the addition the yellow color remained and the reaction mixture was heated at 50°C for 90'. The hot reaction is poured into a vial followed by the addition of amylamine (410mg, 4.7mmol). The vial was sealed and heated at 65°C overnight. The reaction mixture was evaporated to dryness and the crude was purified by flash chromatography on silica gel using EtOAc/methanol 10:1 to obtain 180 mg (78%) of **(196)** as a colourless oil. H^1 NMR ($CDCl_3$) δ 7.43-7.25 (m, 4H), 7.05 (m, 2H), 6.75 (m, 1H), 4.82 (d, J = 6.0 Hz, 2H), 3.76 (s, 3H), 3.77 (d, J = 11.7, 2H), 2.63 (d, J = 7.3 Hz, 2H), 2.54 (d, J = 6.8 Hz, 2H), 2.35 (t, J = 11.1, 2H), 1.85 (d, J = 11.1 Hz, m, 2H), 1.70-1.50 (m, 4H), 1.30-1.20 (m, 6H), 0.89 (t, J = 6.8, 3H), M/Z APCI: 494.2 (M+1).

The below listed compounds (desinated as Example No.) were prepared in a similar way by following the above set out protocole and using the corresponding starting compounds (HPLC conditions: C8 Symmetry a- MeCN, 0.09%TFA, 0 to 100% (10min); b MeCN, 0.09%TFA, 0 to 100% (8min); Mass spectrum APCI).

Example No.	Compound Name	Rt HPLC	Purity (%)	Gradient HPLC	Mass M+1	Mass_M
196	N-{[5-({4-[2-(butylamino)ethyl]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	4.33	94.2	a	494	492
197	N-{[5-({4-[(4-butylanilino)methyl]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide	4.44	94.0	b	556	554

Example 198 (Protocole F; see Schemes 2 & 7) :

Preparation of 2-Oxo-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)-sulfonyl]-2-thienyl}methyl)-1,2-dihydro-3-pyridinecarboxamide **(198)**

N-{[5-(1,4-Dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)-2-thienyl]methyl}-2-oxo-1,2-dihydro-3-pyridinecarboxamide **198a**

The bisallylamine **122c** (22.9 g, 57.5 mmol, 1.0 eq), N,N'-dimethylbarbituric acid (NDMBA, 17.9 g, 156.1 mmol, 2.0 eq), and $Pd(PPh_3)_4$ (3.32 g, 2.87 mmol, 0.05 eq) were dissolved in CH_2Cl_2 (250 ml). The solution was degassed by bubbling argon for 10 min, and stirred under Ar at r.t for 15h. Verification by TLC (EtOAc:cyclohexane 1:1) indicated complete cosumption of the starting material. The mixture was evaporated, and redissolved in DMF (150 ml). Then, 2-hydroxynicotinic acid (9.59 g, 69.0 mmol, 1.2 eq), HOBt (9.32 g, 69.0 mmol, 1.8 eq), and EDC (16.5 g, 86.1 mmol, 1.5 eq) were added.

After stirring overnight at r.t., the mixture was concentrated, diluted with EtOAc (500 ml), and rinsed with water (100 ml). The aqeous phase was reextracted twice with ethyl-acetate. The combined organic phases were concentrated, and the crude was redissolved in CH_2Cl_2 (500 ml), before resuming $NaHCO_3$ rinse. The crude was concentrated to give approx 31 g of material, which was dissolved in 80 ml of $CHCl_3$:acetone 2:1. Upon standing for 1 h at r.t., a precipitated appeared, which was filtered and washed (EtOAc:cyclohexane 1:2) to give additional product (6.1 g, 24%). The rest was chor-matographed on the biotage Flash75 (short column, $CHCl_3$:acetone 2:1) to give more product (3.6 g, 14%). Thus, the three products (precipitate 1, precipitate 2, and chro-matographed product) were combined to give a total of 17.9 g (70%) of the desired pyridone as a white solid.

^{1}H NMR (DMSO-*d6*) δ 12.51–12.61 (br. s, 1H), 10.29 (t, J = 6.0 Hz, 1H), 8.36 (dd, J = 7.2, 2.2 Hz, 1H), 7.70–7.75 (br. d, $J \approx$ 4.0 Hz, 1H), 7.47 (d, J = 3.7 Hz, 1H), 7.17 (d, J = 3.7 Hz, 1H), 6.49 (dd, $J \approx$ 7,6 Hz, 1H), 4.53 (d, J = 6.0 Hz, 2H), 3.82 (s, 4H), 3.00 (t, J = 5.7 Hz, 4H), 1.67 (t, J = 5.7 Hz, 4H).

2-Oxo-N-({5-[(4-oxo-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-1,2-dihydro-3-pyridinecarboxamide **(198b)**

A solution of the ketal **198a** (6.0 g, 13.7 mmol) in acetone (60 ml), HCl aq. 1N (30 ml) and conc. aq. formaldehyde (8 ml) was heated to 48 °C for 15h. The mixture was concentrated to a total weight of 46 g, whereupon an orange oil separated out, and CH_2Cl_2 was added (200 ml). The orange oil went in the organic phase, while water (27 ml) separated out and was removed. The CH_2Cl_2 layer was rinsed with a small amount of water (20 ml), dried ($MgSO_4$), and concentrated to afforded the crude ketone as hemiaminal (5.1 g, 88%).

A solution of the hemiaminal (5.1 g, 12 mmol) in acetone (8 ml) and HCl aq. 1N (4 ml) was heated at 49 °C for 15h. The mixture was poured into a separatory funnel containing 200 ml EtOAc, and the aqueous layer was removed. Drying ($MgSO_4$), and concentration afforded 286 mg of the crude pyridinone **198b** (81%) as a white solid very clean by NMR. ^{1}H NMR (DMSO-*d6*) δ 12.57 (s, 1H), 10.27 (t, J = 6.1 Hz, 1H), 8.36 (dd, J = 7.1, 2.2 Hz, 1H), 7.73 (dd, J = 6.3, 2.1 Hz, 1H), 7.52 (d, J = 3.8 Hz, 1H), 7.16 (d, J = 3.7 Hz, 1H), 6.49 (dd, J = 7.1, 6.4 Hz, 1H), 4.72 (d, J = 6.0 Hz, 2H), 3.32 (q, J = 6.2 Hz, 4H), 2.43 (q, J = 6.2 Hz, 4H).

2-Oxo-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-1,2-dihydro-3-pyridinecarboxamide (198)

A suspension of the ketone **198b** (2.33 g, 5.89 mmol, 1.0 eq), 4-(trifluoromethyl)benzylamine (0.98 g, 5.59 mmol, 0.95 eq) and NaBH(OAc)3 (1.62 g, 7.66 mmol, 1.3 eq) in 1,2-dichloroethane (70 ml) was stirred for at r.t. After 3 days, it was poured in CH2Cl2 (600 ml), rinsed with sat. aq. NaHCO3 (100 ml), dried (MgSO4), and concentrated. The colourless oily crude was dissolved in MeOH (100 ml) and treated with 2 ml fuming HCl (pre-diluted with 20 ml MeOH). After 30 seconds, a white precipitate started appearing. This was collected after 10 minutes by filtration to give the desired product as its HCl salt, and in excellent purity (1.6 g, 47% yield). Concentration of the filtrate to 10 ml afforded more precipitate (0.6 g, 17% yield).

Mp = 288–289 °C, ^{1}H NMR (DMSO-*d6*) δ 12.5 (s, 1H), 10.38 (t, J = 6.0 Hz, 1H), 9.90–9.70 (br.s, 1.5H), 8.37 (dd, J = 7.2 & 2.1 Hz, 1H), 7.85–7.70 (m, 5H), 7.48 (d, J = 3.7 Hz, 1H), 7.16 (d, J = 3.8 Hz, 1H), 6.49 (t, J = 6.8 Hz, 1H), 4.73 (d, J = 5.8 Hz, 2H), 4.24–4.16 (br s, 2H), 3.66 (d, J = 11.7 Hz, 2H), 3.20–3.05 (br. m, 1H), 2.39 (t, J = 11.3

Hz, 2H), 2.19 (d, J = 10.7 Hz, 2H), 1.76 (qd, J = 11.5, 3.2 Hz, 2H). ^{19}F NMR (DMSO-*d6*) –61.64.

The following compound was prepared in a similar fashion according to the protocole of example **198** described above :

Example No.	Compound Name	Rt HPLC	Purity (%)	Gradient HPLC	Mass M+1	Mass M
199	N-[(5-{[4-(hexylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-oxo-1,2-dihydro-3-pyridinecarboxamide	3.23	100.0	a	481	479
200	N-[(5-{[4-(hexylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-hydroxybenzamide	4.41	99.0	a	480	478
201	2-hydroxy-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide	4.53	96.0	A	554	552
204	N-[(5-{[4-(hexylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-thioxo-1,2-dihydro-3-pyridinecarboxamide	3.62	99.0	A	497	495
205	2-thioxo-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-1,2-dihydro-3-pyridinecarboxamide	3.75	89	A	571	569
206	N-[(5-{[4-(butylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-oxo-1,2-dihydro-3-pyridinecarboxamide	1.99	97	A	453	451

Example 205 (Protocole G)

Preparation of 3-Methoxy-N-({5-[(4-{methyl[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)-sulfonyl]-2-thienyl}methyl)benzamide (205)

A solution of the hydrochloride salt of 1 (50 mg, 0.08 mmol), DIEA (12 ul, 0.08 mmol), formaldehyde solution 37% aq. (32 ul, 0.4 mmol) and Sodiumcyanoborohydride (10 mg, 0.16 mmol) in THF were heated under reflux for 15h, whereupon complete alkylation took place. The reaction was diluted with DCM and the inorganic salts were extracted with water. The crude was dried over MgSO4, and the solution was evaporated to dryness. The oily residue was taken up in THF, 1N HCl in ether was added slowly

upon which colourless crystalls of compound **205** were formed (yield: 51 mg, 97%). Anal. HPLC: R,t = 4.39 min (method b). M/Z APCI: 582.1 (M+1), 580.4 (M–1).

The following compound was prepared in a similar fashion according to the example 205 described above :

Example No.	Compound Name	Rt HPLC	Purity (%)	Gradient HPLC	Mass M+1	Mass M
206	N-({5-[(4-{ethyl[4-(trifluoromethyl)benzyl]-amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide	4.51	100.0	a	596	594

Example 207: (Protocole H; see Scheme 6)

Preparation of 4-Chloro-N-[(5-{[4-({imino[4-(trifluoromethyl)phenyl]-methyl}-amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide 207

The corresponding 1-[(5-{[(4-Chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]-piperidin-4-ammonium trifluoroacetate 208a was prepared according to the synthesis of 1d. 202a was neutralized before use. 50 mg (0.12 mmol) of **208a** were dissolved in 2 mls DCE. A solution of Trimethylaluminum in toluene (2M, 86 ul, 0.16 mmol) was added at 0°C under Argon. The reaction was stirred for 15 min. at 0°C, followed by 3h at r.t.. A solution of 4-Trifluoromethylbenzonitrile (41 mg, 0.24 mmol) in DCE was added slowly to the above reaction. The reaction was closed and heated at 70°C in an Argon atmosphere for 15h. The reaction vessel was cooled and the solution was diluted with DCE, followed by aqeuous extraction with brine. The organic layer was dried over MgSO4.. The starting material amine was sequestered by means of polymerbound isocyanate (3 eq.). The remaining solution was treated with polymerbound tosylate in order to trap the basic amidine. Rinsing the resins removed quantitatively the starting nitrile. The tosylate resin was ultimately treated with NH3 in MeOH to release the free amidine 208. The later was dissolved in THF, followed by treatment with 1N HCl in ether affording the hydrochlride salt of **207** in pure form (35 mg, 48%). Anal. HPLC: R.t = 3.67 min (method b). M/Z APCI: 585.1 (M+1), 583 (M–1).

Example 208 : Preparation of a pharmaceutical formulation

The following formulation examples illustrate representative pharmaceutical compositions according to the present invention being not restricted thereto.

Formulation 1 – Tablets

A sulfonamide compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ration. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active sulfonamide compound per tablet) in a tablet press.

Formulation 2 – Capsules

A sulfonamide compound of formula I is admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active sulfonamide compound per capsule).

Formulation 3 – Liquid

A sulfonamide compound of formula I (1250 mg), sucrose (1.75 g) and xanthan gum (4 mg) are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously prepared solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added to produce a total volume of 5 mL.

Formulation 4 – Tablets

A sulfonamide compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active sulfonamide compound) in a tablet press.

Formulation 5 – Injection

A sulfonamide compound of formula I is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/ml.

Example 209 : Biological assays

Biological Results

The biological activities of the compounds according to formula I may be assessed using the following *in vitro* and *in vivo* assays.

JNK2 and -3 in vitro assays:

The phosphorylation of c-jun by JNK2 or JNK3 may be followed by monitoring the incorporation of ^{33}P into c-jun following the protocol below. The inhibitory activity of the compounds according to formula I, in respect of c-jun phosphorylation through JNK, is determined by calculating the phosphorylation activity of a JNK in the presence or absence of the test compounds according to formula I.

JNK3 and/or -2 assays are performed in 96 well MTT plates: incubation of 0.5 µg of recombinant, pre-activated GST-JNK3 or GST-JNK2 with 1 µg of recombinant, biotinylated GST-c-Jun and 2 µM $^{33}\gamma$-ATP (2 nCi/µl), in the presence or absence of compounds according to formula I and in a reaction volume of 50 µl containing 50 mM Tris-HCl, pH 8.0; 10 mM $MgCl_2$; 1 mM Dithiothreitol, and 100 µM $NaVO_4$. The incubation is performed for 120 min. at R.T and stopped upon addition of 200 µl of a solution containing 250 µg of Streptavidine-coated SPA beads (Amersham, Inc.)*, 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP, in phosphate saline buffer.
After incubation for 60 minutes at RT, beads are sedimented by centrifugation at 1500 x g for 5 minutes, resuspended in 200 µl of PBS containing 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP and the radioactivity measured in a scintillation β counter, following sedimentation of the beads as described above. By replacing biotinylated GST-c Jun with biotinylated GST-$_1$ATF$_2$ or biotinylated myelin basic protein, this assay may also be used to measure inhibition of pre-activated p38 and ERK MAP Kinases, respectively.

Example No	*JNK3 IC_{50} (μ M)*	*JNK2 IC_{50} (μ M)*
1	< 0.6	nd
63	< 0.6	< 0.6
70	< 0.6	< 0.6
132	< 0.6	nd
155	< 0.6	< 0.6
176	< 0.6	< 0.6
195	< 0.6	< 0.6

The values indicated in respect of JNK2 and 3 refer to the IC_{50} (μM), i.e. the amount necessary to achieve 50% inhibition of JNK3 and JNK2.

The tested compounds according to formula I display an inhibition (IC_{50}) with regard to JNK3 of less than 0.4 μM, more preferred, equal or less than 0.2 μM.

The tested compounds according to formula I display an inhibition (IC_{50}) with regard to JNK2 of less than 0.2 μM, more preferred, equal or less than 0.02 μM.

Compounds of Examples 1, 63, 86, 198 display an inhibition (IC_{50}) with regard to JNK1 of between 0.1-0.7 μM.

Sympathetic Neuron Culture and Survival Assay

The ability of the compounds according to formula I to increase the survival rate of neuronal cells having been induced to cell death was assessed using the following protocol

Sympathetic neurons from superior cervical ganglia (SCG) of new-born rats (p4) are dissociated in dispase, plated at a density of 10^4 cells/cm^2 in 48 well MTT plates coated with rat tail collagen, and cultured in Leibowitz medium containing 5% rat serum, 0.75 µg/mL NGF 7S (Boehringer Mannheim Corp., Indianapolis, IN.) and arabinosine 10^5M. Cell death is induced at day 4 after plating by exposing the culture to medium contain-

ing 10 μg/mL of anti NGF anti-body (Boehringer Mannheim Corp., Indianapolis, IN.) and no NGF or arabinosine, in the presence or absence of sulfonamide inhibitors. 24 hours after cell death induction, determination of cell viability is performed by incubation of the culture for 1 hour, at 37°C in 0.5 mg/mL of 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide (MTT). After incubation in MTT cells are resuspended in DMSO, transferred to a 96 MTT plate and cell viability is evaluated by measuring optical density at 590 nm.

The results of this assay with various test compounds demonstrate that compounds of Formula I are rescuing neurons from cell death (% neurons alive between 10 and 80).

The above assay with test compound (63) demonstrates a rescue rate of 35 % of SCG cells at 3 μM.

Il-2 Release Assay:

The ability of the compounds according to formula I to modulate the inflammatory response by inhibiting the release of IL-2 was assessed using the following protocol

JNK pathway activation triggers the production of inflammatory cytokines such as IL-2. JNK can be activated by external stimuli such as PMA and Ionomycine and IL-2 production can be measured via an IL-2 ELISA test. Comparative measurements with and without the compounds of the invention according to the following protocol measure the ability of the compounds to prevent to stress-mediated IL-2 release.

Jurkat cells, a human T cell leukemia cell line (American Type Culture Collection # TIB 152) were cultured in RPMI 1640 medium (Gibco, BRL) supplemented with 10% of heat-activated fetal calf serum (FCS), Glutamine and Penstrep. The cell suspension in the medium is diluted to give 2.10^6 cells/mL. The cells were plated (2.10^5 cells/well) on a 96-well plate containing different concentrations of a compound according to formula I (final concentration of compounds, 10, 3, 1, 0.3, 0.1 μM). This mixture is incubated 30 minutes at 37°C in a humidified CO_2 atmosphere. Cells were then treated with 10 μl PMA (Phorbolmyristate-13 Acetate-12) + Ionomycine (0.1 μM and 1 μM final concentration) in all wells except negative control. In wells without compounds, 10 μl of RPMI 2% DMSO (=0.1% final) is added. Cells are incubated 24 hours at 37°C and then the

supernatant harvested (freeze at –20°C if not used the same day) prior to performing IL-2 ELISA test on the supernatant.

IL-2 ELISA Assay:

IL-2 release into the medium by (PMA + Ionomycin)-stimulated Jurkat cells, in presence or absence of test compounds may be assayed by ELISA. Following the procedure described below.

Monoclonal anti-human IL-2 antibody (MAB602) (capture), biotinylated anti-human IL-2 antibody (BAF202) (detection) and recombinant human IL-2 (202-IL-010) (standard) from From R&D Systems are used.

Plate preparation

100 µl capture antibody diluted in PBS at 5 µg/mL (PBS- Tween 0.05%) are transferred into a 96 well ELISA plate and incubated overnight at room temperature.

Each well is aspirated and washed 3 times with wash buffer (PBS- Tween 0.05%). After the last wash, the plate is damped.

Assay procedure

1. 100 µl of sample or standard are added (2000, 1000, 500, 250, 125, 62.5, 31.25pg/mL) and incubated 2 hours at room temperature.
2. 3-time-wash
3. 100 µl of biotinylated anti-human IL-2 at 12.5 ng/mL are added and incubated 2 hours at room temperature.
4. 3-time-wash
5. 100 µl streptavidin-HRP (Zymed #43-4323) at 1:10'000 are added and incubate 30 minutes at room temperature.
6. 3-time-wash
7. 100 µl substrate solution (citric acid/ Na_2HPO_4 (1:1) + H_2O_2 1:2000 + OPD) are added and incubated 20-30 minutes at room temperature.
8. 50 µl of stop solution (H_2SO_4 20%) are added to each well.
9. Optical density is measured using a microtiter plate reader set to 450 nm with correction at 570 nm.

The result of this assay shows that various test compounds decrease the production of IL-2 of more than 30% at 3 μM.

For instance compounds (1), (64) and (68) show an IC_{50} value of less 800 nM in this assay.

C-Jun Reporter Assay

The phosphorylation of the transcriptional factor, c-jun, by JNK in the MAP kinase signal transduction pathway can be followed via a trans-reporting system such as the commercially available PathDetect ® **(32).**

Inhibition of phosphorylation by compounds according to formula I can then be assessed.

A trans-reporting system allows one to follow, via Luciferase activity, the activation status of a fusion trans-activator protein. The trans-activator protein consists of the activation domain of the transcriptional factor of interest (c-jun) fused with a yeast transcriptional activator, GAL4 DNA binding domain (dbd). The GAL4 dbd has the advantage that no known mammalian transcriptional factors can bind to it and therefore the background noise of the assay is very low.

In the present case, Hela luciferase reporter-c-Jun (HLR-c-Jun) cell lines which constitutively express GAL4-cJun were used.

The MEKK-1 gene was inserted. MEKK-1 is a MAPKKK which triggers the activation of JNK. Expression of wild type MEKK-1 is sufficient for JNK activation **(33).**

Once, JNK is activated it can induce the phosphorylation of the c-jun domain of the fusion trans-activator protein (GAL4dbd -cJun) which forms a dimer. The dimer is then is able to bind to a GAL4 upstream activating sequence (GAL4 UAS) of the reporter which activates Luciferase expression.

Luciferase expression is detected by luminescence using a simple assay such as Dual-Luciferase ® Reporter Assay System **(34)** in which Renilla is used as a "control reporter".

Inhibition of JNK is observed as a decrease in Luciferase expression and detected by a decrease in luminescence.

Cell culture

HLR-c-Jun cells are cultured in DMEM High Glc supplemented with 10% FCS (Sigma), 2mM Glutamine (Gibco), P/S, Hygromycin b 100μg/mL and G418 250μg/mL.

Cell culture preparation

Cell Banks

The cells are stored frozen in cryotubes under liquid nitrogen, as 1.8 mL volumes of cell suspension in culture medium containing 10% dimethyl sulfoxide.

Cell culture thawing

When necessary, frozen vials of cells are thawed rapidly at 37°C in a water bath by gently swirling up to semi-complete thawing. Then the cell suspension is added to 10 mL of culture medium and then centrifuged for 5 minutes at 1200 rpm. The supernatant is removed and the cell pellet reconstituted in the medium. The flasks are incubated at 37° C in an atmosphere of 5 % CO_2.

Cell passage

The cells are serially sub-cultured (passaged) when 80% confluent monolayers have been obtained.

The medium of each flask is removed and the monolayer is washed with 10-15 mL of phosphate buffer solution (PBS).

Trypsin-EDTA solution is added to the cell monolayer, incubated at 37° C and tapped gently at intervals to dislodge the cells. Complete detachment and disaggregation of the cell monolayer is confirmed by microscopy examination. The cells are then re-suspended in 10 mL of complete medium and centrifuged for 5 minutes at 1200 rpm. The supernatants are discarded, the cells are re-suspended in culture medium and diluted 1/5 in 175 cm^2 flasks.

Day 0 morning

Prepare cells for transfections

The cells of near-confluent cultures are detached and disaggregated by treatment with trypsin as described above.

The cells are re-suspended in culture medium and counted.

The cell suspensions are diluted with medium to give about $3.5x10^6$ cells/mL and 1mL μl of cell suspension are put onto 2 10cm culture dishes containing 9 mL of culture medium.

The plates are incubated at 37° C in a humidified atmosphere of 5 % CO_2 in air.

Day 0 evening

Transfections

Control :0.2μg pTK Renilla, 5.8μg pBluescript KS, 500μl OPTIMEM (GIBCO), 18μl Fugene 6.

Induced :0.1μg pMEKK1, 0.2μg pTK Renilla, 5.7μg pBluescript KS, 500μl OPTIMEM (GIBCO), 18μl Fugene 6 30' RT.

The transfection mixture is added to the plated cells. The plates are incubated over night at 37° C in a humidified atmosphere of 5 % CO_2 in air.

Day 1

A 96 wells plate (100 μl of culture medium per well) is prepared.

Negative control (vehicle): 2μl of DMSO is added to the 100μl (in triplicate).

2 μl of compound according to formula I stock dilutions (3, 1 and 0.1mM in 100% DMSO) are added to the 100μl (in triplicate).

The transfected cells are trypsinised and re-suspended in 12 mL of culture medium.

100μl of the dilution are added to each of the 96 wells plate.

The plate is incubated over night at 37° C in a humidified atmosphere of 5 % CO_2 in air.

Day 2

Test procedure: Dual-Luciferase ® Reporter Assay System **(34).**

The medium is removed from the plate and the cells are washed two times with 100μl PBS. Lysis reagent is applied (Passive Lysis Buffer, PLB). Into each culture well 5μl of 1X PLB are dispensed. The culture plates are placed on a rocking platform or orbital shaker with gentle rocking/shaking to ensure complete coverage of the cell monolayer with 1X PLB. The culture plates are rocked at room temperature for 15 minutes. 20 μl

of the lysate are transferred into a white opaque 96 well plate. The luminometer reading is recorded.

- 50 µl of Luciferase Assay Reagent II are injected and readings are recorded at 5 and 10 minutes.

50µl of Stop & Glo ® Reagent are injected and readings are recorded at 5 and 10 minutes.

The relative luminescence is then measured: RLU Luciferase/RLU Renilla.

The result of this assay shows that various test compounds inhibit more than 20% of the activity of JNK at 10 µM.

For instance compounds (1), (10), (11) or (117) display in this assy an IC_{50} value of less than 0.7 µM.

LPS induced endotoxin shock in mice

The ability of the JNK inhibitors described in formula I to significantly reduce the level of inflammatory cytokines induced by LPS challenge was assessed using the following protocol:

Endotoxins are the lipopolysaccharides (LPS) constituents of the outer membrane of Gram negative bacteria. Response to LPS has been shown to involve the activation of different cell populations and to lead to the expression of various inflammatory cytokines that include tumor necrosis factor-alpha (TNFα) and interferon gamma (IFN-γ).

As LPS is known to stimulate the activation of various MAP kinase pathways, including JNK **(35)**, the ability of JNK inhibitors can be tested after the JNK signaling pathway has been switched on by a LPS challenge.

The activity as JNK inhibitors of compounds of formula may be assessed after a LPS challenge using the following protocol:

LPS (S. abortus-Galanos Lab.-) is injected (200 µg/kg, i.v.) to Male C57BL/6 mice to induce endotoxin shock. Compounds according to formula I (0.1, 1, 10 mg/kg) or NaCl (200uM) are injected intravenously (10 mL/kg) 15 min before the LPS challenge. Heparinized blood was obtained from the orbital sinus at different time points after the LPS challenge, and the blood was centrifuged at 9'000 rpm for 10 min at 4^0 C to collect su-

pernatant. Measurement of cytokines production such as TNFα and IFNγ by mouse is performed with an ELISA kit such as Duoset ® DY410 for TNFα and DY 485 for IFN γ. Other ELISA assays such as described in **(36)** can be used.

Thus, the compound of Example (63) shows an inhibition of IFN γ production of 65% at 1 mg/kg and 40 % inhibition of TNFα production at 10 mg/kg.

Global Ischemia in Gerbils

The ability of the JNK inhibitors described in formula I to protect cell death during a stroke event was assessed using the following protocol:

The gerbil bilateral carotid occlusion is a well-described animal model of acute ischemic stroke and involves relatively easy surgical techniques.

The neuronal degeneration in the hippocampus develops over several days and is often referred as "delayed neuronal death". In addition, the neurodegeneration observed histologically is obvious and easily quantified **(37).** Furthermore, the histopathology seen in the gerbil is similar to that observed in the hippocampal CA1 region of the human brain following a cardiac arrest. Behavior observations, such as memory tests, could even be performed in the case of gerbils. This kind of tests for appreciation of the degree of recovery is not easily manageable in other models such as in rat whose learning abilities are much poorer **(38).**

The neuroprotective effect according to formula I to protect may be assessed using the gerbil global ischemia model and such a protocol:

-1- METHOD

* Surgery

- Anesthesia with isoflurane (0.5-4%).
- The common carotid arteries (left and right) are freed from tissue.
- Occlusion of the arteries using Bulldog microclamps during 5 min.
- Removal of clamps (reperfusion)
- Stabulation of the animals under heating lamp until awake.
- Stabulation of the animals in the animalry in individual cages.

* Sacrifice of the animals

- 7 days after ischemia (Decapitation or overdose of pentobarbital).
- Sampling of the brain.

* Histological parameters

- Freezing of the brain in isopentane (-20°C)
- Slicing of the hippocampus using a cryo-microtome (20 μm).
- Staining with cresyl violet method
- Evaluation of the lesions (in CA1/CA2 subfields of the hippocampus) by a modified Gerhard & Boast score **(39).**

-2- TREATMENT

- Administration of the compound according to formula I or the vehicle: 15 min, 24 hours and 48 hours after reperfusion (5-10 min after the recovery of the anesthesia).
- Standard protocol

50 animals : 5 groups of 8 (group A : control, groups B-D : test article at 3 doses and group E : reference compound (Orotic acid 3x300 mg/kg, *ip*).

Thus, the compound of Example (68) shows an inhibition of global ischemia of 64% (% inhibition of total lesion) at 80 mg/kg.

Solubility of compounds of formula (I)

The compounds have been assessed in respect of their solubility in water, at a pH of 7.4 at room temeprature. In general the solubility of compounds of formula (I) is in a range of at least 50 μg/mL solvent, more preferably of at least 100 μg/mL solvent. For instance compounds (63), (163), (198) display a solubility in water of at least 200 μg/mL solvent.

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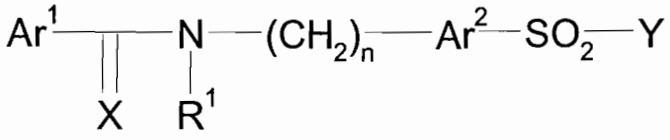
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Claims

1. Sulfonamide derivatives according to formula I

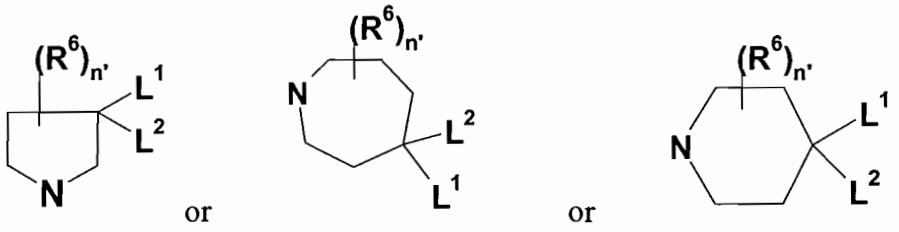


I

with its geometrical isomers, in an optically active form as enantiomers, diastereomers, as well as in the form of racemates, as well as pharmaceutically acceptable salts thereof, wherein

Ar^1 and Ar^2 are independently from each other aryl or heteroaryl,
X is O or S;
R^1 is hydrogen or a C_1-C_6-alkyl group, or R^1 forms a 5-6-membered saturated or unsaturated ring with Ar^1;
n is an integer from 0 to 5;

Y is a pyrrolidine, an azepan or a piperidine moiety of the below formulae



or or

whereby R^6 is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo (=O), sulfoxy, acyloxy, thioalkoxy and where R^6 is not hydrogen, n' is an integer from 0 to 4, whereby at least one of L^1 and/or L^2 is an ionisable moiety selected from an amine to which a lipophilic chain selected from optionally substituted C_4-C_{18}-alkyl groups or a substituted or unsubstituted alkyl-aryl group is attached.

2. A sulfonamide derivative according to any of the preceding claims, wherein Ar^1 and Ar^2 are independently selected from the group consisting of phenyl, thienyl, furyl, pyrrolo, pyridyl, optionally substituted by C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, C_1-C_6-

alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfonyl, C_1-C_6-thioalkoxy.

3. A sulfonamide derivative according to claim 2, wherein Ar^1 is a phenyl.

4. A sulfonamide derivative according to any of the preceding claims, wherein Ar^2 is a thienyl or furanyl group.

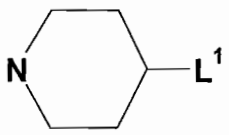
5. A sulfonamide derivative according to any of the preceding claims, wherein Ar^1 is selected from a halogenophenyl, nitrophenyl, hydroxyphenyl, alkoxyphenyl, pyridyl, 3,4,-dihydroxyphenyl, thioxo-dihydropyridine or its tautomer, pyrazole and X is O, R^1 is hydrogen, n is 1, Ar^2 is thienyl or furanyl.

6. A sulfonamide derivative according to claims 1 to 5 wherein n is 1.

7. A sulfonamide derivative according to any of claims 1 to 6, wherein R^6 is H, L^2 is H, L^1 is $-NR^{3'}R^3$; where at least one of $R^{3'}$ and R^3 is not hydrogen, but a substituent selected from the group consisting of straight or branched C_4-C_{18}-alkyl, aryl-C_1-C_{18}-alkyl, heteroaryl-C_2-C_{18}-alkyl, C_1-C_{14}-alkyl substituted with a C_3-C_{12}-cycloalkyl or -bicyclo or -tricyloalkyl, and whereby said alkyl chain may contain 1-3 O or S atoms.

8. A sulfonamide derivative according to claim 7, wherein L^1 is $-NHR^3$; where R^3 is a straight or branched C_4-C_{12}-alkyl, preferably a C_6-C_{12}-alkyl, optionally substituted with a cyclohexyl group or a benzyl group.

9. Sulfonamide derivatives according to claim 8, wherein Y is a piperidine group



L^1 is $-NHR^3$; where R^3 is a straight or branched C_6-C_{12}-alkyl, preferably a C_8-C_{12}-alkyl, or a benzyl group.

10. A sulfonamide derivative according to any of the preceding claims selected from the following group :

4-chloro-N-[(5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-Methoxy-N-{[5-({4-[(4-trifluoromethylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-[(5-{[4-(1,3-thiazol-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-[(5-{[4-(heptylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-[(5-{[4-(pentylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-[(5-{[4-(butylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(dodecylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-{[5-({4-[(2-cyclohexylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[(cyclohexylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-({5-[(4-{[(1R)-1-cyclohexylethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

4-chloro-N-{[5-({4-[(2-propoxyethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(1-adamantylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({4-[(2-pyridin-2-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[(2-piperidin-1-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[(2-ethylhexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-({5-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-[(5-{[4-(octylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(heptylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
3-methoxy-N-[(5-{[4-(octylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
3-methoxy-N-[(5-{[4-(pentylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
N-[(5-{[4-(butylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
N-[(5-{[4-(dodecylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

N-{[5-({4-[(2-cyclohexylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-({5-[(4-{[(1R)-1-cyclohexylethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

3-methoxy-N-{[5-({4-[(2-propoxyethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(1-adamantylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[(3,3-diethoxypropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(3-morpholin-4-ylpropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-methoxy-N-{[5-({4-[(2-pyridin-2-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(2-piperidin-1-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(2-ethylhexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-({5-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
N-[(5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
N-[(5-{[4-(heptylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
3-methoxy-N-[(5-{[4-(octylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-methoxy-N-[(5-{[4-(pentylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
N-[(5-{[4-(butylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

N-[(5-{[4-(dodecylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
N-{[5-({4-[(2-cyclohexylethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-({5-[(4-{[(1R)-1-cyclohexylethyl]amino}azepan-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

3-methoxy-N-{[5-({4-[(2-propoxyethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(cyclohexylmethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[(1-adamantylmethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

3-methoxy-N-{[5-({4-[(3-morpholin-4-ylpropyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-methoxy-N-{[5-({4-[(2-pyridin-2-ylethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(2-piperidin-1-ylethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(2-ethylhexyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-({5-[(4-{[3-(1H-imidazol-1-yl)propyl]amino}azepan-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
4-chloro-N-[(5-{[4-(heptylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(octylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(pentylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(butylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

4-chloro-N-[(5-{[4-(dodecylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-{[5-({4-[(2-cyclohexylethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

4-chloro-N-{[5-({4-[(2-propoxyethyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[(2-ethylhexyl)amino]azepan-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-[(5-{[4-(hexylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(hexylamino)azepan-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
3-methoxy-N-[(5-{[4-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-methoxy-N-({5-[(4-{[2-(4-methylphenyl)ethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

3-methoxy-N-({5-[(4-{[(1S,2R)-2-phenylcyclopropyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

3-methoxy-N-{[5-({4-[(1-naphthylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(2-phenylpropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-({5-[(4-{[2-(4-hydroxyphenyl)ethyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(3-phenylpropyl)amino]piperidin-1-yl}sulfonyl)thien-2-

yl]methyl}benzamide

N-{[5-({4-[(2,3-dihydroxypropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[(2-hydroxyethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-[(5-{[4-(nonylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
3-methoxy-N-[(5-{[4-(decylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
3-methoxy-N-[(5-{[4-(ethylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
N-{[5-({4-[(2-[1,1'-biphenyl]-4-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[([1,1'-biphenyl]-3-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(2-thien-2-ylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-[(5-{[4-({4-[(trifluoromethyl)sulfonyl]benzyl}amino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-methoxy-N-{[5-({4-[(quinolin-4-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[([1,1'-biphenyl]-4-ylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide

4-chloro-N-{[5-({4-[(2-{[(trifluoromethyl)sulfonyl]amino}ethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide

4-chloro-N-[(5-{[4-(propylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide
4-chloro-N-[(5-{[4-({4-[(trifluoromethyl)sulfonyl]benzyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-{[5-({4-[(3,4-dihydroxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
methyl [{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetate
tert-butyl [{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetate
[{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetic acid
N-[(5-{[3-(heptylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
3-methoxy-N-[(5-{[3-(octylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
3-methoxy-N-[(5-{[3-(pentylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
N-[(5-{[3-(butylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-

methoxybenzamide

N-[(5-{[3-(dodecylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
N-{[5-({3-[(2-cyclohexylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-({5-[(3-{[(1R)-1-cyclohexylethyl]amino}pyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
N-{[5-({3-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

3-methoxy-N-{[5-({3-[(2-propoxyethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({3-[(cyclohexylmethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({3-[(1-adamantylmethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({3-[(3-morpholin-4-ylpropyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-methoxy-N-{[5-({3-[(2-pyridin-2-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({3-[(2-piperidin-1-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({3-[(2-ethylhexyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-[(5-{[3-(hexylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
4-chloro-N-[(5-{[3-(heptylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-[(5-{[3-(hexylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-[(5-{[3-(pentylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
N-[(5-{[3-(butylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
4-chloro-N-{[5-({3-[(2-cyclohexylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({3-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

4-chloro-N-({5-[(3-{[(1-hydroxycyclohexyl)methyl]amino}pyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-{[5-({3-[(1-adamantylmethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({3-[(3-morpholin-4-ylpropyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({3-[(2-pyridin-2-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({3-[(2-piperidin-1-ylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({3-[(2-ethylhexyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-[(5-{[3-(octylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
methyl (2S)-1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-(hexylamino)-2-pyrrolidinecarboxylate
3-methoxy-N-{[5-({4-[(pentylamino)methyl]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[2-(butylamino)ethyl]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[(4-butylanilino)methyl]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
4-chloro-N-{[5-({4-[hexyl(methyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[(cyclohexylmethyl)(hexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({4-[benzyl(hexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({4-[hexyl(pyridin-3-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[hexyl(pyridin-4-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[hexyl(pyridin-2-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({4-[butyl(hexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({4-[hexyl(3-phenylpropyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
4-chloro-N-{[5-({4-[hexyl(2-phenylethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[[(5-bromo-2-furyl)methyl](hexyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide
3-methoxy-N-({5-[(4-{methyl[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide

4-chloro-N-{[5-({4-[(3-chlorobenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

3-methoxy-N-{[5-({4-[(3-methylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-methoxy-N-{[5-({4-[(4-propylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-({5-[(4-{[3-(trifluoromethyl)benzyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

3-methoxy-N-({5-[(4-{[4-(trifluoromethoxy)benzyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-({5-[(4-{[4-(difluoromethoxy)benzyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(2,3,4,5,6-pentamethylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-methoxy-N-{[5-({4-[(4-propoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(4-butoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(4-methoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(pyridin-4-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(pyridin-2-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-{[5-({4-[(pyridin-3-ylmethyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
N-{[5-({4-[(4-tert-butylbenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
N-{[5-({4-[(3-ethoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(4-phenoxybenzyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
3-methoxy-N-[(5-{[4-({4-[(trifluoromethyl)sulfanyl]benzyl}amino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-methoxy-N-({5-[(4-{[4-(methylsulfonyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
N-({5-[(4-{[3,5-bis(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

N-({5-[(4-{[2,5-bis(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

N-({5-[(4-{[4-(ethylsulfanyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

3-methoxy-N-[(5-{[4-({3-[(trifluoromethyl)sulfanyl]benzyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

N-({5-[(4-{[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

N-{[5-({4-[(4-iodobenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
N-({5-[(4-{[4-(benzyloxy)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

N-{[5-({4-[(mesitylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
N-{[5-({4-[(4-chlorobenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
N-{[5-({4-[(4-ethylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
3-methoxy-N-{[5-({4-[(4-pentylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
3-methoxy-N-[(5-{[4-({1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

3-methoxy-N-{[5-({4-[(4-methylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
N-{[5-({4-[(4-butylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
N-{[5-({4-[(4-isopropylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide

N-{[5-({4-[(4-isobutylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide
N-({5-[(4-{[(1-hydroxy-1lambda~5~-pyridin-4-yl)methyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

N-{[5-({4-[(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide

N-{[5-({4-[(2,3-dihydro-1-benzofuran-5-ylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-3-methoxybenzamide

4-chloro-N-{[5-({4-[(4-propylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
4-chloro-N-({5-[(4-{[4-(trifluoromethoxy)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
4-chloro-N-({5-[(4-{[4-(difluoromethoxy)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
4-chloro-N-{[5-({4-[(4-propoxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
N-{[5-({4-[(4-butoxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({4-[(4-quinolinylmethyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
N-{[5-({4-[(4-tert-butylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-4-chlorobenzamide
4-chloro-N-{[5-({4-[(4-phenoxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide

4-chloro-N-[(5-{[4-({4-[(trifluoromethyl)sulfanyl]benzyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
3-methoxy-N-({5-[(4-{[2-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
3-methoxy-N-[(5-{[4-({[6-(trifluoromethyl)-3-pyridinyl]methyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

N-[(5-{[4-(benzylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-3-methoxybenzamide
3-methoxy-N-[(5-{[4-({1-[4-(trifluoromethyl)phenyl]propyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

3-methoxy-N-[(5-{[4-({1-methyl-1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-[(5-{[4-({1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-[(5-{[4-({1-methyl-1-[4-(trifluoromethyl)phenyl]ethyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-[(5-{[2-({[4-(trifluoromethyl)benzyl]amino}methyl)-1-pyrrolidinyl]sulfonyl}-2-thienyl)methyl]benzamide

4-chloro-N-[(5-{[(3R)-3-({[4-(trifluoromethyl)benzyl]amino}methyl)pyrrolidinyl]sulfonyl}-2-thienyl)methyl]benzamide
4-chloro-N-({5-[(3-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide
4-chloro-N-{[5-({3-[(hexylamino)methyl]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}benzamide
4-chloro-N-({5-[(3-{[4-(trifluoromethyl)benzyl]amino}-1-pyrrolidinyl)sulfonyl]-2-thienyl}methyl)benzamide
4-chloro-N-{[5-({(3R)-3-[(hexylamino)methyl]pyrrolidinyl}sulfonyl)-2-thienyl]methyl}benzamide

4-chloro-N-[(5-{[3-({[4-(trifluoromethyl)benzyl]amino}methyl)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

2-oxo-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-1,2-dihydro-3-pyridinecarboxamide

N-[(5-{[4-(hexylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-oxo-1,2-dihydro-3-pyridinecarboxamide
N-[(5-{[4-(hexylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-hydroxybenzamide
2-hydroxy-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)benzamide

N-[(5-{[4-(hexylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-thioxo-1,2-dihydro-3-pyridinecarboxamide

2-thioxo-N-({5-[(4-{[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-1,2-dihydro-3-pyridinecarboxamide

N-[(5-{[4-(butylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-oxo-1,2-dihydro-3-pyridinecarboxamide

N-({5-[(4-{ethyl[4-(trifluoromethyl)benzyl]amino}-1-piperidinyl)sulfonyl]-2-thienyl}methyl)-3-methoxybenzamide

4-chloro-N-[(5-{[4-({imino[4-(trifluoromethyl)phenyl]methyl}amino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]benzamide

1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-(hexylamino)proline

ethyl 2-{[4-(hexylamino)piperidin-1-yl]sulfonyl}-5-{[(3-methoxybenzoyl)amino]methyl}thiophene-3-carboxylate

N-{[5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}-4-(trimethylsilyl)thien-2-yl]methyl}-3-methoxybenzamide

N-({5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}-4-[hydroxy(phenyl)methyl]thien-2-yl}methyl)-3-methoxybenzamide

5-[(3-Methoxy-benzoylamino)-methyl]-2-[4-(4-trifluoromethyl-benzylamino)-piperidine-1-sulfonyl]-thiophene-3-carboxylic acid ethyl ester

N-[(4-chloro-5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

11. A sulfonamide derivative according to any of the preceding claims for use as a medicament.

12. Use of a sulfonamide derivative according to any of claims 1-10 for the preparation of a medicament for the treatment of a neuronal disorder selected from epilepsy, Alzheimer's disease, Huntington's disease, Parkinson's disease, retinal diseases, spinal cord injury, Multiple Sclerosis, head trauma and ischemia, an autoimmune disease selected from inflammatory bowel disease (IBD), rheumatoid arthritis, asthma, septic shock, transplant rejection, a cancer selected from breast-, colorectal-, pancreatic, ovarian, prostate, testicular, hepatic, kidney, lung cancer, a cardiovascular disease including stroke, arterosclerosis, myocordial infarction, myocordial reperfusion injury and an ischemic condition including heart, renal, kidney and brain reperfusion injuries, renal failure.

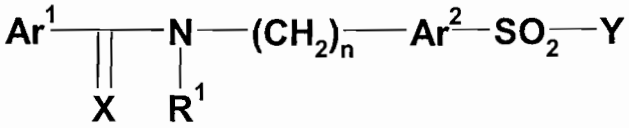
13. Use of a sulfonamide derivative according to to claim 12, for the modulation of the JNK pathway.

14. Use according to claim 13 for the treatment or prevention of disorders associated with the abnormal expression or activity of JNK.

15. Use according to claim 14 for the treatment or prevention of disorders associated with abnormal expression or activity of JNK2 and/or JNK3.

16. A pharmaceutical composition containing at least one sulfonamide derivative according to any of the claims 1 to 10 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

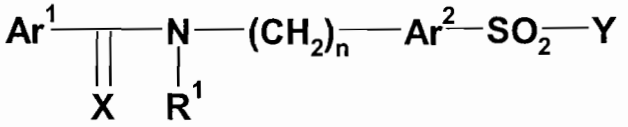
17. Process for the preparation of a sulfonamide derivative according to any of claims 1 to 10, whereby a sulfonamide of formula (XIX)



(XIX)

wherein Ar^1, Ar^2, X, R^1, R^2 and n are as above defined and Y is a pyrrolidine-3-one or a piperidine 4-one, is subjected to a reductive amination using an amine H_2N-R^3 with R^3 being as above defined.

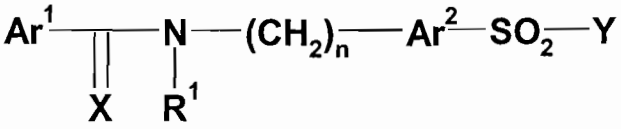
18. Process for the preparation of a sulfonamide derivative according to any of claims 1 to 10, wherein a sulfonamide of formula (XIX)



(XIX)

whereby Ar^1, Ar^2, X, R^1, R^2 and n are as above defined and Y is a pyrrolidine-3-amine or a piperidine 4-amine, is reacted with an aldehyde R^3-CHO of the formula (Xa) with R^3 being as above defined.

19. Sulfonamide compounds of formula (XIX)



(XIX)

wherein

Ar^1 and Ar^2 are independently from each other aryl or heteroaryl,

X is O or S;

R^1 is hydrogen or a C_1-C_6-alkyl group,

n is an integer from 0 to 5, and

Y is a pyrrolidine-3-one, a piperidine 4-one, pyrrolidine-3-amine or a piperidine 4-amine.