(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/23378 A1

(51) International Patent Classification[7]: C07D 409/12, 333/34, 333/36, 413/12, 495/04, 471/04, 409/14, 405/12, A61K 31/496, 31/445 // (C07D 495/04, 333:00, 221:00)

(21) International Application Number: PCT/IB00/01380

(22) International Filing Date:
28 September 2000 (28.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99810869.0 28 September 1999 (28.09.1999) EP

(71) Applicant *(for all designated States except US)*: **APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.** [NL/NL]; Pietermaai 15, Curacao (AN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ARKINSTALL, Stephen** [GB/FR]; La Bergerie/Les Goths, F-74350 Cruseilles (FR). **HALAZY, Serge** [FR/FR]; 3, allée des Jonquilles, F-74100 Vetraz-Monthoux (FR). **CHURCH, Dennis** [US/CH]; 4, chemin des Vignes, CH-1291 Commugny (CH). **CAMPS, Montserrat** [ES/CH]; 7, chemin du Pré-Colomb, CH-1290 Versoix (CH). **RUECKLE, Thomas** [DE/CH]; 142A, route de St. Julien, CH-1228 Plan-les-Ouates (CH). **GOTTELAND, Jean-Pierre** [FR/FR]; 423, chemin des Crets, F-74160 Beaumont (FR). **BIAMONTE, Marco** [US/CH]; 13, rue St. Joseph, CH-1227 Carouge (CH).

(74) Agents: **MOINAS, Michel** et al.; Moinas Savoye & Cronin, 42, rue Plantamour, CH-1201 Geneva (CH).

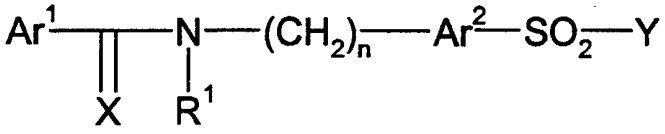
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICALLY ACTIVE SULFONAMIDE DERIVATIVES



(I)

(57) Abstract: The present invention is related to sulfonamide derivatives of formula (I) notably for use as pharmaceutically active compounds, as well as to pharmaceutical formulations containing such sulfonamide derivatives. Said sulfonamide derivatives are efficient modulators of the JNK pathway, they are in particular efficient and selective inhibitors of JNK 2 and 3. The present invention is furthermore related to novel sulfonamide derivatives as well as to methods of their preparation. The compounds of formula (I) according to the present invention being suitable pharmaceutical agents are those wherein Ar^1 and Ar^2 are independently from each other substituted or unsubstituted aryl or heteroaryl groups, X is O or S, preferably O; R^1 is hydrogen or a C_1-C_6-alkyl group, or R^1 forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar^1; n is an integer from 0 to 5, preferably between 1-3 and most preferred 1; Y within formula (I) is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula (I) thus providing a sulfonamide.

WO 01/23378 A1

Pharmaceutically Active Sulfonamide Derivatives

Field of the invention

The present invention is related to sulfonamide derivatives for use as pharmaceutically active compounds, as well as pharmaceutical formulations containing such sulfonamide derivatives. In particular, the present invention is related to sulfonamide derivatives displaying a substantial modulatory, notably an inhibitory activity of the JNK (Jun-Kinase) function or pathways respectively, and which are therefore particularly useful in the treatment and/or prevention of disorders of the autoimmune and the neuronal system. The present invention is furthermore related to novel sulfonamide derivatives as well as to methods of their preparation.

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).

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 activa-tion 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.

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 JNK1 and 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 JNK1 and JNK2.

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 biosynthesis 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.

Hence, it is an objective of the present invention to provide relatively small molecules that avoid essentially all of the above-mentioned drawbacks arising from the use of peptides or proteins, however, which are suitable for the treatment of a variety of diseases, in particular of neuronal or the autoimmune system related disorders. It is notably an objective of the present invention to provide relatively small molecule chemical compounds which are able to modulate, preferably to down-regulate or to inhibit the JNK (Jun kinase) pathway so to be available as a convenient method of treating diseases which are preferably mediated by the JNK function. Moreover, it is an objective of the present invention to provide methods for preparing said small molecule chemical compounds. It is furthermore an objective of the present invention to provide a new category of pharmaceutical formulations for the treatment of diseases, preferably 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 and terms 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.

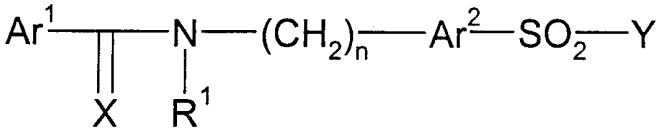
"Pharmaceutically acceptable salts or "complexes" refers to salts or complexes of the below-identified compounds of formula I that retain the desired biological activity. Examples of such salts include, but are not restricted to acid addition salts formed with inorganic acids (e.g. hydrochloric acid,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

"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 JunK2 and/or 3 inhibitors.

Quite surprisingly, it was now found that sulfonamide derivatives according to formula I are suitable pharmaceutically active agents, by effectively modulating, in particular by down-regulating inhibiting the action of JNK's, notably of JNK 2 and/or 3.



I

The compounds of formula I according to the present invention being suitable pharmaceutical agents are those wherein

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

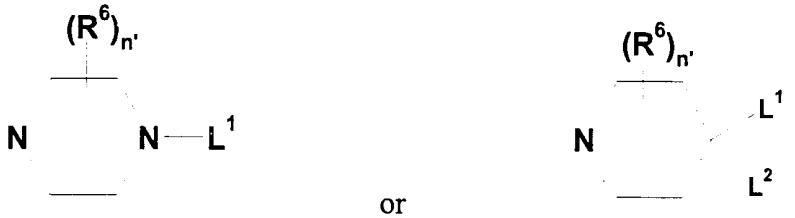
X is O or S, preferably O;

R^1 is hydrogen or a C_1-C_6-alkyl group, preferably H, or R^1 forms a substituted or unsubstituted 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 formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing the sulfonamide.

In a preferred embodiment of the present invention, Y is a piperidine or piperazine moiety according to the below formula



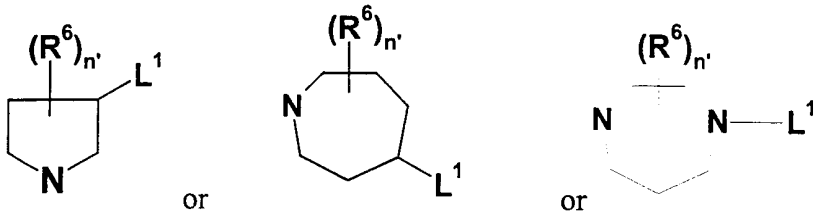
or

In said piperidine or piperazine groups, L^1 and $L^2$are independently selected from each other from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, substituted or unsubstituted cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L^1 and L^2 are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl, -C(O)-OR^3, -C(O)-R^3, -C(O)-$NR^{3'}R^3$, -$NR^{3'}R^3$, -$NR^{3'}C(O)R^3$, -$NR^{3'}C(O)NR^{3'}R^3$, -(SO)R^3, -(SO_2)R^3, -NSO_2R^3, -$SO_2NR^{3'}R^3$.

Thereby, R^3 and $R^{3'}$ are substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl-C_1-C_6-alkyl, substituted or unsubstituted heteroaryl-C_1-C_6-alkyl.

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 n' is an integer from 0 to 4, preferably 1 or 2.

According to a further preferred embodiment of the present invention, Y is a pyrrolidine, an azepan or a 1,4-diazepan moiety of the below formulas



In said moieties, L^1 is selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, substituted or unsubstituted cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L^1 and L^2 are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl, -C(O)-OR^3, -C(O)-R^3, -C(O)-$NR^{3'}R^3$, -$NR^{3'}R^3$, -$NR^{3'}C(O)R^3$, -$NR^{3'}C(O)NR^{3'}R^3$, -(SO)R^3, -(SO_2)R^3, -NSO_2R^3, -$SO_2NR^{3'}R^3$.

Thereby, R^3 and $R^{3'}$ are substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl-C_1-C_6-alkyl, substituted or unsubstituted heteroaryl-C_1-C_6-alkyl.

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 n' is an integer from 0 to 4, preferably 0.

Most preferred azepan or a 1,4-diazepan moieties are those wherein , L^1 is -$NR^{3'}R^3$, with R^3 being hydrogen and $R^{3'}$ being a C_1-C_{12}, preferably C_4-C_6-alkyl which is optionally substituted with cycloalkyl, aryl or heteroaryl group.

All of the above mentioned aryl or heteroaryl groups could optionally be substituted by at least one of the groups selected from substituted or unsubstituted C_1-C_6-alkyl,like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, acyloxy, substituted or unsub-

stituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfonyl, sulfoxy, C_1-C_6-thioalkoxy.

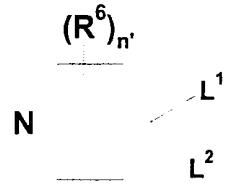
Also L^1 and L^2 taken together could form a 4-8-membered saturated cyclic alkyl or heteroalkyl group, like triazolines, tetrazolines, oxazolines, isoxazolines, oxazoles or isoxazoles. In a preferred embodiment L^1 and L^2 form together 5-6-membered saturated cyclic alkyl ring containing 2-3 nitrogen atoms.

The present invention also includes the geometrical isomers, the optical 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, 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, e.g. a 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.

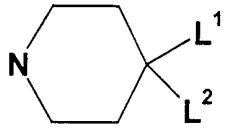
Where Ar^1 is a 4-chlorophenyl, nitrophenyl, hydroxyphenyl, alkoxy phenyl, pyridyl, 3,4,-dihydroxyphenyl, thioxo-dihydropyridine or its tautomer, pyrazole group, X is preferably O, R^1 is hydrogen, n is 1 and Ar^2 is thienyl or furanyl.

A particularly preferred embodiment of the present invention is related to the sulfonamide derivatives, wherein Y is a substituted or unsubstituted piperidine residue,



whereby R^6, n', L^1 and L^2 are as above defined.

In a more preferred embodiment of the sulfonamide derivatives according to formula I, Ar^1 is 4-chlorophenyl, X is O, R^1 is hydrogen, n is 1, Ar^2 is thienyl, Y is



whereby L^2 is H and L^1 is a 5-membered cyclic group containing 3 heteroatoms, preferably a triazole ring, being preferably fused with a substituted or unsubstituted aryl group, e.g. a benzotriazole; or L^2 is -C(O)-R^3, or -NHR^3.

Thereby, R^3 is a substituent selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl-C_1-C_6-alkyl, substituted or unsubstituted heteroaryl-C_1-C_6-alkyl.

Said aryl or heteroaryl groups may optionally be substituted by halogen, hydroxy, nitro, sulfonyl, e.g. a trifluoromethylsulfonyl group.

Specific examples of compounds of formula I include the following :

4-chloro-*N*-[5-(piperazine-1-sulfonyl)-thiophen-2-yl-methyl]-benzamide

4-Chloro-N-{5-[4-(3-Trifluoromethanesulfonyl-phenylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

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

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

4-chloro-N-{[5-({4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

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

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

4-chloro-N-[(5-{[4-(4-hydroxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide_

4-chloro-N-[(5-{[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

4-chloro-N-[(5-{[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

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

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

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

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

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

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

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

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

4-chloro-N-{[5-({4-[4-chloro-3-(trifluoromethyl)phenyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

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

4-chloro-N-[(5-{[4-(6-methylpyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

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

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

4-chloro-N-[(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]benzamide

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

4-chloro-N-({5-[(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-{[5-({4-[2-(methylanilino)-2-oxoethyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

4-chloro-N-[(5-{[4-(3-cyanopyrazin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

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

4-chloro-N-{[5-({4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)-thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[3-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

methyl 5-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-7-(trifluoromethyl)thieno[3,2-b]pyridine-3-carboxylate

ethyl 2-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-5-cyano-6-methylnicotinate

4-chloro-N-{[5-({4-[5-cyano-4,6-bis(dimethylamino)pyridin-2-yl]piperazin-1-yl}-sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[6-methyl-2-(trifluoromethyl)quinolin-4-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

tert-butyl 4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazine-1-carboxylate

2-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-8-ethyl-5-oxo-5,8-dihydropyrido[2,3-d]pyrimidine-6-carboxylic acid

7-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid

7-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

4-chloro-N-[(5-{[4-(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-{[5-({4-[(2E)-3-phenylprop-2-enyl]piperazin-1-yl}sulfonyl)thien-2-yl]-methyl}benzamide

4-chloro-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

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

N-[(5-{[4-(4-tert-butylbenzyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chloro-benzamide

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

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

4-chloro-N-{[5-({4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

tert-butyl 1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-ylcarbamate

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

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

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

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

4-chloro-N-{[5-({4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

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

N-[(5-{[(1R,4R)-5-benzyl-2,5-diazabicyclo[2.2.1]hept-2-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

4-chloro-N-[(5-{[4-(2-chlorodibenzo[b,f][1,4]oxazepin-11-yl)piperazin-1-yl]sulfonyl}-thien-2-yl)methyl]benzamide

N-(4-chlorophenyl)-2-(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)acetamide

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

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

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

4-chloro-N-[(5-{[4-(3-methoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

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

N-{[5-({4-[(2-tert-butyl-1H-indol-5-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

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

4-chloro-N-[(5-{[4-(tetrahydrofuran-2-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(6-chloropyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

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

N-[(5-{[4-(2H-1,2,3-benzotriazol-2-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

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

N-{[5-({4-[benzyl(methyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

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

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

4-chloro-N-[(5-{[4-(2,3,4,5,6-pentamethylbenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(phenylacetyl)-1,4-diazepan-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

4-chloro-N-{[5-({4-[5-(4-methoxyphenyl)-1H-pyrazol-3-yl]piperidin-1-yl}sulfonyl)-thien-2-yl]methyl}benzamide

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

4-chloro-N-[(5-{[4-(3-phenyl-1,2,4-thiadiazol-5-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

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

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

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

2-(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)-N-(4-chlorophenyl)acetamide

2-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-2H-1,2,3-benzotriazole-5-carboxylic

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

methyl 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-5-carboxylate

methyl 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1*H*-1,2,3-benzotriazole-6-carboxylate

methyl 2-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-2H-1,2,3-benzotriazole-5-carboxylate

4-chloro-N-[(5-{[4-(6-chloro-1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

N-[(5-{[4-(7-aza-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-5-carboxylic

1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-6-carboxylic

N-[(5-{[4-(2-amino-9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

4-chloro-N-[(5-{[4-(9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

N-[(5-{[4-(6-amino-9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

4-chloro-N-({5-[(4-{6-nitro-1H-benzimidazol-1-yl}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

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

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

N-[(5-{[4-(1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

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

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

methyl

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

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

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

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

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

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

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

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

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

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

N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

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

N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitro-benzamide

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

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

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

N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide

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

N-[(5-{[4-(2-aminoanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenz-amide

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

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

4-chloro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

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

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

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

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

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

4-chloro-N-{[5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

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

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

N-{[5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

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

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

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

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

N-({5-[(4-{3-[(butylamino)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide

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

4-chloro-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]benzamide

N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

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

4-chloro-N-[(5-{[4-(quinolin-8-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

4-Chloro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

4-chloro-N-{[5-({4-[(2E)-3-phenylprop-2-enoyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

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

4-chloro-N-{[5-({4-[4-(trifluoromethyl)benzoyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[4-(dimethylamino)benzoyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

4-chloro-N-[(5-{[4-(2,6-difluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

4-chloro-N-[(5-{[4-(3-fluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

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

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

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

4-chloro-N-[(5-{[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

N-[(5-{[4-(2,1,3-benzoxadiazol-5-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

4-chloro-N-[(5-{[4-(2,4-difluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

4-chloro-N-[(5-{[4-(2,4,6-trifluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

4-chloro-N-[(5-{[4-(2,6-dichlorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

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

4-chloro-N-[(5-{[4-(quinolin-8-ylsulfonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitro-benzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitro-benzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

3-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

3-nitro-N-{[5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]-methyl}benzamide

N-{[5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

3-nitro-N-{[5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]-methyl}benzamide

3-nitro-N-{[5-({4-[3-(methylsulfanyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]-methyl}benzamide

N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

methyl

N-{[5-({4-[3-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

3-nitro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

3-nitro-N-[(5-{[4-(2-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

3-nitro-N-{[5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]-methyl}benzamide

3-nitro-N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitro-benzamide

3-nitro-N-{[5-({4-[4-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]-methyl}benzamide

3-nitro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitro-benzamide

N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitro-benzamide

4-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

4-nitro-N-{[5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]-methyl}benzamide

N-{[5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide

4-nitro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

4-nitro-N-{[5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-nitro-N-{[5-({4-[3-(methylsulfanyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide

methyl

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

4-nitro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

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

4-nitro-N-{[5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]-methyl}benzamide

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

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

4-nitro-N-{[5-({4-[4-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]-methyl}benzamide

4-nitro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide

N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide

N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide

N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}-methyl)-3-nitrobenzamide

N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide

N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide

N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide

N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide

3-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

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

N-{[5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl}-sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)-methyl]-3-nitrobenzamide

3-nitro-N-[(5-{[4-(2-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

3-nitro-N-[(5-{[4-(4-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitro-benzamide

3-nitro-N-{[5-({4-[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-nitro-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl)sulfonyl]-thien-2-yl}methyl)-3-nitrobenzamide

N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitro-benzamide

3-nitro-N-{[5-({4-[3-(morpholin-4-ylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-nitro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-nitro-N-[(5-{[4-(pyrimidin-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

N-{[5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide

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

N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)-methyl]-4-nitrobenzamide

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

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

N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitro-benzamide

4-nitro-N-{[5-({4-[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]-methyl}benzamide

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

N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl)sulfonyl]-thien-2-yl}methyl)-4-nitrobenzamide

N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitro-benzamide

4-nitro-N-{[5-({4-[3-(morpholin-4-ylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-[(5-{[4-(2-aminoanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

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

N-{[5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

N-({5-[(4-{2-nitro-4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide

3-nitro-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

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

N-[(5-{[4-(3-cyclohexyl-4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

N-({5-[(4-{3-[(butylamino)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide

N-[(5-{[4-(3-ethylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

3-nitro-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]benzamide

4-nitro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

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

2-Hydroxy-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]-thien-2-yl}methyl)benzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-hydroxybenzamide

N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

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

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

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

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

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

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

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

methyl

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

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

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

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

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

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

N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

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

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

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

N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide

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

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

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

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

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

3-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

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

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

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

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

N-{[5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl}sulfonyl)-thien-2-yl]methyl}-3-methoxybenzamide

N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)-methyl]-3-methoxybenzamide

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

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

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

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

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

N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

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

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

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

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

3-methoxy-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

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

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

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

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

3-methoxy-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]-sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-5-nitro-1H-pyrazole-3-carboxamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-oxo-1,2-dihydropyridine-3-carboxamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-thioxo-1,2-dihydropyridine-3-carboxamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3,4-dihydroxybenzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-pyridine-2-carboxamide

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

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

4-chloro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide

4-chloro-N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide

4-chloro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide

4-chloro-N-{[5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]-methyl}benzamide

4-chloro-N-{[5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)-2-furyl]-methyl}benzamide

4-chloro-N-{[5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]-methyl}benzamide

4-chloro-N-{[5-({4-[3-(methylsulfanyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]-methyl}benzamide

N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}-4-chlorobenzamide

methyl 3-({1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-furyl)sulfonyl]piperidin-4-yl}amino)benzoate

3-({1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-furyl)sulfonyl]piperidin-4-yl}amino)-benzamide

4-chloro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]-2-furyl}methyl)benzamide

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

4-chloro-N-{[5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]-methyl}benzamide

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

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

4-chloro-N-{[5-({4-[4-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]-methyl}benzamide

4-chloro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]-2-furyl}methyl)benzamide

N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}-4-chlorobenzamide

4-chloro-N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]-methyl}benzamide

N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]-2-furyl}methyl)-4-chlorobenzamide

4-chloro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]-2-furyl}methyl)benzamide

N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]-2-furyl}methyl)-4-chlorobenzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]2-furyl}methyl)benzamide

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

4-chloro-*N*-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}azepan-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

Thereby, the most preferred compounds are those which are selected from the group consisting of :

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

4-chloro-N-[(5-{[4-(phenylacetyl)-1,4-diazepan-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

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

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

N-[(5-{[4-(1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

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

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

N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

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

4-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

methyl 3-{[1-({5-[({4-nitrobenzoyl}amino)methyl]thien-2-yl}sulfonyl)piperidin-4-yl]amino}benzoate

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-hydroxybenzamide

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

A further aspect of the present invention consists in the use of the sulfonamide derivatives according to formula I for the preparation of pharmaceutical compositions for the modulation – notably for the down-regulation, e.g. up to the inhibition - of the JNK function or signalling pathway associated disorders, in particular against neuronal disorders and/or against disorders of the immune system as well as said pharmaceutical compositions themselves. Preferred JNK pathways are the JNK 1 and/or 2 and/or JNK3.

As above pointed out, the compounds of formula I are suitable to be used as a medicament. Some few of the compounds falling into the above generic formula I have been disclosed prior to the filing of the present application, whereby for 9 of them no medical or biological activity whatsoever was described so far. Hence, it is herein reported that both the novel and the few known compounds falling under the above set out generic formula I are indeed suitable for use in treating disorders of the autoimmune system and neuronal system of mammals, notably of human beings. More specifically, 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 abnormal 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 could be triggered by numerous stimuli (e.g. stress, septic schock, oxidative stress, cytokines) and could lead to out-of-control apoptosis or autoimmune diseases that is frequently involved in the below enumerated disorders and disease states. Hence, the compounds according to formula I could be used for the treatment of disorders by modulating the JNK function or signalling pathways. Said modulation of the JNK function or pathways could involve its activation, but preferably it involves the down-regulation up to inhibition of the JNK pathways, notably of the JNK 1 and/or 2 and/or JNK3. The compounds according to formula I could be employed alone or in combination with further pharmaceutical agents, e.g. with a further JNK modulator.

Specifically, the compounds pursuant to formula I are useful for the treatment or prevention of immuno- and/or neuronal-related diseases or pathological states in which inhibition of JNK2 or JNK3 plays a critical role such as epilepsy; neurodegenerative diseases including Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases; spinal cord injury; head trauma, autoimmune diseases including multiple sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis; asthma; septic shock; transplant rejection; cancers including breast, colorectal, pancreatic and cardiovascular diseases including stroke, cerebral ischemia, arterosclerosis, myocordial infarction, myocordial reperfusion injury.

Quite surprisingly it turned out that the inventively found compounds according to formula I do show a considerable activity as inhibitors of JNK2 and 3. According to a preferred embodiment, the compounds according to the invention are essentially inactive in view of 2 further apoptosis modulating enzymes, i.e. p38 and/or ERK2, belonging incidentally to the same family as JNK2 and 3. Hence, the compounds according to the present invention offer the possibility to selectively modulate the JNK pathway, and in particular to treat disorders related to the JNK pathways, while being essentially inefficient with regard to other targets like said p38 and ERK2, so that they could indeed be viewed as selective inhibitors. This is of considerable significance, as these related en-

zymes are generally involved in different disorders, so that for the treatment of a distinct disorder, it is desired to employ a correspondingly selective medicament.
As a matter of fact, prior to the herein reported, surprisingly found pharmaceutically active sulfonamide derivatives according to formula I, nothing was known in respect of the use of small molecule chemical compounds as inhibitors of the JNK kinase pathway.

Still a further aspect of the present invention consists in the actually novel sulfonamide derivatives of formula I, i.e. those sulfonamide derivatives according to formula I that have not been disclosed by the prior art. Thereby, a total of 9 compounds have been disclosed by the CEREP company (www.cerep.fr) in as far as they are mentioned in a company catalogue, without any medical indication, though.
Generally, the compounds according to formula I of the CEREP company are only those wherein Ar^1 is 4-chlorophenyl and X is O and R^1 is H, Ar^2 is a thienyl group, while Y is a piperazino-, a 3-methyl piperazino-, a piperazino-3, 5-dione- or a piperidino group being substituted in the following way :

- where Y is a piperazino group, L^1 is diphenylmethyl, benzo[1,3]dioxol-5-yl-methyl, 4-methoxy phenyl, 2-hydroxyethyl, methyl group, 4-chlorophenyl methyl,
- where Y is a 3-methyl piperazino, L^1 is 4-chlorophenyl methyl,
- where Y is a piperazino-3, 5-dione group, L^1 is 2-phenyl ethyl, and
- where Y is a piperidino group, L^1 is H, and L^2 is 2-hydroxy ethyl.

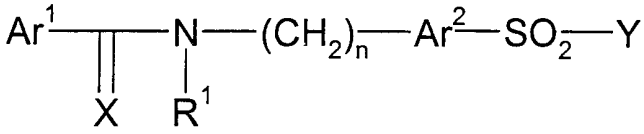
Compounds according to formula I that have been disclosed by the prior art together with a medical indication are those, wherein :

- Y is a piperidino- or a pyrrolidino group being substituted at the β–position of said sulfonamide nitrogen by one R^6 = benzo[5, 6]cyclohepta[1, 2b]pyridine, or a benzo[5, 6]cyclohept (3,4) ene [1, 2b]pyridine, whereby Ar^1 is phenyl, Ar^2 is thienyl, X is oxygen, R^1 is hydrogen; L^1 and L^2 are H and n is 1 for the treatment of proliferative diseases (WO 96/30017).
- X is oxygen, R^1 is hydrogen and n is 1, while Y is a piperazino group, whereby L^1 is a substituent that includes a phenyl being imperatively substituted by a

group –C(=NH)-NH_2 (benzamidine) or a protected form thereof to be used as factor XA inhibitors (WO 99/16751).

- Two further compounds are rather incidentally disclosed in WO 97/45403 (i.e. 2-{[2-(benzoylaminomethyl)-thiophene]-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyanopent[f]isoindol-6-amine as selective dopamine D3 ligand) and in WO 97/30992 (i.e. N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]–2-thienyl] methyl] benzamide and its hydrochloride to be used for inhibiting farnesyl-protein transferase).
- Finally, compounds of formula I wherein X is oxygen and Y is a 4-8 membered saturated cyclic alkyl containing one or two nitrogen atoms, said Y being imperatively substituted by an amido group (C=O)N(R,R') at the alpha position of the sulfonamide nitrogen are disclosed within WO 98/ 53814. Said compounds are mentioned to be useful in the inhibition of cell adhesion.

Hence, the entirely novel sulfonamide derivatives are those of the below set out general formula I whereby the above identified known compounds are excluded.



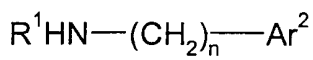
I

Still a further object of the present invention is a process for preparing the novel sulfamide derivatives according to formula I which have been set out above.

The sulfonamide derivatives of this invention can be prepared from readily available starting materials using the following general methods and procedures.

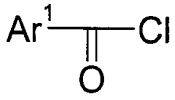
It will be appreciated that where typical or preferred experimental conditions (i.e., reaction temperatures, time, moles of reagents, solvents, etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or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

In a preferred method of synthesis, the sulfonamide derivatives of the invention are prepared by first coupling an amine of formula II:



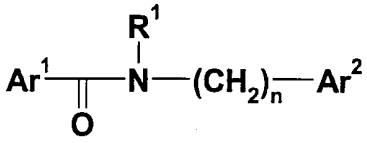
II

where Ar^2 and R^1 are as defined above, with an acyl chloride of formula III:



III

where Ar^1 is as defined above, to provide an amide of formula IV:



IV

Amines of formula II are either known compounds or can be prepared from known compounds by conventional procedures. Preferred amines as starting materials include thien-2-yl-methylamine, furan-2-yl-methylamine, pyridyl-2-ylmethylamine and the like. The acyl chlorides of formula III are also commercially available or previously described compounds. Preferred acyl chlorides include 4-chlorobenzoyl chloride, 4-fluorobenzoyl chloride, 4-trifluoromethylbenzoyl chloride and the like. If not known, the acid halide can 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, this reaction is performed upon using about 1 to 5 molar equivalents of the inorganic acid 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*-dimethylformamide, may also be used in this reaction.

When an acyl halide is employed in the coupling reaction, 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.

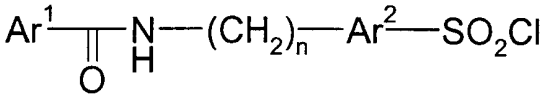
Alternatively, the carboxylic acid of compound III can be employed in the coupling reaction. The carboxylic acid of III are usually commercially available reagents or can be prepared by conventional procedures.

The coupling reaction of carboxylic acid of III (i.e. the acyl chloride) is conducted upon 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 acid 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 sulfonyl-piperidines or piperazines of formula I are prepared using conventional sulfonating methods:



V

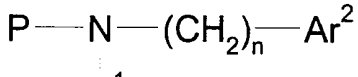
A preferred sulfonating reagent for use in this reaction is chlorosulfonic acid. Typically, the sulfonation reaction is performed by treating the carboxamide of formula (IV) with about 5 to about 10 molar equivalent of the sulfonating reagent in an inert solvent, such as dichloromethane, at a temperature 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.

According to a further preferred method of preparation notably in case that the above pointed out method leading to the preliminary synthesis of sulfonyl chloride of formula V is not applicable, the sulfonyl piperidines and piperazines of this invention are prepared by the following steps:

- Protection of the amine function of compounds of formula II;
- Chlorosulfonylation of the aromatic group;
- Formation of the sulfonamide function;

- Deprotection of the protectiong group;
- Acylation of the above generated free amine;

Amines of formula II are protected with a suitable protecting group of an amine moiety to provide intermediate of formula VI wherein P denotes the protecting group.

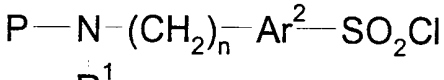


VI

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 can 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 are then sulfonated using a conventional very mild sulfonating procedure that allows the obtention of sulfonyl chloride of formula VII.

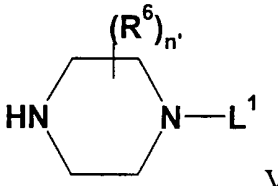


VII

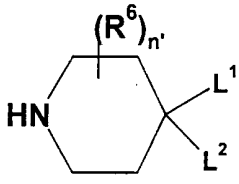
Typically, protected amine VI is treated with a base such as n-butyllithium or tert-butyllithium under an inert atmosphere, in a polar aprotic solvent such as tetrahydrofuran, ether or dioxane at a temperature ranging from –70°C to 0°C during a time ranging from 15 minutes to 4 hours. The so formed anion 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 sulfonate obtained is

°C to 20°C during a time ranging from 5 minutes to 1 hour. The sulfonate obtained is then transformed "*in situ*" to the sulfonyl chloride of formula VII by contacting with *N*-chlorosuccinimide at a temperature ranging from 0°C to 70°C.

The sulfonamide derivatives of formula I are then prepared from the corresponding above mentioned sulfonyl chloride V or VII, by reaction with a corresponding cyclic amine, e.g. either with a piperazine or piperidine derivative of the general formula VIII or IX.

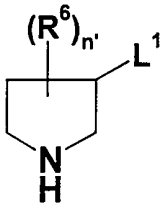


VIII or

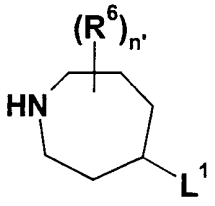


IX

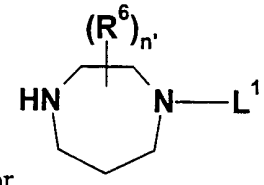
or a pyrrolidine, an azepan or a 1,4-diazepan of the below formulas



or



or



whereby R^6, n L^1 and L^2 are as above defined.

The above set out cyclic amines, notably those of formula VIII or IX are either commercially available compounds or compounds that can be prepared by known procedures.

Typically, piperazines of type VIII can be prepared upon using conventional methods known by a person skilled in the art.

For L^1 and/or L^2 = aryl, suitable methods of preparation are described in *Tetrahedron Lett.* **1996**, *37*, 8487-8488 and references cited therein.

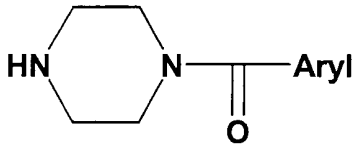
For L^1 and/or L^2 = aryl C_1-C_6 alkyl, a further preferred method is the reaction of the corresponding piperazine or mono-*N*-protected piperazine with compounds of formula X

$$\text{Aryl}\text{---}(CH_2)_n\text{---}X \qquad \text{X}$$

wherein X is Cl, Br, I, OTs, OMs

The reaction is generally conducted in the presence of a base such as triethylamine, diisopropylethylamine, potassium carbonate and the like in solvent such as N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

For L^1 and/or L^2 = -C(S)-, a further preferred method is the conversion of compounds of type XI using the Lawesson's reagent which allows the transformation of an amide into a thioamide group as described in *Bull. Soc.Chim. Belgium*, **1978**, *87*, 229.



XI

The sulfonamides of formula I are readily prepared by contacting the sulfonyl chlorides V 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 solvent such as N,N-dimethyformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

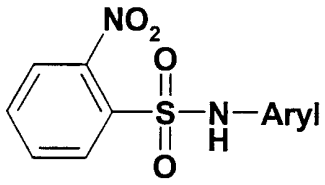
Alternatively, the sulfonamide derivatives of formula I are readily prepared from the corresponding sulfonyl chloride V or VII, by reaction with a piperidine of general formula IX. Piperidines of formula IX are either commercially available compounds or compounds that can be prepared by known procedures. Typically, piperidines of type IX can be prepared using conventional methods known by one skilled in the art and 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.

Preferred methods of obtaining piperidines of formula IX are the following:

For L^1 = H and L^2 = (CH_2)n-Aryl wherein n = 0,1,2; addition of an organometallic species such as $Ar^3(CH_2)_nLi$ or $Ar^3(CH_2)_nMgBr$ on mono-protected 4-piperidone followed by reduction of the so-formed double bound which allows the formation of compounds of type IX.

For L^2 = -NR-(CH_2)n-Aryl wherein n = 0,1,2, a preferred method is the reductive amination of 4-piperidone with amines of type Aryl-(CH_2)n-NR-H.

A further preferred method in the case where n = 0 is a "Mitsunobu type" coupling between an activated aniline of type XII with mono-N-protected 4-piperidol as described in *Tetrahedron Lett.* **1995**, *36*, 6373-6374.

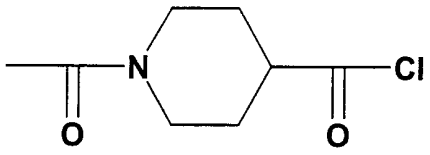


XII

Deprotection of the sulfamino group is then carried out using thiophenol in the presence of potassium carbonate.

For L^2 = -NR^3'C(O)R^3, -NR^3'C(O)NR^3'R^3, NR^3'SO_2-R^3, a preferred method of synthesis of compounds of formula IX is the reaction of commercially available N-BOC-4-aminopiperidine with respectively acyl chlorides, isocyanates and sulfonyl chloride under classical conditions very well known by one skilled in the art.

When L^2 = -CO-Aryl, compounds of formula IX are readily prepared by contacting well chosen aromatic or heteroaromatic rings with intermediate of type XIII



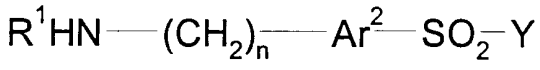
XIII

in the presence of a Lewis acid such as aluminum trichloride or titanium tetrachloride in a polar aprotic solvent such as dichloromethane. Intermediate XIII can be easily obtained by first acetylation of piperid-4-yl carboxylic acid and their formation of the acyl chloride by treatment with thionyl chloride.

The sulfonamides of formula I are readily prepared by contacting the sulfonyl chloride V with an amine of formula IX 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 prefera-

bly conducted in solvent such as N,N-dimethyformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

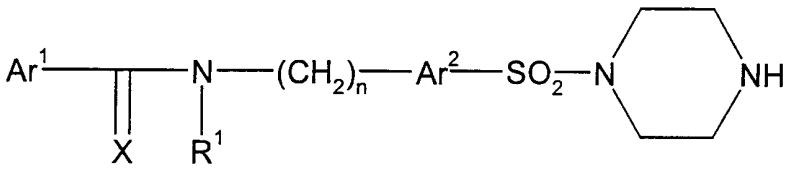
The sulfonamides of formula XIV are readily prepared by contacting the sulfonyl chloride VII with an amine of formula VIII or IX in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is preferably conducted in solvent 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 prefered conditions described above leading to compounds of general formula I
In the particular case of compounds of general formula I where Y represents a piperazine derivative, an alternative method of preparation which has also to be considered as part of this invention, said method of preparation consisting in the condensation of a piperazine derivative of formula XV



XV

with electrophiles L^1 which will be chosen depending on the nature of L^1 (see the above definition of L^1, L^2). Procedures and methods to perform these types of condensation are well-known and have been well described on various synthesis of N-substituted piperazine derivatives.

If the above set out general synthetic methods are not applicable for obtaining 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 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 JNK2 and JNK3, 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 compound 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 gelatine; 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.

Examples

Protocol #1

Example 1: Preparation of 4-chloro-*N*-[5-(piperazine-1-sulfonyl)-thiophen-2-yl-methyl]-benzamide 1

4-Chloro-*N*-thiophen-2-ylmethyl-benzamide **1a**

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 **1b**

Chlorosulfonic acid (20.1 mL, 198 mmol) in CH_2Cl_2 (80 mL) was added dropwise to a solution of **1a** (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 **1b**; 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-(piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **1**

A solution of **1b** (1 g, 2.9 mmol) in 0.5 mL DMF and 2 mL CH_2Cl_2 was added slowly at 0°C to piperazine (985 mg, 11.4 mmol) in CH_2Cl_2 (11 mL). The reaction was stirred for 2h while room temperature was reached. The reaction mixture was washed with sat. $NaHCO_3$ and dried over $MgSO_4$. After evaporating the solvent 1.76 g (62%) of **1c** was isolated. ^{1}H NMR (DMSO-*d6*) δ 9.38 (t, J = 5.27 Hz, 1H), 7.90 (d, J = 8.67 Hz, 2H), 7.56 (d, J = 8.67 Hz, 2H), 7.46 (d, J = 3.77 Hz, 1H), 7.18 (d, J = 4.14 Hz, 1H), 4.67 (d, J = 6.03 Hz, 2H), 2.66-2.84 (m, 8H).

Example 2 : Preparation of 4-Chloro-N-{5-[4-(3-Trifluoromethanesulfonyl-phenylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **2**

To a stirred solution of 4-((3-Trifluoromethanesulfonyl)-phenylamino)-piperidine (580 mg, 1.88 mmol) and iPr_2NEt (1.46 µl, 8.6 mmol) in CH_2Cl_2 (250 mL) was added **1b** (600 mg, 1.71 mmol) in DMF/CH_2Cl_2 (1:3,15mL). After 3 h the reaction mixture was washed with HCl (0.1 N) and sat. NaCl solution, and dried over $MgSO_4$. The solvent was evaporated and the residue was filtered through silica gel using cyclohex-ane/ethylacetate 1:1 as eluent. **2** was isolated as white solid (840 mg, 79%).mp.: 198-199°C. ^{1}H NMR (DMSO-*d6*) δ 9.38 (t, J = 5.6 Hz, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.45-7.33 (m, 4H), 7.28 (d, J = 7.9 Hz, 1H), 7.06 (d, J = 3.8 Hz, 1H), 7.02 (s, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.69 (t, J = 5.6 Hz, 1H), 4.68 (d, J = 5.6 Hz, 2H), 4.00 (s, b, Hz, 1H), 3.71 (d, J = 12.1 Hz, 2H), 3.32 (s, b, 1H), 2.62 (dd, J = 12.1 Hz, 2.26 Hz, 2H), 2.11 (d,

J = 13.56 Hz, 2H), 1.65-1.48 (m, 2H). M/Z APCI: 622.2 (M+1), 620.1 (M-1). $C_{24}H_{23}ClF_3N_3O_5S_3$ Calc.: C: 46.34%. H: 3.73%. N: 6.75%. Found: C: 46.05%, H: 3.84%, N: 6.69%.

Alternatively **2** can be synthesised in a parallel solution phase approach.

In a 4 mL Alltech® tube 1 eq. of amine is shaked with polymerbound NMM (4eq.) in 1.2 mL CH_2Cl_2/DMF. After 15 min 1 mL of a stock solution of **1b** in CH_2Cl_2/DMF (1.2eq.) is added and the reaction slurry is shaked. After 3h Aminomethyl Merryfield resin (0.4 eq) is added and the reaction is shaked overnight. The solution is filtered off, the resins are washed 3 x with CH_2Cl_2, and the solvents are evaporated at medium temperature in a Savant Speed Vac® Plus vacuum centrifuge for 1h.

The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned examples. [1],[2].

Exemple	Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
3	4-chloro-N-({5-[(4-pyridin-2-ylpiperazin-1-yl)-sulfonyl]thien-2-yl}methyl)benzamide	17.87	97	c	477	475
4	4-chloro-N-[(5-{[4-(4-fluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	15.33	96.2	b		
5	4-chloro-N-{[5-({4-[4-(trifluoromethyl)phenyl]-piperazin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	15.82	93	b	545	543
6	4-chloro-N-({5-[(4-{2-nitrophenyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	14.43	99	b	521	519
7	4-chloro-N-({5-[(4-{4-nitrophenyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	13.99	93.3	b	522	520
8	4-chloro-N-[(5-{[4-(2-furoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	11.76	82	b	494	492
9	4-chloro-N-[(5-{[4-(4-hydroxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	11.98	78	b	492	490
10	4-chloro-N-[(5-{[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	11.05	90	b	511	509
11	4-chloro-N-[(5-{[4-(2-morpholin-4-yl-2-oxoethyl)-piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	10.44	89	b	527	525

[1] HPLC conditions: C8 Symmetry a- MeCN, 0.09%TFA, 0 to 100% (10min)
HPLC conditions: C18 b- MeCN, 0.09%TFA, 0 to 100% (20min), c- MeCN, 0.09%TFA, 0 to 100% (30min).
[2] Mass spectrum APCI

12	4-chloro-N-[(5-{[4-(pyridin-4-ylmethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	11.62	89	b	491	489
13	4-chloro-N-[(5-{[4-(2-thien-2-ylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.58	90	b	510	508
14	4-chloro-N-[(5-{[4-(3,5-dimethoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.04	93	b	536	534
15	4-chloro-N-[(5-{[4-(cyclohexylmethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	17.27	88	b	496	494
16	4-chloro-N-[(5-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.59	88	b	506	504
17	N-({5-[(4-benzylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide	14.75	82	b	490	488
18	4-chloro-N-[(5-{[4-(2-phenylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	10.27	93	b	504	502
19	4-chloro-N-[(5-{[4-(4-fluorobenzyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.82	91	b	508	506
20	4-chloro-N-[(5-{[4-(2-cyanophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.14	87	b	501	499
21	4-chloro-N-{[5-({4-[4-chloro-3-(trifluoromethyl)-phenyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	16.49	94	b	578.5	576.5
22	4-chloro-N-[(5-{[4-(3-piperidin-1-ylpropyl)-piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	7.87	95	b	525	523
23	4-chloro-N-({5-[(4-{4-chloro-2-nitrophenyl}-piperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	15.38	99	b	555.5	553.4
24	4-chloro-N-[(5-{[4-(6-methylpyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	9.3	91	b	491	489
25	4-chloro-N-({5-[(4-hydroxy-4-phenylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	12.84	94	b	491	489
26	N-({5-[(4-benzoylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide	14.35	90	b	503	501
27	4-chloro-N-[(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	12.22	93	b	531	529
28	N-({5-[(4-benzylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide	16.03	93	b	489	487
29	4-chloro-N-({5-[(4-oxo-1-phenyl-1,3,8-triazaspiro-[4.5]dec-8-yl)sulfonyl]thien-2-yl}methyl)benzamide	13.14	89	b	545	543
30	4-chloro-N-{[5-({4-[2-(methylanilino)-2-oxoethyl]-piperazin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	9.86	97	b	547	545
31	4-chloro-N-{[5-({4-[hydroxy(diphenyl)methyl]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	15.36	96	b	581	579
32	4-chloro-N-[(5-{[4-(3-cyanopyrazin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	13.06	86	b	503	501
33	4-chloro-N-({5-[(4-{5-nitropyridin-2-yl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	13.76	76	b	522	520
34	4-chloro-N-{[5-({4-[3-chloro-5-(trifluoromethyl)-pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	16.32	90	b	579.5	577.6
35	4-chloro-N-{[5-({4-[5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	14.88	80	b	545	543
36	4-chloro-N-{[5-({4-[3-(trifluoromethyl)pyridin-2-	14.63	95	b	545	543

	yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide					
37	4-chloro-N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.72	95	b	539	537
38	methyl 5-{4-[(5-{[(4-chlorobenzoyl)amino]-methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-7-(trifluoromethyl)thieno[3,2-b]pyridine-3-carboxylate	16.13	93	b	659	657
39	ethyl 2-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}-thien-2-yl)sulfonyl]piperazin-1-yl}-5-cyano-6-methylnicotinate	14.97	89	b	588	586
40	4-chloro-N-{[5-({4-[5-cyano-4,6-bis(dimethyl-amino)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	12.79	85	b	588	586
41	4-chloro-N-{[5-({4-[6-methyl-2-(trifluoromethyl)-quinolin-4-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	15.88	96	b	609	607
42	tert-butyl 4-[(5-{[(4-chlorobenzoyl)amino]-methyl}thien-2-yl)sulfonyl]piperazine-1-carboxylate	14.04	94	b	500	498
43	2-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-8-ethyl-5-oxo-5,8-dihydropyrido[2,3-d]pyrimidine-6-carboxylic acid	12.9	73	b	617	615
44	7-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid	13.05	87	b	634	632
45	7-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	13.1	96	b	633	631
46	4-chloro-N-[(5-{[4-(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	13.5	95	b	562	560
47	4-chloro-N-{[5-({4-[(2E)-3-phenylprop-2-enyl]-piperazin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	10.65	93	b	516	514
48	4-chloro-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	10.61	97	b	518	516
49	4-chloro-N-[(5-{[4-(3,4,5-trimethoxyphenyl)-piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	13.16	90	b	566	564
50	N-[(5-{[4-(4-tert-butylbenzyl)piperazin-1-yl]-sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	11.81	95	b	546	544
51	4-chloro-N-[(5-{[4-(4-fluorophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.93	90	b	494	492
52	4-chloro-N-[(5-{[4-(2-hydroxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	12.1	93	b	492	490
53	4-chloro-N-{[5-({4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	14.42	91	b	545	543
54	4-chloro-N-[(5-{[4-(5-cyanopyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	13.15	94	b	502	500
55	tert-butyl 1-[(5-{[(4-chlorobenzoyl)amino]-methyl}thien-2-yl)sulfonyl]piperidin-4-ylcarbamate	13.77	98	b	514	512
56	4-chloro-N-({5-[(4-phenylpiperazin-1-yl)sulfonyl]-thien-2-yl}methyl)benzamide	14.18	94	b	476	474
57	4-chloro-N-{[5-(piperidin-1-ylsulfonyl)thien-2-yl]methyl}benzamide	13.13	96	b	399	397
58	4-chloro-N-[(5-{[4-(1-naphthyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	16.38	75	b	526	524

59	4-chloro-N-[(5-{[4-(3,4-dichlorophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	16.48	81	b	545	543
60	4-chloro-N-{[5-({4-[3-(trifluoromethyl)phenyl]-piperazin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	15.86	93	b	544	542
61	4-chloro-N-{[5-({3-hydroxy-4-[3-(trifluoromethyl)-phenyl]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	14.79	95	b	559	557
62	4-chloro-N-[(5-{[4-(2-methylphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	15.64	79	b	490	488
63	N-[(5-{[(1R,4R)-5-benzyl-2,5-diazabicyclo[2.2.1]-hept-2-yl]sulfonyl}thien-2-yl)methyl]-4-chloro-benzamide	9.51	97	b	502	500
64	N-[(5-{[4-(benzyloxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	15.08	93	b	505	503
65	4-chloro-N-[(5-{[4-(2-chlorodibenzo[b,f][1,4]-oxazepin-11-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	12.86	94	b	627.5	625.6
66	N-(4-chlorophenyl)-2-(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)acetamide	12.76	84	b	531	529
67	4-chloro-N-({5-[(4-hydroxypiperidin-1-yl)sulfonyl]-thien-2-yl}methyl)benzamide	10.35	95	b	415	413
68	N-[(5-{[4-(4-acetylphenyl)piperazin-1-yl]sulfonyl}-thien-2-yl)methyl]-4-chlorobenzamide	13.15	96	b	518	516
69	4-chloro-N-[(5-{[4-(3,5-dichloropyridin-4-yl)-piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	13.89	92	b	546	544
70	4-chloro-N-[(5-{[4-(3-methoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.24	89	b	506	504
71	N-({5-[(4-benzyl-4-hydroxypiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide	13.72	92	b	505	503
72	N-{[5-({4-[(2-tert-butyl-1H-indol-5-yl)amino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	11.55	97	b	585	583
73	4-chloro-N-{[5-({4-[(phenylacetyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	12.61	88	b	532	530
74	4-chloro-N-[(5-{[4-(tetrahydrofuran-2-ylcarbonyl)-piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	10.87	94	b	498	496
75	4-chloro-N-[(5-{[4-(6-chloropyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.93	95	b	511	509
76	4-chloro-N-[(5-{[4-(4-chlorophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	15.49	91	b	510	508
77	N-[(5-{[4-(2H-1,2,3-benzotriazol-2-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	6.57	89	a	516	514
78	4-chloro-N-[(5-{[4-(4-chlorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.99	92.1	b	537	535
79	4-chloro-N-({5-[(4-phenoxypiperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	6.81	72	a	491	489
80	N-{[5-({4-[benzyl(methyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	4.93	93.3	a	518	516
81	4-chloro-N-{[5-({4-[3-(2,4-dichlorophenyl)-1H-pyrazol-5-yl]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	6.89	92.6	a	609	607
82	4-chloro-N-[(5-{[4-(5-thien-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]sulfonyl}thien-2-	5.93	93.8	a	547	545

	yl)methyl]benzamide					
83	4-chloro-N-[(5-{[4-(2,3,4,5,6-pentamethylbenzoyl)-piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	7.48	90.6	a	573	571
84	4-chloro-N-[(5-{[4-(phenylacetyl)-1,4-diazepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.83	94.5	a	532	530
85	4-chloro-N-{[5-({4-[5-(4-methoxyphenyl)-1H-pyrazol-3-yl]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	5.72	92.7	a	571	-499
86	N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide	4.84	91	a	490	488
87	4-chloro-N-[(5-{[4-(3-phenyl-1,2,4-thiadiazol-5-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	6.76	98.7	a	560	558
88	4-chloro-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	7.62	99	a	503	501
89	4-chloro-N-({5-[(4-heptylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	5.29	99.1	a	498	496
90	4-chloro-N-({5-[(4-octylpiperazin-1-yl)sulfonyl]-thien-2-yl}methyl)benzamide	5.59	97.8	a	512	510

Example 91: Preparation of N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide **91**

4-(1*H*-1,2,3-benzotriazol-1-yl)piperidinium trifluoroacetate, **91a**

To a solution of Boc-4-hydroxy-piperdine (201 mg, 1 mmol), Benzotriazole (238mg, 2 mmol) and Triphenylphosphine (523 mg, 2 mmol) in 15 mL THF was added a solution of Diethylazodicarboxylate (326 ul, 2 mmol) in 10 mL THF. The yellow solution was stirred overnight, the solvent was evaporated to dryness and the crude residue was eluted on silica gel (AcOEt/cyclohexane 7:3). The fractions were isolated containing the 1- and 2-regiosiomers.

Fraction 1 contained the 2-benzotriazole-piperdine isomer (250mg, 82%). ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 2H), 7.38 (m, 2H), 4.90 (quint., J = 6.8 Hz.), 4.20 (m, 2H), 3.09 (m, 2H), 2.27 (m, 4H), 1.68 (s, 9H). M/Z APCI: 303.2 (M+1), 247 (M-^{t}butyl+1), 203 (M-Boc+1).

Fraction 2 contained the 1-benzotriazole-piperidine isomer (50 mg, 16%):^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 8.3 Hz., 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.58 (t, J = 8.3 Hz.), 7.42 (t, J = 8.3 Hz.), 5.25 (m, 1H), 3.52 (m, 2H), 3.20 (m, 2H), 2.55-2.25 (m, 4H), 1.66 (s, 9H). M/Z APCI: 303.2 (M+1), 247 (M-^{t}butyl+1), 203 (M-Boc+1).

91a (250 mg, 0.82 mmol) was dissolved in 5 mL CH_2Cl_2. 1mL of TFA was added dropwise and the solution was stirred for 3h. The solvents were evaporated to dryness and the oily residue was precipitated with diethylether to give 240 mg (95%) of XX1: ^{1}H NMR (DMSO-*d6*) δ9.10 (b, m, 1H), 8.72 (b, m, 1H), 8.07 (d, J= 8.3 Hz., 1H), 7.96 (d, J= 8.3 Hz, 1H), 7.55 (t, J= 8.3 Hz.), 7.40 (t, J= 8.3 Hz.), 5.25 (m, 1H), 3.52 (m, 2H), 3.20 (m, 2H), 2.55-2.25 (m, 4H), M/Z APCI: 203.2 (M+1).

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide **91**

91 was synthesised according to the protocol for the synthesis of **2**. After flash chromatography the main fractions were recrystallized from CH_2Cl_2/Cyclohexane. Isolated yield: 3.1 g (71%). mp.: 174-175°C. ^{1}H NMR (DMSO-*d6*) δ 9.41 (t, J= 6.0 Hz, 1H), 8.03 (d, J= 7.9 Hz, 1H), 7.91 (d, J= 8.7 Hz, 2H), 7.87 (d, J= 8.7 Hz, 1H), 7.61-7.54 (m, 3H), 7.52 (t, J= 8.3 Hz, 1H), 7.39 (t, J= 8.3 Hz, 1H), 7.23 (d, J= 3.77 Hz, 1H),), 5.01 (m, 1H), 4.70 (d, J= 5.6 Hz, 2H), 3.78 (d, J= 10.6 Hz, 2H), 2.80-2.64 (m, 2H), 2.34-2.17 (m, 4H). M/Z APCI: 516.2 (M+1), 514.1 (M-1). $C_{23}H_{22}ClN_5O_3S_2$ Calc.: C: 53.53%. H: 4.30%. N: 13.57%. Found: C: 52.74%, H: 4.29%, N: 13.26%.

Alternatively **3** can be synthesised in a parallel solution phase approach using the protocol applied for **2**.

The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned examples

Exemple	Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
92	2-(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)-N-(4-chlorophenyl)-acetamide	6.37	91	a	516	514
93	2-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-2H-1,2,3-benzotriazole-5-carboxylic acid	5.62	100	a		
94	4-chloro-N-[(5-{[4-(5-chloro-1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.46	99	a	550	548
95	methyl 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-	6.19	83.7	a	574	572

	thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-5-carboxylate					
96	methyl 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-thien-2-yl)sulfonyl]piperidin-4-yl}-1*H*-1,2,3-benzotriazole-6-carboxylate	6.18	90.5	a	574	572
97	methyl 2-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-thien-2-yl)sulfonyl]piperidin-4-yl}-2H-1,2,3-benzotriazole-5-carboxylate	6.51	94.5	a	574	572
98	4-chloro-N-[(5-{[4-(6-chloro-1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	6.53	96	a	550	548
99	4-chloro-N-{[5-({4-[5-(trifluoromethyl)-1H-1,2,3-benzotriazol-1-yl]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide	6.85	94.3	a	584	582
100	N-[(5-{[4-(7-aza-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.5	97.6	a	0	514
101	1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-5-carboxylic acid	5.46	95.5	a	0	0
102	1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-6-carboxylic acid	5.36	97.9	a	0	0
103	N-[(5-{[4-(2-amino-9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.07	94.6	a	532	530
104	4-chloro-N-[(5-{[4-(9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.67	98.4	a	517	515
105	N-[(5-{[4-(6-amino-9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.15	91.7	a	532	530
106	4-chloro-N-({5-[(4-{6-nitro-1H-benzimidazol-1-yl}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	5.31	67	a	0	558
107	4-chloro-N-({5-[(4-{5-nitro-1H-benzimidazol-1-yl}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	5.46	86.6	a	560	558
108	4-chloro-N-[(5-{[4-(2H-1,2,3-triazol-2-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.77	96.8	a	466	464
109	N-[(5-{[4-(1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.43	99	a	515	513

Example 110: Preparation of 4-chloro-N-{[5-({4-[3-propylanilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide **110**

4-(3-propylanilino)piperidine trifluoroacetate salt, 110b

Boc-piperidin-4-one (2.5g, 12.5 mmol) and 3-propylaniline hydrochloride (2.15g, 12.5 mmol) and 2.1 mL DIEA were stirred in 15 mL DCE for 1h. To this solution acetic acid (750ul, 12.5mmol) and sodium triacetoxyborohydride (3.72g, 17.6mmol) were added and the solution was stirred overnight under Ar. The reaction mixture was diluted with diethylether, and 12mL of NaOH (2N) were added (pH9-10). The organic phase was washed twice with brine and dried over $MgSO_4$. The crude was purified by flash chro-

matography on silica gel using petroleum ether/EtOAc 7:1 as eluant. 3.7 g (94%) of pure **110a** were isolated as a colorless solid. ^{1}H NMR (DMSO-*d6*) δ 6.93 (t, J = 7.7, 1H), 6.31-6.39 (m, 3H), 5.31 (d, J = 8.2, 1H), 3.84 (d, J = 13.2 Hz, 2H), 3.33 (m, 1H.), 2.89 (m, 2H), 2.39 (t, J = 7.7 Hz, 2H), 1.84 (d J = 11.3 Hz, 2H), 1.55 (m, 2H), 1.51 (s, 9H), 1.20 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H), M/Z ESI: 319.2 (M+1).

110a (1.5 g, 4.71 mmol) was dissolved in 20 mL CH_2Cl_2. 5 mL of TFA were added dropwise and the solution was stirred for 3h. The solvents were evaporated to dryness and the oily residue was precipitated with diethylether to give 1.45 g (92%) of **110b**. ^{1}H NMR (DMSO-*d6*) δ 8.59 (m, 2H), 7.00 (t, J = 7.7, 1H), 6.44-6.50 (m, 3H), 3.51 (m, 1H), 3.27 (m, 2H), 3.00 (m, 2H.), 2.42 (t, J = 7.7 Hz, 2H), 2.00 (d J = 11.3 Hz, 2H), 1.57-1.47 (m, 4H), 0.87 (t, J = 7.3 Hz, 3H), M/Z ESI: 219.2 (M+1).

4-chloro-N-{[5-({4-[3-propylanilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide **110**

110 was synthesised according to the protocol for the synthesis of **2**. After flash chromatography the main fractions were recrystallized from CH_2Cl_2/Cyclohexane. Isolated yield: 430 mg (56%). mp.: 169-170°C. ^{1}H NMR (DMSO-*d6*) δ 9.36 (t, J = 5.8 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 3.8 Hz, 1H), 7.19 (d, J = 3.8 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H), 6.49-6.42 (m, 3H), 5.33 (d, J = 7.9 Hz, 1H), 4.68 (d, J = 5.6 Hz, 2H), 3.51 (d, J = 11.7 Hz, 2H), 3.29 (m, 1H), 2.55 (t, J = 10.5 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 1.97 (d, J = 10.9 Hz, 2H). 1.56-1.37 (m, 4H), 0.84 (t, J = 7.3 Hz, 3H). M/Z APCI: 532.2 (M+1), 530.1 (M-1). $C_{26}H_{30}ClN_3O_3S_2$ Calc.: C: 58.70%. H: 5.68%. N: 7.90%. Found: C: 58.55%, H: 5.67%, N: 7.93%.

Alternatively **110** can be synthesised in a parallel solution phase approach:
In a 4 ml Alltech® tube 1 eq. of piperidine trifluroacetate salt is shaked with polymer-bound NMM (4eq.) in 1.2 mL CH_2Cl_2/DMF. After 15 min 1 mL of a stock solution of **1b** in CH_2Cl_2/DMF (1.2eq.) is added and the reaction slurry is shaked. After 3h Aminomethyl Merryfield resin (0.4 eq) is added and the reaction is shaked overnight. Occasionally remaining amine is removed with polymerbound isocyanate (0.2 eq.). The slurry is again shaked for 1h. The solution is filtered off, the resins are washed 3 x with

CH_2Cl_2, and the solvents are evaporated at medium temperature in a Savant Speed Vac® Plus vacuum centrifuge for 1h.

The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned examples

Exemple	Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
111	4-chloro-N-{[5-({4-[3-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	7.4	96	a	558	556
112	4-chloro-N-{[5-({4-[3-(dimethylamino)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	4.86	94.8	a	533	531
113	methyl 3-({1-[(5-{[(4-chlorobenzoyl)amino]-methyl}thien-2-yl)sulfonyl]piperidin-4-yl}amino)-benzoate	6.33	96.6	a	548	546
114	4-chloro-N-{[5-({4-[3-(methylsulfanyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	6.07	97.4	a	536	534
115	4-chloro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	6.93	88.3	a	535	533
116	4-chloro-N-[(5-{[4-(2-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.12	96.2	a	520	518
117	3-({1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}amino)benzamide	4.52	69	a	533	531
118	4-chloro-N-{[5-({4-[2-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	7.7	97.5	a	558	556
119	4-chloro-N-({5-[(4-{2-nitro-4-[(trifluoromethyl)-sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	7.55	84.8	a	667	665
120	4-chloro-N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.6	86.2	a	524	522
121	4-chloro-N-{[5-({4-[4-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	7.45	96.8	a	558	556
122	4-chloro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	7.3	95.5	a	622	620
123	4-chloro-N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	7.13	92.8	a	535	533
124	N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	4.9	74	a	533	531
125	4-chloro-N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-	6.2	94.2	a	594	0

	benzamide					
126	N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-3-nitrobenzamide	6.68	97.8	a	535	533
127	4-chloro-N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	7.06	93.9	a	524	522
128	4-chloro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.4	92	a	519	517
129	4-chloro-N-{[5-({4-[3-(methylsulfonyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	6.06	91.7	a	568	566
130	N-({5-[(4-{3-[amino(imino)methyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide	4.3	91.4	a	532	530
131	4-chloro-N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	5.16	92.3	a	598	596
132	N-[(5-{[4-(2-aminoanilino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-4-chlorobenzamide	4.63	78	a	506	504
133	4-chloro-N-[(5-{[4-(2-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.47	94.3	a	506	504
134	4-chloro-N-[(5-{[4-(4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.3	86.8	a	506	504
135	4-chloro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	7.1	89.1	a	590	588
136	4-chloro-N-[(5-{[4-(3-toluidino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.73	85.3	a	504	502
137	4-chloro-N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	7.58	99	a	593	591
138	4-chloro-N-{[5-({4-[3-(1,3-oxazol-5-yl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.68	86.5	a	557	555
139	N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	5.77	98	a	546	544
140	4-chloro-N-[(5-{[4-(2-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.42	96.1	a	532	530
141	4-chloro-N-{[5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl}sulfonyl)-thien-2-yl]methyl}benzamide	5.47	95	a	580	578
142	4-chloro-N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	5.15	97.4	a	530	528
143	4-chloro-N-[(5-{[4-(4-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.49	98.7	a	532	530
144	4-chloro-N-[(5-{[4-({3-nitropyridin-2-yl}amino)-piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	6.62	99.3	a	537	535
145	N-{[5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	4.37	96.1	a	506	504
146	N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	6.25	92.4	a	566	564
147	N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	7.29	96.1	a	589	587
148	4-chloro-N-[(5-{[4-(pyrimidin-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.55	97.7	a	492	490

149	4-chloro-N-{[5-({4-[4-(morpholin-4-ylsulfonyl)-anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	6.2	96.2	a	639	637
150	4-chloro-N-({5-[(4-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	6.06	94.2	a	560	558
151	4-chloro-N-[(5-{[4-(3-cyclohexyl-4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.01	85.2	a	588	586
152	N-({5-[(4-{3-[(butylamino)sulfonyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide	6.05	99.7	a	626	624
153	4-chloro-N-[(5-{[4-(3-ethylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.86	98.4	a	518	516
154	4-chloro-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.36	86.9	a	544	542
155	N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide	5.57	98.9	a	0	566
156	4-chloro-N-[(5-{[4-(quinolin-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.57	95.8	a	541	539
157	4-chloro-N-[(5-{[4-(quinolin-8-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.65	97	a	541	539

Example 158: Preparation of 4-Chloro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide **158**

4-(3-propylphenoxy)piperidinium trifluoroacetate, **158a**

To a solution of Boc-4-hydroxy-piperidine (1g, 4.97mmol), 3-propylphenol (677mg, 4.97 mmol) and Triphenylphosphine (1.304g, 4.97 mmol) in 30 mL THF was added a solution of Diethylazodicarboxylate (866 mg, 4.97 mmol) in 10 mL THF. The yellow solution was stirred overnight, the solvent was evaporated to dryness and the crude residue was eluted on silica gel (AcOEt/cyclohexane 1:9) to provide 880 mg (56%) of pure **158a**.

158a was dissolved in 10 mL CH_2Cl_2 and 2 mL TFA were added. After 3h the reaction mixture was evaporated to dryness and the residual oil was precipitated with diethylether to afford 800mg (92%) of pure TFA salt **158a**: ^{1}H NMR (DMSO-*d6*) δ 8.42 (b, m, 2H), 7.04 (d, J = 7.7 Hz, 1H), 6.65 (m, 3H), 4.47 (m, 1H), 3.20-2.80 (b, m, 4H), 2.46 (m, 2H), 1.90 (m, 2H), 1.65 (m, 2H), 1.43 (m, 2H), 0.74 (t, J = 7.3 Hz, 3H).

4-Chloro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide **158**

158 was synthesised according to the protocol for the synthesis of **2**. After flash chromatography the main fractions were recrystallized from CH_2Cl_2/Cyclohexane. Isolated yield: 24 mg (88%).. ^{1}H NMR (DMSO-*d6*) δ 9.38 (t, J = 5.6 Hz, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 3.7 Hz, 1H), 7.19 (d, J = 3.7 Hz, 1H), 7.09 (t, J = 8.1 Hz, 1H), 6.85-6.66 (m, 3H), 4.68 (d, J = 5.6 Hz, 2H), 3.51 (d, J = 11.7 Hz, 2H), 3.29 (m, 1H), 2.87 (t, J = 10.5 Hz, 2H), 2.45 (t, J = 7.3 Hz, 2H), 2.00 (d, J = 10.9 Hz, 2H). 1.56-1.37 (m, 4H), 0.84 (t, J = 7.2 Hz, 3H). M/Z APCI: 533.2 (M+1), 531.1 (M-1).

Protocol #2

Example 159 : Preparation of 4-chloro-N-{[5-({4-[(2E)-3-phenylprop-2-enoyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide **159**

To a stirred solution of **1** (36 mg, 0.09 mmol) and iPr_2NEt (32 µl, 0.189 mmol) in $CHCl_3$ (2 mL) was added [(2E)-3-phenylprop-2-enoyl]chloride (15 mg, 0.09 mmol). After 4 h the reaction mixture was washed with HCl (1 N) and sat. NaCl solution, and dried over $MgSO_4$. The solvent was evaporated and the residue was filtered through silica gel using AcOEt/MeOH 1% as eluent to afford **159** as white solid (10 mg, 20%). M/Z APCI: 531.2 (M+1), 529.1 (M-1). Anal. HPLC: rt. = 6.18 min (method a).

The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned examples

Exemple	Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
160	4-chloro-N-({5-[(4-{4-nitrobenzoyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	12.75	96	b	549	547
161	N-({5-[(4-benzoylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide		85	b	504	502
162	4-chloro-N-{[5-({4-[4-(trifluoromethyl)benzoyl]-piperazin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide		98	b	572	570

163	4-chloro-N-{[5-({4-[4-(dimethylamino)benzoyl]-piperazin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide		93	b	547	545
164	4-chloro-N-[(5-{[4-(2-fluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide		98	b	522	520
165	4-chloro-N-[(5-{[4-(2,6-difluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide		96	b	540	538
166	4-chloro-N-[(5-{[4-(3-fluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide		93	b	522	520
167	4-chloro-N-[(5-{[4-(2-naphthoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	13.6	90	b	554	552
168	4-chloro-N-[(5-{[4-(1-naphthoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	13.44	93	b	554	552
169	4-chloro-N-({5-[(4-{2-nitrobenzoyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	12.26	87	b	549	547
170	4-chloro-N-[(5-{[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	9.17	84	b	505	503
171	N-[(5-{[4-(2,1,3-benzoxadiazol-5-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	12.75	99	b	546	544
172	4-chloro-N-[(5-{[4-(2,4-difluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	12.84	90	b	540	538
173	4-chloro-N-[(5-{[4-(2,4,6-trifluorobenzoyl)-piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	13.06	89	b	558	556
174	4-chloro-N-[(5-{[4-(2,6-dichlorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	13.19	95	b	574	572
175	4-chloro-N-({5-[(4-heptanoylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	6.35	99.4	a	512	510
176	4-chloro-N-[(5-{[4-(quinolin-8-ylsulfonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.86	93.6	a	591	589

Protocol #3

Example 177: Preparation of 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide **177**

{[(3-Nitrobenzoyl)amino]methyl}thiophene-2-sulfonyl chloride **177a**

To a solution of 2-Aminomethylthiophene (10.6mL, 103mmol) and pyridine (9.1mL, 104mmol) in 100mL of chloroform was added at 0°C a solution of 3-Nitrobenzoyl-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-Nitro-*N*-(thien-2-ylmethyl)-benzamide (10.1g) precipitated. The solid was filtered of and washed with water. The remaining organic layer was washed with brine, dried over $MgSO_4$ and evaporated to dryness to afford additional 3-Nitro-*N*-(thien-2-ylmethyl)benzamide (15.2g). The over-all yield was 25.3 g (99.9%). 3-Nitro-*N*-(thien-2-ylmethyl)benzamide 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 3-Nitro-*N*-(thien-2-ylmethyl)benzamide (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 $MgSO_4$ and evaporated to dryness to afford a slightly colored foam of Tetrabutylammonium 5-{[(3-Nitrobenzoyl)amino]methyl}thiophene-2-sulfonate (24g, 97%). NMR spectra indicated pure compound, which was used for the following chlorination step.

To a solution of Tetrabutylammonium 5-{[(3-Nitrobenzoyl)amino]methyl}thiophene-2-sulfonate (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. **177a** (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).

<u>3-Nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide **177**</u>

A suspension of the sulfonyl chloride **177a** (573 mg, 1.58 mmol), 4-(3-trifluoro-methanesulfonyl-phenylamino)-piperidine (490 mg, 1.58 mmol), and Et_3N (330 ul, 2.38 mmol) in CH_2Cl_2 (30 mL) was stirred for 3h at 23°C, whereupon the suspension turned to a clear solution. The standard work-up (HCl 1N; brine; $MgSO_4$) gave the crude product as a yellow foam. This was dissolved in DMSO (1 mL) and CH_3CN (3 mL), and injected on a reverse-phase prep. HPLC (C8, gradient H_2O:CH_3CN 60:40 → 0:100 over

40 min, retention time = 20 min). Freeze-drying of the desired fractions afforded 667 mg (67%) of the title sulfonamide as a pale yellow powder: ^{1}H NMR (DMSO-*d6*) δ 9.69 (t, J = 5.8 Hz, 1H), 8.72 (t, J = 1.9 Hz, 1H), 8.41 (dd, J = 8.3, 1.9 Hz, 1H), 8.34 (d, J = 7.9 Hz, 1H), 7.81 (t, J = 8.1 Hz, 1H), 7.50 (d, J = 3.8 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.23 (d, J = 3.8 Hz, 1H), 7.15–7.11 (m, 3H), 6.52 (d, J = 7.9 Hz, 1H), 4.73 (d, J = 5.7 Hz, 2H), 3.57–3.42 (br. d, J = 11.7 Hz, 2H), 3.52–3.33 (m, 1H), 2.62 (t, J = 10.4 Hz, 2H), 2.00–1.90 (br. d, J = 10.6 Hz), 1.43 (qd, $J \approx$ 10.2, 3 Hz, 2H). ^{13}C NMR (DMSO-*d6*) δ164.66 (s, C=O), 150.51 (s), 149.32 (s), 148.20 (s), 135.30 (s), 134.22 (s), 134.11 (d), 132.98 (d), 131.49 (d), 130.67 (d), 130.44 (s), 127.00 (d), 126.60 (d), 122.38 (d), 120.41 (d), 119.81 (q, J = 326 Hz, CF_3), 116.72 (d), 112.79 (d), 47.43 (d), 45.15 (t), 38.58 (t), 30.66 (t). M/Z APCI : 633 (M+1), 631 (M–1). Anal. HPLC: R.t = 6.41 min (method a). $C_{24}H_{23}F_3N_4O_7S_3$ Calc.: C: 45.56%. H: 3.66%. N: 8.86%. Found: C: 45.30%, H: 3.73%, N: 8.85%.

In the here-described sequence, the 3-nitrobenzoyl chloride initially used could be replaced with other acylating reagents, which include (but are not limited to): 4-nitrobenzoyl, 4-chlorobenzoyl chloride, 3-methoxybenzoylchloride, trifluoroacetic anhydride.

The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned examples

Exemple	Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
178	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	5.62	63.1	a	527	525
179	4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	6.77	87.3	a	633	631
180	N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	6.3	92.7	a	550	548
181	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	5.6	77.3	a	527	525
182	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	5.62	63.1	a	527	525
183	4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	6.77	87.3	a	633	631
184	N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]-	6.3	92.7	a	550	548

	sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide					
185	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	5.6	77.3	a	527	525
186	3-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.86	88.3	a	533	531
187	3-nitro-N-{[5-({4-[3-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	7.03	91	a	568	566
188	N-{[5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide	4.2	97.5	a	544	542
189	3-nitro-N-{[5-({4-[3-(methylsulfonyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.71	91.4	a	579	0
190	3-nitro-N-{[5-({4-[3-(methylsulfanyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.64	92.2	a	547	0
191	N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide	5.32	63	a	580	0
192	methyl 3-{[1-({5-[({3-nitrobenzoyl}amino)methyl]-thien-2-yl}sulfonyl)-piperidin-4-yl]amino}benzoate	5.89	88.3	a	559	557
193	N-{[5-({4-[3-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide	4.44	65.2	a	0	542
194	3-nitro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	6.53	88.4	a	546	544
195	3-nitro-N-[(5-{[4-(2-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.71	86.1	a	532	530
196	3-nitro-N-{[5-({4-[2-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	7.23	94.5	a	569	567
197	3-nitro-N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	6.68	91.4	a	546	544
198	N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	6.12	94.7	a	535	533
199	3-nitro-N-{[5-({4-[4-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	7.09	91.3	a	569	567
200	3-nitro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	6.92	92.4	a	633	631
201	N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide	4.91	61.1	a	544	542
202	N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	5.44	81.3	a	543	541
203	N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-4-nitrobenzamide	6.18	92.5	a	535	533
204	4-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.01	97	a	531	529
205	4-nitro-N-{[5-({4-[3-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	6.98	97.1	a	569	567
206	N-{[5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide	4.23	89.7	a	544	542
207	4-nitro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.44	97.5	a	543	541
208	4-nitro-N-{[5-({4-[3-(methylsulfonyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-	5.36	92.1	a	579	577

	benzamide					
209	4-nitro-N-{[5-({4-[3-(methylsulfanyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.29	90.1	a	547	545
210	N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide	4.96	90.8	a	580	578
211	methyl 3-{[1-({5-[({4-nitrobenzoyl}amino)methyl]-thien-2-yl}sulfonyl)piperidin-4-yl]amino}benzoate	5.5	99	a	559	557
212	3-{[1-({5-[({4-nitrobenzoyl}amino)methyl]thien-2-yl}sulfonyl)piperidin-4-yl]amino}benzamide	4.4	87	a	544	542
213	4-nitro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	6.13	86.3	a	546	544
214	4-nitro-N-[(5-{[4-(2-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.4	97.8	a	531	529
215	4-nitro-N-{[5-({4-[2-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	6.76	97.7	a	569	567
216	4-nitro-N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	6.66	99.5	a	546	544
217	N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	6.11	99	a	535	533
218	4-nitro-N-{[5-({4-[4-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	6.62	94.7	a	569	567
219	4-nitro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	6.48	96.8	a	633	631
220	N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide	4.92	96.7	a	543	541
221	N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide	5.41	92.4	a	605	603
222	N-({5-[(4-{3-[amino(imino)methyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide	4.24	90.4	a	543	541
223	N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide	5.22	94.7	a	610	608
224	N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide	4.35	87.9	a	501	499
225	N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitro-benzamide	4.91	94	a	610	608
226	N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide	4.34	94.4	a	501	499
227	N-({5-[(4-{3-[amino(imino)methyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide	4.23	90.8	a	543	541
228	3-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	7.23	88	a	601	599
229	4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	7.28	90.4	a	601	599
230	3-nitro-N-[(5-{[4-({3-nitropyridin-2-yl}amino)-piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	6.35	95.8	a	547	545

231	N-{[5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide	5.18	94.5	a	591	589
232	N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)-piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	4.88	92	a	541	539
233	3-nitro-N-[(5-{[4-(2-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.14	90.2	a	543	541
234	3-nitro-N-[(5-{[4-(4-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.23	93.2	a	543	541
235	N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	5.5	94.4	a	557	555
236	3-nitro-N-{[5-({4-[3-(1,3-oxazol-5-yl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.44	91.1	a	568	566
237	3-nitro-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	7.36	97.5	a	514	512
238	N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide	7.27	90.3	a	604	602
239	N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	5.97	82.3	a	577	575
240	N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	5.86	69	a	591	589
241	3-nitro-N-{[5-({4-[3-(morpholin-4-ylsulfonyl)-anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.92	96.4	a	650	648
242	3-nitro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	7.56	75	a	544	542
243	4-nitro-N-[(5-{[4-(pyrimidin-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.28	92	a	503	501
244	N-{[5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide	4.06	90	a	517	515
245	4-nitro-N-[(5-{[4-({3-nitropyridin-2-yl}amino)-piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	6.31	94.3	a	547	545
246	N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)-piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	4.92	89.9	a	541	539
247	4-nitro-N-[(5-{[4-(2-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.17	93.9	a	543	541
248	4-nitro-N-[(5-{[4-(4-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.27	93.8	a	543	541
249	N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	5.54	92.7	a	557	555
250	4-nitro-N-{[5-({4-[3-(1,3-oxazol-5-yl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.43	94.3	a	568	566
251	4-nitro-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	7.32	97.9	a	514	512
252	N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide	7.29	86.1	a	604	602
253	N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	6	85.2	a	577	575
254	N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}-	5.9	90.4	a	591	589

	thien-2-yl)methyl]-4-nitrobenzamide					
255	4-nitro-N-{[5-({4-[3-(morpholin-4-ylsulfonyl)-anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.95	95.5	a	650	648
256	N-[(5-{[4-(2-aminoanilino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-3-nitrobenzamide	4.37	75.6	a	516	514
257	3-nitro-N-[(5-{[4-(pyrimidin-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.24	89.1	a	503	501
258	N-{[5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide	4.03	80	a	517	515
259	N-({5-[(4-{2-nitro-4-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	6.66	96.8	a	690	988
259	ethyl 5-{[(3-methoxybenzoyl)amino]methyl}-2-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thiophene-3-carboxylate	6.66	96.8	a	690	988
260	3-nitro-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.41	99.3	a	529	527
261	3-nitro-N-({5-[(4-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	5.78	99.3	a	571	569
262	N-[(5-{[4-(3-cyclohexyl-4-hydroxyanilino)-piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	4.78	81	a	599	597
263	N-({5-[(4-{3-[(butylamino)sulfonyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide	5.8	99.4	a	636	634
264	N-[(5-{[4-(3-ethylanilino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-3-nitrobenzamide	4.64	97.6	a	529	527
265	3-nitro-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	5.13	88.5	a	555	553
266	4-nitro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	7.57	75.8	a	544	542
267	N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	6.33	97.7	a	550	553

Protocol #4

Example 268: Preparation of N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-3-methoxybenzamide **268**

{[(3-Methoxybenzoyl)amino]methyl}thiophene-2-sulfonyl chloride **268a**

The title sulfonylchloride was prepared according to the synthetic **protocol#3** (example 177).

After flash chromatography using cyclohexane/EtOAc 1:1 as eluent, the main fractions were recrystallized from CH_2Cl_2/cyclohexane to afford pure 17.5g of **268a**.

^{1}H NMR ($CDCl_3$) δ 7.79 (t, J = 4.0 Hz, 1H), 7.65 (t, J = 7.9Hz, 1H), 7.58 (m, 1H), 7.70-7.35 (t, J = 8.1 Hz, 1H), 7.06 (m, 2H), 5.07 (d, J = 3.8 Hz, 2H), 3.88 (s, 3H).

N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide, **268**

268 was prepared using the general procedure protocol applied for the preparation of **2** and could be isolated as colorless solid in 98% yield (62mg).). M/Z APCI : 535 (M+1), 533 (M–1). Anal. HPLC: rt. = 6.22 min (method a).

Example 269: Preparation of 2-Hydroxy-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide **269**

Diallyl-thiophen-2-ylmethylamine **269a**

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 ($CDCl_3$) δ 7.25 (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 **269b**

A solution of the allyl-protected thiophene **269a** (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 **269b** as a pale brown oil which was used without further purification.

N,N-Diallyl-*N*-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]-thien-2-yl}methyl)amine **269c**

A solution of 4-(3-trifluoromethanesulfonyl-phenylamino)-piperidine (731 mg, 2.37 mmol) and Et_3N (0.5 mL, 3.58 mmol) in CH_2Cl_2 (20 mL) was treated with the diallylamino sulfonyl chloride **269b** 23°C. A thick precipitate appeared within 5 min, and the mixture was stirred overnight (even if complete within minutes). Dilution with CH_2Cl_2 (50 mL), washing (H2O; brine), drying ($MgSO_4$), and evaporation afforded the crude product, which was filtered over silica gel (AcOEt:cyclohexane 1:1) to afford 1.15 g (86%) of the title bisallylamine, which was used in the next step without further purification.

2-Hydroxy-*N*-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]-thien-2-yl}methyl)benzamide **269**

A solution of the bisallylamine **269c** (1.15 g, 2.04 mmol), N,N'-dimethylbarbituric acid (NDMBA, 637 mg, 4.08 mmol), and $Pd(PPh_3)_4$ (110 mg, 0.096 mmol) in CH_2Cl_2 (20 mL) was degassed by bubbling argon for 10 min. The reaction was stirred at 23°C over the week-end (3 d), concentrated, diluted with DMF (12 mL), and treated with salicylic acid (290 mg, 2.10 mmol), 1-hydroxybenzotriazole (HOBt, 283 mg, 2.10 mmol), and N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide (EDC, 402 mg, 2.10 mmol) for 24 h at 23°C. Dilution with EtOAc, washing (H_2O, $NaHCO_3$ sat., brine), drying ($MgSO_4$), and evaporation afforded the crude 3-hydroxybenzamide. Purification by reverse-phase prep. HPLC (C8, H_2O:CH_3CN 60:40 → 0:100 over 40 min, r.t. = 23 min) and freeze-drying afforded 466 mg (38% from **269c**) of the title 3-hydroxybenzamide as a white powder: ^1H NMR (DMSO-*d6*) δ 12.1 (s, 1H), 9.48 (t, J = 5.9 Hz, 1H), 7.86 (dd, 7.9,1.5 Hz, 1H), 7.50 (d, J = 3.8 Hz, 1H), 7.45 (t, J = 8.1 Hz, 1H), 7.41 (dd, J = 8.9, 1.5 Hz, 1H), 7.21 (d, J = 3.8 Hz, 1H), 7.18–7.10 (m, 3H), 6.93 (d, J = 8.3 Hz, 1H), 6.91 (td, J = 8.4, 1.1 Hz, 1H), 6.52 (d, J = 7.7 Hz, 1H), 4.73 (d, J = 5.8 Hz, 2H), 3.57–3.47 (br. d, J = 12.1, 2H), 3.52–3.35 (br. m., 1H), 2.62 (t, J =10.4 Hz, 2H), 2.07 (s, 1.2H, residual CH_3CN), 2.02–1.92 (br. d, J = 10.4 Hz, 2H), 1.47 (qd, $J \approx$ 11.2, 3.6 Hz, 2H). ^{13}C NMR (DMSO-*d6*) δ167.52 (s, C=O), 158.36 (s), 148.98 (s), 147.85 (s), 132.83 (d), 132.74 (s),

131.47 (d), 130.00 (d), 128.98 (s), 127.09 (d), 125.52 (d), 124.83 (s), 118.92 (q, residual CH_3CN), 118.34 (q, J = 326 Hz, CF_3), 117.75 (d), 116.24 (d), 115.23 (d), 114.19 (q), 111.33 (d), 45.93 (d), 43.66 (t), 36.66 (t), 29.18 (t), 0.00 (s, residual CH_3CN). M/Z APCI : 604 (M+1), 602 (M–1). Anal. HPLC: R.t = 6.60 min (method a).

$C_{24}H_{24}F_3N_3O_6S_3 \cdot 0.3\ CH_3CN \cdot 1.0\ H_2O$ Calc.: C: 47.53%. H: 4.36%. N: 7.44%. Found: C: 47.41%, H: 4.09%, N: 7.49%.

In this protocol, salicylic acid could be replaced with other carboxylic acids, which include (but are not limited to): 4-chlorobenzoic acid, 4-nitrobenzoic acid, 3-nitrobenzoic acid, 3-methoxybenzoic acid, 5-nitro-1H-pyrazole-3-carboxylic acid, 2-hydroxynicotinic acid, 2-mercaptonicotinic acid, 3,4-dihydroxybenzoic acid, 2-picolinic acid.

The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned examples

Exemple	Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
270	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	5.55	91.6	a	512	510
271	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-hydroxybenzamide	5.6	89.4	a	498	496
272	N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide	5.74	88.1	a	605	603
273	3-methoxy-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.58	88.6	a	516	514
274	3-methoxy-N-{[5-({4-[3-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	6.5	97.5	a	554	552
275	N-{[5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxy-benzamide	4.4	83.1	a	530	528
276	3-methoxy-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.29	93.3	a	528	526
277	3-methoxy-N-{[5-({4-[3-(methylsulfonyl)-anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.59	95.7	a	564	562
278	3-methoxy-N-{[5-({4-[3-(methylsulfanyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.5	97	a	532	530

279	N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxy-benzamide	5.2	93.8	a	565	563
280	methyl 3-({1-[(5-{[(3-methoxybenzoyl)amino]-methyl}thien-2-yl)sulfonyl]piperidin-4-yl}amino)-benzoate	5.76	96.8	a	544	542
281	N-{[5-({4-[3-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxy-benzamide	4.08	95.4	a	529	527
282	3-methoxy-N-[(5-{[4-(2-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.58	90.2	a	516	514
283	N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	6.44	89.3	a	531	529
284	3-methoxy-N-{[5-({4-[2-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	7.15	96.9	a	554	552
285	N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]-thien-2-yl}methyl)-3-methoxybenzamide	6.59	95.2	a	531	529
286	N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxy-benzamide	4.57	95.2	a	529	0
287	N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxy-benzamide	5.64	96.6	a	599	597
288	N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-3-methoxybenzamide	6.57	97.7	a	520	518
289	N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-3-methoxybenzamide	6.86	100	a	520	518
290	3-methoxy-N-({5-[(4-{4-[(trifluoromethyl)-sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	6.88	98	a	618	616
291	N-({5-[(4-{3-[amino(imino)methyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	4.18	91.3	a	528	526
292	N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	5.11	92.2	a	594	592
293	3-methoxy-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	6.55	88.1	a	618	616
294	N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	4.52	88.5	a	486	484
295	3-methoxy-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	6.54	92.9	a	586	584
296	N-[(5-{[4-(4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	3.98	88	a	502	500
297	3-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	7.23	88	a	601	599
298	4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide	7.28	90.4	a	601	599
299	N-[(5-{[4-(2-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.12	89.8	a	502	500
300	3-methoxy-N-[(5-{[4-(pyrimidin-2-ylamino)-	4.15	92.7	a	488	486

	piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide					
301	N-{[5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxy-benzamide	3.96	93.1	a	502	500
302	N-[(5-{[4-({3-nitropyridin-2-yl}amino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	6.22	100	a	532	530
303	N-{[5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide	5.04	98.5	a	576	574
304	N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)-piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.81	97.1	a	526	524
305	3-methoxy-N-[(5-{[4-(2-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.99	99	a	528	526
306	3-methoxy-N-[(5-{[4-(4-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.15	97.9	a	528	526
307	N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	5.41	98.9	a	542	540
308	N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	7.23	96.1	a	589	587
309	3-methoxy-N-{[5-({4-[3-(1,3-oxazol-5-yl)anilino]-piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.25	94.9	a	553	551
310	N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	5.82	97.1	a	562	560
311	3-methoxy-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	7.55	78.7	a	529	527
312	3-methoxy-N-{[5-({4-[3-(morpholin-4-ylsulfonyl)-anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-benzamide	5.85	96.9	a	635	633
313	3-methoxy-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	7.2	98.3	a	499	497
314	N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-3-methoxybenzamide	5.77	97.6	a	576	574
315	3-methoxy-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.33	99.7	a	514	512
316	3-methoxy-N-({5-[(4-{[4-(trifluoromethyl)-pyrimidin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	5.69	100	a	556	554
317	N-[(5-{[4-(3-cyclohexyl-4-hydroxyanilino)-piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.76	91.7	a	584	582
318	N-({5-[(4-{3-[(butylamino)sulfonyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide	5.77	99.3	a	621	619
319	N-[(5-{[4-(3-ethylanilino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-3-methoxybenzamide	4.54	94.4	a	514	512
320	3-methoxy-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.02	88.2	a	540	538
321	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-5-nitro-1H-pyrazole-3-carboxamide	5.12	96.2	a	517	515
322	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-	4.15	93	a	499	497

	yl]sulfonyl}thien-2-yl)methyl]-2-oxo-1,2-dihydropyridine-3-carboxamide					
323	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-thioxo-1,2-dihydropyridine-3-carboxamide	4.43	85.8	a	515	513
324	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3,4-dihydroxybenzamide	4.62	89.1	a	514	512
325	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]pyridine-2-carboxamide	5.22	98.9	a	483	481

Example 326: Preparation of N-[(5-{[4-(hexyloxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide **326**

N,N-diallyl-*N*-[(5-{[4-(hexyloxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]amine **326a**

To a solution of 4-hydroxy-piperidine (190mg, 1.88 mmol) and DIEA (0.87mL, 5.13 mmol) in 10 mL CH_2Cl_2 was added a solution of 5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl chloride 1b (500mg, 1.71mmol) in hot DCE. The reaction mixture was stirred for 4h. 100mL EtOAc were added and excess of amines were removed by extraction with HCl (1N). The sulfonamide intermediate was used without any further purification, where 300mg (0.84mmol) were dissolved in dry DMF under Ar. NaH (60mg, 50% in parafine oil, 1.01mmol) were added as a solid. The colour of the reaction changed to orange. The reaction mixture was stirred for 15' until no gas evolution was observed anymore. Iodohexane (356mg, 1.68mmol) dissolved in 1mL DMF was added to the above solution and the reaction mixture was heated at 70°C overnight. DMF was evaporated to dryness and the crude was taken up in CH_2Cl_2. The organic layer was washed twice with water, dried over $MgSO_4$ and evaporated to dryness. The crude was purified on silica gel using cyclohexane/EtOAc 3:1 as eluent to obtain 210 mg (59%) of pure **326a** as a colorless oil.

N-[(5-{[4-(hexyloxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide **326**

A solution of **326a** (134mg, 0.3mmol), 1,3 Dimethylbarbituric acid (94mg, 0.6mmol) and Tetrakis(triphenylphosphine)palladium (12mg, 0.01mmol) were stirred under Argon in 3 mL CH_2Cl_2. The reaction was followed by HPLC until all starting material disappeared. The crude was evaporated to dryness and taken up in dry THF. To this solu-

tion was added DIEA (230ul, 1.5mmol) and 3-anisoylchloride (51mg, 0.3mmol). The reaction was stirred for 3h, EtOAc was added and the organic layer was extracted with NaHCO3 sat., HCl (0.1N) and brine. The dry solution was evaporated and purified by flash chromatography on silica gel using cyclohexane/EtOAc 7:3 as eluent. **326** was obtained as an oil (54mg, 37%): H^1 NMR ($CDCl_3$) δ 7.43-7.25 (m, 4H), 7.15-7.05 (m, 2H), 6.60 (m, 1H), 4.83 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 3.35 (d, J = 6.6, 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: 495.2 (M+1).

Example 327: Preparation of *N*-({5-[(4-heptanoylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide **327**

Methyl 1-({5-[(diallylamino)methyl]thien-2-yl}sulfonyl)piperidine-4-carboxylate **327a**

5-Diallylaminomethyl-thiophene-2-sulfonyl chloride **229b** (270 mg, 1.88mmol) and DIEA (0.88mL, 5.13mmol) were dissolved in 10 mL chloroform. This solution was added methylisonipecotate (269 mg, 1.88mmol) in 1 mL chloroform. The reaction was stirred for 3h, diluted with CH_2Cl_2 and extracted with HCl (0.1N), $NaHCO_3$ sat. and brine. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The crude was purified by flash chromatography on silica gel using cyclohexane/EtOAc 1:1 as eluent to obtain 440 mg (65%) of **327a** as colorless oil: H^1 NMR ($CDCl_3$) δ 7.30 (d, J = 3.6 Hz, 1H), 6.83 (d, J = 3.6 1H), 5.78 (m, 2H), 5.18 (m, 4H), 3.70 (s, 2H), 3.52 (m, 6H), 3.07 (m, 4H), 2.50 (m, 2H), 2.25 (m, 1H), 1.93 (m, 2H), 1.84 (m, 2H). M/Z APCI: 399.2 (M+1)

1-({5-[(diallylamino)methyl]thien-2-yl}sulfonyl)-*N*-methoxy-*N*-methylpiperidine-4-carboxamide **327b**

327a (390mg, 1mmol) and N,O-dimethylhydroxylamine (148mg, 1.52mmol) were stirred at –20°C in anhydrous THF, while Isopropylmagnesium chloride in THF (2M, 1.65mL, 3.23mmol) were slowly added. The reaction mixture was allowed to warm to r.t. during 30', followed by an additonal stirring at r.t. for 30'. The reaction is quenched

with ammoniumchloride solution (20%). The aqueous layer is extracted with t-butylmethylether, and the combined organic layers are washed with brine, dried over $MgSO_4$ and evaporated to dryness. The crude is purified by flash chromatography on silica gel using cyclohexan/EtOAc 1:1 as eluent. **327b** (380 mg, 90%) was obtained as a colourless solid: H^1 NMR (DMSO *d6*) δ 7.53 (d, J = 3.7 Hz, 1H), 7.16 (d, J = 3.6 1H), 5.89 (m, 2H), 5.24 (m, 4H), 3.86 (s, 2H), 3.62 (m, 5H), 3.15 (m, 7H), 2.74 (m, 1H), 2.50 (m, 2H), 2.25 (m, 2H), 1.84 (m, 2H), 1.63 (m, 2H). M/Z APCI: 428.1 (M+1).

1-[1-({5-[(diallylamino)methyl]thien-2-yl}sulfonyl)piperidin-4-yl]heptan-1-one **327c**

327b (376mg, 0.88mmol) was dissolved in anhydrous THF and cooled to –20 °C. To this solution was added dropwise at –20°C hexyllithium (2M in hexane) (2.46mL, 6.2 mmol).The reaction was allowed to warm to rt. during 3h and poured on 100mL HCl /EtOH (5%). The aqeous phase was extracted with CH_2Cl_2 and the combined organic layers are washed with NaOH (2N) and brine, dried over $MgSO_4$ and evaporated to dryness. The crude material was purified by flash chromatography on silica gel using cyclohexane/EtOAc 4:1 as eluent to obtain 186 mg (47%) of (327c) as a brownish oil: H^1 NMR ($CDCl_3$) δ 7.40 (d, J = 3.6 Hz, 1H), 7.25 (d, J = 3.6 1H), 5.95 (m, 2H), 5.50 (m, 4H), 4.32 (s, 2H), 3.70-3.50 (m, 6H), 2.50 (m, 2H), 2.32 (m, 3H), 1.85 (m, 2H), 1.68 (m, 2H), 1.46 (m, 2H), .1.30-1.12 (m, 6H), 0.80 (t, J = 6.6 Hz, 3H), M/Z APCI: 453.2 (M+1)

N-({5-[(4-heptanoylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide **327**

A solution of **327c** (100mg, 0.22mmol), 1,3Dimethylbarbituric acid (69mg, 0.44mmol) and Tetrakis(triphenylphosphine)palladium (12 mg, 0.01mmol) were stirred in 3 mL CH_2Cl_2 overnight. The deprotection was followed by TLC. After complete cleavage of the protecting groups, the solvent was evaporated to dryness. The crude was taken up in THF, DIEA (76ul, 0.33mmol) was added, followed by the slow addition of 3-anisoylchloride (38mg, 0.22mmol) in THF. The reaction was stirred for 3h, diluted with EtOAc and extracted with $NaHCO_3$ and brine. The organic layers were dried over Na2SO4 and evaporated to dryness. The crude mixture was purified by flash chroma-

tography on silica gel using cyclohexane/EtOAc 1:1 as eluent to obtain 30mg (50%) of **327** as a colorless oil: H^1 NMR ($CDCl_3$) δ 7.40-7.10 (m, 3H), 6.95 (m, 2H), 6.45 (m, 1H), 4.70 (d, J = 6.0 Hz, 2H), 3.74 (s, 3H), 3.58 (m, 2H), 2.40 (m, 2H), 2.27 (t, J = 7.5 Hz, 2H), 2.19 (m, 1H), 1.77 (m, 2H), 1.64 (m, 2H), .1.13 (m, 8H), 0.74 (t, J = 6.8 Hz, 3H), M/Z APCI: 506.3 (M+1).

Example 328: Preparation of 4-chloro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide **328**

4-Chloro-*N*-2-furylmethyl-benzamide **328a**

A solution of 4-chlorobenzoyl chloride (3.2g, 18.5 mol) in 50 ml dry CH_2Cl_2 was added over 30 min to a stirred solution of 2-furfurylamine (2g, 20.6 mol) and $^iPr_2NEt$ (7ml, 41 mol) in CH_2Cl_2 (200 ml) at 0°C. The reaction was allowed to warm to room temperature over 3 h. The mixture was diluted with 200 ml of CH_2Cl_2, washed twice with HCl aq. (1N) and dried over $MgSO_4$. Evaporation of the solvent afforded 4g (83%) of the title benzamide as a white solid: ^1H NMR (DMSO-d^6) δ 9.05 (t, J = 5.7 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.57 (m, 1H), 7.53 (d, J = 8.7 Hz, 2H), 6.40 (dd, J = 3.7, 1.1 Hz, 1H), 6.28 (d, J = 3.7 Hz, 1H), 4.46 (d, J = 5.6 Hz, 2H). M/Z APCI : 236.6 (M+1), 234.8 (M–1).

5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-furane-2-sulfonyl chloride **328b**

Chlorosulfonic acid (494mg, 4.24 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of **9a** (500mg, 2.12 mmol) in CH_2Cl_2 (20 ml) at –80°C. The mixture was allowed to reach room temperature in 5h. Excess of sulfonic acid was quenched with ice and $NaHCO_3$. 1.62 ml (40% aqueous sol., 2.54 mmol) of Tetrabutylammonium hydroxide were added, and the so formed salt was extracted with DCM. The organic layer was dried over MgSO4, filtered and evaporated to dryness. A red coloured oil (1.11g) could isolated in 94% yield, which was used for the following step with any further purification.

The intermediate sulfonic acid tetrabutylammonium salt (1.1g, 1.97 mmol) was dissolved in 20ml DCM and flushed with Argon. Triphosgene (410mg, 1.38 mmol) was

added as a solid followed by the addition of a solution of 60 µl DMF in 2ml DCM. The reaction was stirred under Ar. for 3h at r.t. The solvent was evaporated using reduced pressure, and the crude oily residue was purified by flash chromatography using PE/EtOAc 2:1 as eluant. Main fractions afforded 450mg (69%) of title sulfonylchloride **328b.** ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 3.4 Hz, 1H), 6.43 (t, b, 1H), 6.40 (d, J = 3.4 Hz, 1H), 4.57 (d, J = 6.0 Hz, 2H).

4-chloro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide **328**

328 was synthesised according to the protocol for the synthesis of **2**. Isolated yield: 21 mg (82%). Anal. HPLC: R.t = 5.34 min (method a). M/Z APCI: 516.2 (M+1), 514.1 (M-1).

The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned examples

Exemple	Name	rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
329	4-chloro-N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide	6.41	97.8	a	508	506
330	4-chloro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide	4.86	92	a	504	502
331	4-chloro-N-{[5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide	6.73	96.8	a	542	540
332	4-chloro-N-{[5-({4-[3-(dimethylamino)anilino]-piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide	4.29	93.6	a	517	515
333	4-chloro-N-{[5-({4-[3-(methylsulfonyl)anilino]-piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide	5.42	98	a	552	550
334	4-chloro-N-{[5-({4-[3-(methylsulfanyl)anilino]-piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide	5.46	96	a	520	518
335	N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}-4-chlorobenzamide	5.08	94	a	553	551
336	methyl 3-({1-[(5-{[(4-chlorobenzoyl)amino]-methyl}-2-furyl)sulfonyl]piperidin-4-yl}amino)-benzoate	5.64	98	a	532	530
337	3-({1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-furyl)sulfonyl]piperidin-4-yl}amino)benzamide	4.3	97.1	a	517	515
338	4-chloro-N-({5-[(4-{3-nitroanilino}piperidin-1-	6.22	87.4	a	519	517

	yl)sulfonyl]-2-furyl}methyl)benzamide					
339	4-chloro-N-[(5-{[4-(2-methoxyanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide	4.56	98.4	a	504	502
340	4-chloro-N-{[5-({4-[2-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide	6.86	97.6	a	542	540
341	4-chloro-N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]-2-furyl}methyl)benzamide	6.29	97.9	a	519	517
342	4-chloro-N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide	5.88	98.1		508	506
343	4-chloro-N-{[5-({4-[4-(trifluoromethyl)anilino]-piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide	6.73	96.9		542	540
344	4-chloro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]-2-furyl}methyl)-benzamide	6.57	99.1		606	604
345	N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}-4-chlorobenzamide	4.61	94.3		517	515
346	4-chloro-N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]-piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide	5.55	96.7		578	576
347	N-({5-[(4-{3-[amino(imino)methyl]anilino}-piperidin-1-yl)sulfonyl]-2-furyl}methyl)-4-chloro-benzamide	4.07	94.5		516	514
348	4-chloro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]-2-furyl}methyl)-benzamide	6.77	94.7	a	606	604
349	N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]-2-furyl}-methyl)-4-chlorobenzamide	4.52	93.8		474	472
350	4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]-anilino}piperidin-1-yl)sulfonyl]2-furyl}methyl)-benzamide	7.12	97	a	574	572

Example 351 Preparation of 4-chloro-*N*-({5-[(3-{3-[(trifluoromethyl)sulfonyl]-anilino}pyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide **351**

4-chloro-*N*-[(5-{[(3*R*)-3-hydroxypyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide **351a**

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 1b (1.0g, 2.86mmol). 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 **351a** (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 **351b**

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 15'. **351a** (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' 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. **351b** (80mg, 80%) was obtained as a colourless solid.: H^1 NMR ($CDCl_3$) δ7.72 (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-{3-[(trifluoromethyl)sulfonyl]anilino}pyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide **351**

351b was prepared according to the protocol #1 example 110 and was isolated as colourless solid in 84% yield (15mg). M/Z APCI: 609 (M+1), 607 (M–1).)

Example 352 : Preparation of 4-chloro-*N*-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}-azepan-1-yl)sulfonyl]thien-2-yl}methyl)benzamide **352**

352 was prepared according to the protocol #1 example 110 and was isolated as colourless solid in 47% yield (12mg). M/Z APCI: 637 (M+1), 639 (M–1).).

Example 353 : 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 354: Biological assays

Biological Results

The activities of the sulfonamide derivatives claimed in the formula I were assessed using the above described *in vitro* and *in vivo* biological assays.

JNK 2 and 3 in vitro assays: JNK3 and/or 2 assays are performed in 96 well MTT plates, by 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 sulfonamide inhibitors if 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 substituting GST-c Jun for biotinylated GST-$_1$ATF$_2$ or myelin basic protein, this assay can be used to measure inhibition of preactivated p38 and ERK MAP Kinases, respectively.

Exemple	*JNK3*	*JNK2*	*p38*	*ERK2*
37	0.68	1.19	>30	>30
84	0.86	1.30	>30	>30
86	0.80	1.05	>30	>30
91	0.15	0.64	>30	>30
109	0.23	0.59	>30	>30
110	0.11	0.31	>30	>30
120	0.40	0.56	>30	>30
131	0.71	2.23	>30	>30

155	0.53	0.50	>30	>30
168	0.89	1.20	>30	>30
204	0.17	0.22	>30	>30
211	0.27	0.39	>30	>30
271	0.36	0.22	>30	>30
285	0.19	0.23	>30	>30

The values indicated in respect of JNK2 and 3, p38 and ERK2 refer to the IC_{50} (μM), i.e. the amount necessary to achieve 50% inhibition of said target (e.g. JNK2). From the above table it could be derived that said test compounds according to formula I do have a significant effect both on JNK2 and 3, but virtually no effect onto p38 and ERK2, thus delivering a quite selective inhibitory effect.

Sympathetic Neuron Culture and Survival Assay

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 containing 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 cells death (% neurons alive between 10 and 80)

Il-2 Release Assay:

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 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 concentration of test compound (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 ul PMA + 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+Iono-stimulated Jurkat cells, in presence or absence of test compounds is assayed by ELISA. Following the procedure described below

Solutions

Wash buffer: PBS- Tween 0.05%

Diluent: PBS- Tween 0.05%

Substrate solution: Citric acid 0.1M/Na_2HPO_4 0.1M

Stop solution: H_2SO_4 20%

Matched Antibody pairs/ standard:

From R&D Systems

Monoclonal anti-human IL-2 antibody (MAB602) (capture)

Biotinylated anti-human IL-2 antibody (BAF202) (detection)

Recombinant human IL-2 (202-IL-010) (standard)

Plate preparation

Transfer 100 μl capture antibody diluted in PBS at 5 μg/mL into a 96 well ELISA plate and incubate overnight at room temperature.

Aspirate each well and wash 3 times with Wash buffer. After the last wash, damp the plate.

1. Saturate with 200 µl PBS-10% FCS. Incubate 1 hour at room temperature.
2. Repeat the wash step 2.

Assay procedure

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

The result of this assay with various test compounds is summarized below:

Exemple	*% Inhibition of IL2 Production @3uM*
37	> 30
84	> 30
86	> 30
91	> 30
109	> 30
110	> 30
120	> 30
131	> 30
155	> 30

168	> 30
204	> 30
211	> 30
271	> 30
285	> 30

C-Jun Reporter Assay

Cell culture

Hlr c-Jun HeLa 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.

Cells are kept in culture for no more than 20 passages.

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 are added to 10 mL of culture medium.

The cell suspension is then centrifuged for 5 minutes at 1200 rpm, the supernatant is removed and the cell pellet reconstituted in the medium and add to a 175 cm^2 flask containing 25 mL medium. The flasks are incubated at 37° C in an atmosphere of 5 % CO_2.

Cell passage

The cells are serially subcultured (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 resuspended in 10 mL of complete medium and centrifuged for 5 minutes at 1200 rpm.

The supernatant are discarded, the cells are resuspended in culture medium and diluted 1/5 in 175 cm^2 flasks.

Day 0 morning

Prepare cells for transfections

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

The cells are resuspended in culture medium and counted.

The cell suspension 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 containing100 µl of culture medium per well is prepared

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

Compound : 2 µl of Hit compound stock dilution are added to the 100µl(in triplicate).

The transfected cells are trypsinised and ressuspend 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

Hit compound dilutions

Hit compound stock concentrations are the following:

3, 1 and 0.1mM in 100% DMSO.

Day 2

Test procedure

Dual-Luciferase™ Reporter Assay System (Promega)

The medium is removed from the plate and the cells washed two times with 100µl PBS Completely remove the rinse solution before applying PLB reagent. Dispense into each culture well 5µl of 1X PLB. Place the culture plates on a rocking platform or orbital shaker with gentle

rocking/shaking to ensure complete and even coverage of the cell monolayer with 1X PLB. Rock the culture plates at room temperature for 15 minutes. Transfer 20 µl of the lysate into a white opaque 96 wells plate. Read in a luminometer.

-Inject 50µl of Luciferase Assay Reagent II wait 5'', read 10''

-Inject 50µl of Stop & Glo ® Reagent wait 5'', read 10''

Check RLU Luciferase/RLU Renilla*1000

The result of this assay with various test compounds is summarized below:

Exemple	*% inhibition @10uM*
37	> 30
84	> 30
86	> 30
91	> 30
109	> 30
110	> 30
120	> 30
131	> 30
155	> 30
168	> 30

204	> 30
211	> 30
271	> 30
285	> 30

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:

LPS (S. abortus-Galanos Lab.-) was injected (200 µg/kg, i.v.) to Male C57BL/6 to induce endotoxin shock and compounds (0.1, 1, 10 mg/kg) or NaCl (200uM) were 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 supernatant for the measurement of cytokines production by mouse ELISA kit such as IFNγ (Duoset R&D Ref. DY485). The test compounds displayed considerable capability to reduce inflammatory related cytokines.

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:

-1- METHOD

* Surgery

- Anesthesia: halothane or isoflurane (0.5-4%).
- Sheaving of the gorge and incision of the skin.
- The common carotid arteries (left and right) are freed from tissue.
- Occlusion of the arteries using Bulldog microclamps during 5 min.
- Disinfection of the surgery plan (Betadine®) and suture of the skin (Autoclip® ou Michel's hooks).
- 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 and/or TUNEL method
- Evaluation of the lesions (in CA1/CA2 subfields of the hippocampus)
  - Gerhard & Boast score modified or
  - Cell counting in the CA1/CA2

* Biochemical parameters

- Microdissection of the cerebral structures
- Parameters determined: DNA fragmentation, lactate, calcium penetration.
- Analytical methods: ELISA, colorimetry, enzymology, radiometry.

-2- TREATMENT

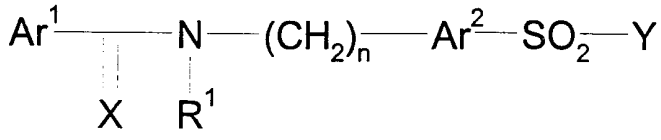
- Administration of the test article or the vehicle: 15 min after reperfusion (5-10 min after the recovery of the anesthesia).
- Standard protocol

50 animals : 5 groups of 10 (group A : control, groups B-D : test article at 3 doses and group E : reference compound (ketamine 3x120 mg/kg, *ip* or Orotic acid 3x300 mg/kg, *ip*).

The test compounds displayed considerable capability to protect from neuronal apoptosis during induced global ischemia.

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 substituted or unsubstituted aryl or heteroaryl groups,

X is O or S, preferably O;

R^1 is hydrogen or a C_1-C_6-alkyl group, or R^1 forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar^1;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1;

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing a sulfonamide,

with the proviso that if Ar^1 is 4-chlorophenyl, X is O, R^1 is H, Ar^2 is thienyl, while Y is a piperazino group, L^1 shall not be diphenylmethyl, benzo[1,3]dioxol-5-yl-methyl, 4-methoxy phenyl, 2-hydroxyethyl, methyl, 4-chlorophenyl methyl, and if Y is a 3-methyl piperazino, L^1 shall not be 4-chlorophenyl methyl, and if Y is piperazino-3, 5-dione, L^1 shall not be 2-phenyl ethyl,

with the further proviso that if Ar^1 is 4-chlorophenyl, X is O, R^1 is H, Ar^2 is thienyl, while Y is a piperidino group with L^1 being H, L^2 shall not be 2-hydroxy ethyl;

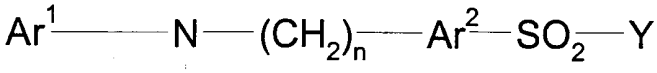
with the further proviso that if Y is a piperidino- or a pyrrolidino group being substituted at the β–position of the piperidino- or a pyrrolidino nitrogen by a benzo[5, 6]cyclohepta[1, 2b]pyridine, or a benzo[5, 6]cyclohept (3,4) ene [1, 2b]pyridine, while Ar^2 is thienyl, X is oxygen, R^1 is hydrogen and n is 1, Ar^1 shall not be a phenyl group;

with the further proviso that if X is oxygen, R^1 is hydrogen and n is 1, while Y is a piperazine, said piperazine at the para-nitrogen shall not be substituted by a group containing a benzamidine or a protected form thereof;

with the further proviso that the compounds 2-{[2-(benzoylaminomethyl)-thiophene]-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyanopent[f]isoindol-6-amine and N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]–2-thienyl] methyl] benzamide and its hydrochloride are excluded;

with the final proviso that if X is oxygen and Y is a 4-8 membered saturated cyclic alkyl containing one or two nitrogen atoms, Y shall not be substituted by a group (C=O)N(R,R') at the α-position of the sulfonamide nitrogen.

2. 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 substituted or unsubstituted aryl or heteroaryl groups,

X is O or S, preferably O;

R^1 is hydrogen or a C_1-C_6-alkyl group, or R^1 forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar^1;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1;

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing a sulfonamide, for use as a medicament;

with the proviso that if Y is a piperidino- or a pyrrolidino group being substituted at the β–position of the piperidino- or a pyrrolidino nitrogen by a benzo[5, 6]cyclohepta[1, 2b]pyridine, or a benzo[5, 6]cyclohept (3,4) ene [1, 2b]pyridine,

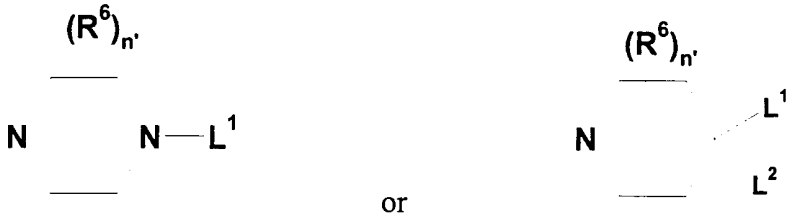
while Ar^2 is thienyl, X is oxygen, R^1 is hydrogen and n is 1, Ar^1 shall not be a phenyl group;

with the further proviso that if X is oxygen, R^1 is hydrogen and n is 1, while Y is a piperazine, said piperazine at the para-nitrogen shall not be substituted by a group containing a benzamidine or a protected form thereof;

with the further proviso that the compounds 2-{[2-(benzoylaminomethyl)-thiophene]-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyanopent[f]isoindol-6-amine and N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]–2-thienyl] methyl] benzamide and its hydrochloride are excluded;

with the final proviso that if X is oxygen and Y is a 4-8 membered saturated cyclic alkyl containing one or two nitrogen atoms, Y shall not be substituted by a group (C=O)N(R,R') at the α-position of the sulfonamide nitrogen.

3. A sulfonamide derivative according to claim 1 or 2, wherein Y is a piperazino- or piperidino group of the general formula



or

whereby, L^1 and L^2 are independently selected from each other from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-aliphatic alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, substituted or unsubstituted cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L^1 and L^2 are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl, -C(O)-OR^3, -C(O)-R^3, -C(O)-$NR^{3'}R^3$, -$NR^{3'}R^3$, -$NR^{3'}C(O)R^3$, -$NR^{3'}C(O)NR^{3'}R^3$, -(SO)R^3, -(SO_2)R^3, -NSO_2R^3, -$SO_2NR^{3'}R^3$, with R^3, $R^{3'}$ being substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted aryl, substituted or un-

substituted heteroaryl, substituted or unsubstituted aryl-C_1-C_6-alkyl, substituted or unsubstituted heteroaryl-C_1-C_6-alkyl;

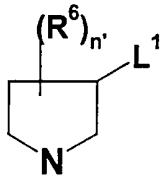
said aryl or heteroaryl groups being optionally substituted C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfonyl, sulfoxy, C_1-C_6-thioalkoxy,

or L^1 and L^2 taken together form a 4-8-membered, substituted or unsubstituted saturated cyclic alkyl or heteroalkyl group; and

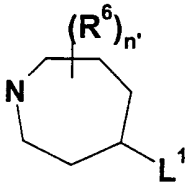
R^6 is selected from the group comprising or consisting of hydrogen, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_1-C_6-alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo (=O), and

n' is an integer from 0 to 4, preferably 1 or 2.

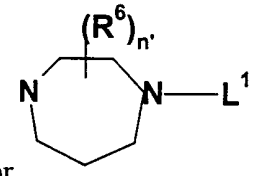
4. A sulfonamide derivative according to claim 1 or 2, wherein Y is a pyrrolidine, an azepan or a 1,4-diazepan moiety of the below formulas



or



or



wherein L^1 is selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, substituted or unsubstituted cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L^1 and L^2 are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl, -C(O)-OR^3, -C(O)-R^3, -C(O)-$NR^{3'}R^3$, -$NR^{3'}R^3$, -$NR^{3'}C(O)R^3$, -$NR^{3'}C(O)NR^{3'}R^3$, -(SO)R^3, -(SO_2)R^3, -NSO_2R^3, -$SO_2NR^{3'}R^3$;

R^3 and $R^{3'}$ are substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl-C_1-C_6-alkyl, substituted or unsubstituted heteroaryl-C_1-C_6-alkyl;

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 n' is an integer from 0 to 4, preferably 0.

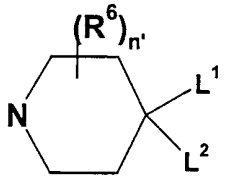
5. A sulfonamide derivative according to any of the preceding claims, wherein Ar^1 and Ar^2 are independently selected from the group comprising or consisting of phenyl, thienyl, furyl, pyridyl, optionally substituted by C_1-C_6-alkyl, preferably trihalomethyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfonyl, C_1-C_6-thioalkoxy.

6. A sulfonamide derivative according to claim 5, wherein Ar^1 is an unsubstituted or substituted phenyl.

7. A sulfonamide derivative according to claim 5, wherein Ar^2 is an unsubstituted or substituted thienyl or furanyl group.

8. A sulfonamide derivative according to any of the preceding claims, wherein Ar^1 is selected from a 4-chlorophenyl, nitrophenyl, hydroxyphenyl, alkoxy phenyl, 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.

9. A sulfonamide derivative according to claim 8, wherein Y is



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

10. A sulfonamide derivative according to claim 9, wherein R^6 is H, L^2 is H, L^1 is a 5-membered cyclic group containing 3 heteroatoms, preferably a triazole ring which is preferably fused with an unsubstituted or substituted aryl or heteroaryl; or L^1 is -C(O)-R^3, or -NHR^3;

with R^3 being a substituent selected from the group comprising or consisting of C_1-C_{12}-alkyl, aryl, heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl; said aryl or heteroaryl groups being optionally substituted by halogen, hydroxy, nitro, sulfonyl.

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

4-chloro-*N*-[5-(piperazine-1-sulfonyl)-thiophen-2-yl-methyl]-benzamide

4-Chloro-N-{5-[4-(3-trifluoromethanesulfonyl-phenylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

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

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

4-chloro-N-{[5-({4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

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

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

4-chloro-N-[(5-{[4-(4-hydroxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide_

4-chloro-N-[(5-{[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

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

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

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

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

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

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

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

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

4-chloro-N-{[5-({4-[4-chloro-3-(trifluoromethyl)phenyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

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

4-chloro-N-[(5-{[4-(6-methylpyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

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

4-chloro-N-[(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

4-chloro-N-({5-[(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-{[5-({4-[2-(methylanilino)-2-oxoethyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

4-chloro-N-[(5-{[4-(3-cyanopyrazin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

4-chloro-N-{[5-({4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[3-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

methyl 5-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-7-(trifluoromethyl)thieno[3,2-b]pyridine-3-carboxylate

ethyl 2-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-5-cyano-6-methylnicotinate

4-chloro-N-{[5-({4-[5-cyano-4,6-bis(dimethylamino)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[6-methyl-2-(trifluoromethyl)quinolin-4-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

tert-butyl 4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazine-1-carboxylate

2-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-8-ethyl-5-oxo-5,8-dihydropyrido[2,3-d]pyrimidine-6-carboxylic acid

7-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid

7-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

4-chloro-N-[(5-{[4-(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-{[5-({4-[(2E)-3-phenylprop-2-enyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

N-[(5-{[4-(4-tert-butylbenzyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

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

4-chloro-N-{[5-({4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

tert-butyl 1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-ylcarbamate

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

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

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

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

4-chloro-N-{[5-({4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

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

N-[(5-{[(1R,4R)-5-benzyl-2,5-diazabicyclo[2.2.1]hept-2-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

4-chloro-N-[(5-{[4-(2-chlorodibenzo[b,f][1,4]oxazepin-11-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-(4-chlorophenyl)-2-(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)acetamide

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

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

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

4-chloro-N-[(5-{[4-(3-methoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

N-{[5-({4-[(2-tert-butyl-1H-indol-5-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

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

4-chloro-N-[(5-{[4-(tetrahydrofuran-2-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(6-chloropyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

N-[(5-{[4-(2H-1,2,3-benzotriazol-2-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

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

N-{[5-({4-[benzyl(methyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

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

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

4-chloro-N-[(5-{[4-(2,3,4,5,6-pentamethylbenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(phenylacetyl)-1,4-diazepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-{[5-({4-[5-(4-methoxyphenyl)-1H-pyrazol-3-yl]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

4-chloro-N-[(5-{[4-(3-phenyl-1,2,4-thiadiazol-5-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

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

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

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

2-(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)-N-(4-chlorophenyl)acetamide

2-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-2H-1,2,3-benzotriazole-5-carboxylic

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

methyl 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-5-carboxylate

methyl 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1*H*-1,2,3-benzotriazole-6-carboxylate

methyl 2-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-2H-1,2,3-benzotriazole-5-carboxylate

4-chloro-N-[(5-{[4-(6-chloro-1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

N-[(5-{[4-(7-aza-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-5-carboxylic

1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-6-carboxylic

N-[(5-{[4-(2-amino-9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

4-chloro-N-[(5-{[4-(9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(6-amino-9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

4-chloro-N-({5-[(4-{6-nitro-1H-benzimidazol-1-yl}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

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

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

N-[(5-{[4-(1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

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

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

methyl

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

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

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

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

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

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

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

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

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

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

N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

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

N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

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

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

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

N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide

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

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

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

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

4-chloro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

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

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

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

N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

4-chloro-N-{[5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

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

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

N-{[5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

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

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

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

N-({5-[(4-{3-[(butylamino)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide

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

4-chloro-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

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

4-chloro-N-[(5-{[4-(quinolin-8-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-Chloro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-{[5-({4-[(2E)-3-phenylprop-2-enoyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

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

4-chloro-N-{[5-({4-[4-(trifluoromethyl)benzoyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-N-{[5-({4-[4-(dimethylamino)benzoyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

4-chloro-N-[(5-{[4-(2,6-difluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(3-fluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

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

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

4-chloro-N-[(5-{[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(2,1,3-benzoxadiazol-5-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

4-chloro-N-[(5-{[4-(2,4-difluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(2,4,6-trifluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(2,6-dichlorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

4-chloro-N-[(5-{[4-(quinolin-8-ylsulfonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

3-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-nitro-N-{[5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

3-nitro-N-{[5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-nitro-N-{[5-({4-[3-(methylsulfanyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

methyl

N-{[5-({4-[3-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

3-nitro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

3-nitro-N-[(5-{[4-(2-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-nitro-N-{[5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-nitro-N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

3-nitro-N-{[5-({4-[4-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-nitro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

4-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-nitro-N-{[5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide

4-nitro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-nitro-N-{[5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-nitro-N-{[5-({4-[3-(methylsulfanyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide

methyl

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

4-nitro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

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

4-nitro-N-{[5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

4-nitro-N-{[5-({4-[4-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-nitro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide

N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide

N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide

N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide

N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide

N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide

N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide

N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide

3-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

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

N-{[5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

3-nitro-N-[(5-{[4-(2-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-nitro-N-[(5-{[4-(4-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

3-nitro-N-{[5-({4-[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-nitro-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide

N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

3-nitro-N-{[5-({4-[3-(morpholin-4-ylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

3-nitro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-nitro-N-[(5-{[4-(pyrimidin-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-{[5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-nitrobenzamide

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

N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

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

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

N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

4-nitro-N-{[5-({4-[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

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

N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide

N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide

4-nitro-N-{[5-({4-[3-(morpholin-4-ylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

N-[(5-{[4-(2-aminoanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

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

N-{[5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

N-({5-[(4-{2-nitro-4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide

3-nitro-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

N-[(5-{[4-(3-cyclohexyl-4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

N-({5-[(4-{3-[(butylamino)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-nitrobenzamide

N-[(5-{[4-(3-ethylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

3-nitro-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-nitro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

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

2-Hydroxy-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-hydroxybenzamide

N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-nitrobenzamide

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

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

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

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

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

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

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

methyl

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

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

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

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

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

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

N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

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

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

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

N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide

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

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

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

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

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

3-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

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

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

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

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

N-{[5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

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

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

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

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

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

N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

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

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

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

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

3-methoxy-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

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

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

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

3-methoxy-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-5-nitro-1H-pyrazole-3-carboxamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-oxo-1,2-dihydropyridine-3-carboxamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-thioxo-1,2-dihydropyridine-3-carboxamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3,4-dihydroxybenzamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]pyridine-2-carboxamide

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

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

4-chloro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide

4-chloro-N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide

4-chloro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide

4-chloro-N-{[5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide

4-chloro-N-{[5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide

4-chloro-N-{[5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide

4-chloro-N-{[5-({4-[3-(methylsulfanyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide

N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}-4-chlorobenzamide

methyl 3-({1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-furyl)sulfonyl]piperidin-4-yl}amino)benzoate

3-({1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-furyl)sulfonyl]piperidin-4-yl}amino)benzamide

4-chloro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]-2-furyl}methyl)benzamide

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

4-chloro-N-{[5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide

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

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

4-chloro-N-{[5-({4-[4-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide

4-chloro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]-2-furyl}methyl)benzamide

N-{[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}-4-chlorobenzamide

4-chloro-N-{[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)-2-furyl]methyl}benzamide

N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]-2-furyl}methyl)-4-chlorobenzamide

4-chloro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]-2-furyl}methyl)benzamide

N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]-2-furyl}methyl)-4-chlorobenzamide

4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]2-furyl}methyl)benzamide

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

4-chloro-*N*-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}azepan-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

12. A sulfonamide derivative according to claim 11, which is selected from the group consisting of

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

4-chloro-N-[(5-{[4-(phenylacetyl)-1,4-diazepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

N-[(5-{[4-(1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

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

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

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

N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide

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

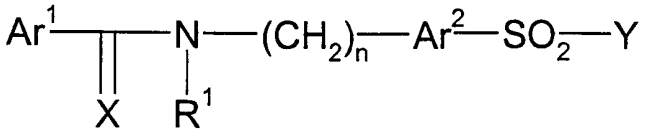
4-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

methyl 3-{[1-({5-[({4-nitrobenzoyl}amino)methyl]thien-2-yl}sulfonyl)piperidin-4-yl]amino}benzoate

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-hydroxybenzamide

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

13. Use of a sulfonamide derivative according to formula I



I

wherein Ar^1 and Ar^2 are independently from each other substituted or unsubstituted aryl or heteroaryl groups;

X is O or S, preferably O;

R^1 is hydrogen or a C_1-C_6-alkyl group, or R^1 forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar^1;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1;

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing a sulfonamide,

for the preparation of a pharmaceutical composition 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 3.

16. Use of sulfonamides according to formula I in particular according to any of claims 13 to 15 for the treatment of neuronal disorders including epilepsy; Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases, spinal cord injury, head trauma.

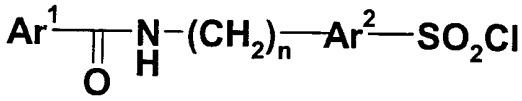
17. Use of sulfonamides according to formula I in particular according to any of claims 13 to 15 for the treatment of autoimmune diseases including Multiple Sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis, asthma, septic shock, transplant rejection.

18. Use of sulfonamides according to formula I in particular according to any of claims 13 to 15 for the treatment of cancer including breast-, colorectal-, pancreatic cancer.

19. Use of sulfonamides according to formula I in particular according to any of claims 13 to 15 for the treatment of cardiovascular diseases including stroke, arterosclerosis, myocordial infarction, myocordial reperfusion injury.

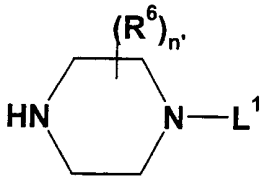
20. A pharmaceutical composition containing at least one sulfonamide derivative according to any of the claims 2 to 12 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

21. Process for the preparation of a sulfonamide derivative according to any of claims 1 to 12, wherein a sulfonyl chloride V

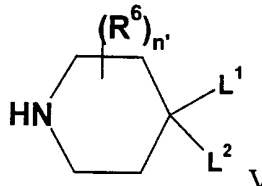


V

is reacted with an amine VII or VIII



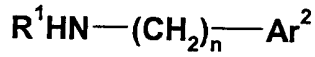
VII or



VIII

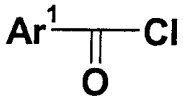
whereby $(R^6)_n$, L^1 and L^2 are as above defined.

22. A process according to claim 21, wherein a sulfonyl chloride V is obtainable by a) coupling an amine of formula II:



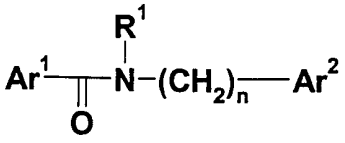
II

where Ar^2 and R^1 are as defined above, with an acyl chloride of formula III:



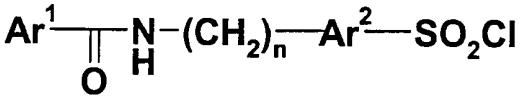
III

where Ar^1 is as defined above, to provide an amide of formula IV:



IV

b) sulfonating the amide of formula IV to provide a sulfonyl chloride V



V

INTERNATIONAL SEARCH REPORT

Interi ıal Application No
PCT/IB 00/01380

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D409/12 C07D333/34 C07D333/36 C07D413/12 C07D495/04
C07D471/04 C07D409/14 C07D405/12 A61K31/496 A61K31/445
//(C07D495/04,333:00,221:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 30992 A (BRISTOL-MYERS SQUIBB CO.;USA) 28 August 1997 (1997-08-28) cited in the application see general formula and provisos in application ---	1-22
A	WO 97 45403 A (PHARMACIA & UPJOHN COMPANY;USA) 4 December 1997 (1997-12-04) see whole application --- -/--	1-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 November 2000	20. 11. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scruton-Evans, I

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr. ial Application No
PCT/IB 00/01380

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	KELLY J ET AL: "Synthesis of isomeric 3-piperidinyl and 3-pyrrolidinyl benzo'5,6!cyclohepta'1,2-b!pyridines: sulfonamido derivatives as inhibitors of Ras prenylation" BIOORG. MED. CHEM. (BMECEP,09680896);1998; VOL.6 (6); PP.673-686, XP000881133 Schering-Plough Research Institute;Kenilworth; 07033; NJ; USA (US) the whole document	1-22
A	WO 98 53814 A (MERCK & CO., INC.;USA) 3 December 1998 (1998-12-03) cited in the application the whole document	1-22
A	WO 99 16751 A (MERCK PATENT G.M.B.H.;GERMANY) 8 April 1999 (1999-04-08) the whole document	1-22
A	WO 99 21859 A (GLAXO GROUP LTD ;GLENNON KIMBERLY CAROLINE (US); PEEL MICHAEL ROBE) 6 May 1999 (1999-05-06) the whole document	1-22
A	WO 96 30017 A (SCHERING CORP) 3 October 1996 (1996-10-03) cited in the application the whole document	1-22

2

INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/IB 00/01380

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

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

2. ☒ Claims Nos.: 1-10,13-22(partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

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

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10,13-22(partly)

Present claims 1-10,13-22 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of the examples and closely related homologous compounds, i.e. wherein Ar1 is substituted phenyl, X is O and Ar2 is 2,5-thienyl or 2,5-furyl.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/IB 00/01380

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9730992 A	28-08-1997	AU 718676 B	20-04-2000
		AU 2136697 A	10-09-1997
		BG 102738 A	30-09-1999
		BR 9707614 A	27-07-1999
		CN 1214685 A	21-04-1999
		CZ 9802696 A	13-10-1999
		EP 0892797 A	27-01-1999
		HU 9902016 A	28-09-1999
		JP 2000502356 T	29-02-2000
		LT 98120 A,B	25-06-1999
		LV 12150 A	20-10-1998
		LV 12150 B	20-12-1998
		NO 983892 A	25-08-1998
		PL 328868 A	01-03-1999
		US 6011029 A	04-01-2000
		ZA 9701621 A	25-08-1998
WO 9745403 A	04-12-1997	AU 720414 B	01-06-2000
		AU 3060197 A	05-01-1998
		CN 1217711 A	26-05-1999
		CZ 9803701 A	12-05-1999
		EP 0923542 A	23-06-1999
		FI 982572 A	27-11-1998
		NO 985599 A	30-11-1998
		PL 330207 A	26-04-1999
WO 9853814 A	03-12-1998	EP 1001764 A	24-05-2000
WO 9916751 A	08-04-1999	DE 19743435 A	08-04-1999
		AU 9540798 A	23-04-1999
		BR 9812699 A	22-08-2000
		EP 1025086 A	09-08-2000
		NO 20001687 A	31-03-2000
		ZA 9808937 A	31-03-1999
WO 9921859 A	06-05-1999	AU 1151099 A	17-05-1999
WO 9630017 A	03-10-1996	US 5684013 A	04-11-1997
		AU 708244 B	29-07-1999
		AU 5307296 A	16-10-1996
		CA 2216291 A	03-10-1996
		EP 0814807 A	07-01-1998
		HU 9801396 A	28-05-1999
		JP 3001982 B	24-01-2000
		JP 10505102 T	19-05-1998
		US 5703090 A	30-12-1997
		US 5958939 A	28-09-1999