JNK Inhibitors for the Treatment of Endometriosis

Background of the Invention

Endometriosis is one of the most frequent diseases of women in their reproductive lifespan. It is characterized by the presence of endometrial tissue outside the uterine cavity, consisting histological of glands and stroma. The anatomical sites most often affected are the ovaries, uterosacral ligaments, pelvic peritoneum, rectovaginal septum, cervix, vagina, the fallopian tubes and vulva.

Endometriosis is considered to be a benign disease, but endometriotic lesions occasionally become malignant. As in other kind of malignancies, the development of endometriosis-derived neoplasms is due to concurrent events, involving alterations in growth factors and/or oncogenes regulation (Kyama e al. 2003). Further, endometriosis is considered as a major cause of infertility (Giudice et al. 2004).

The current treatment of endometriosis consists of hormonal therapy and/or surgery. Hormonal therapies include high dose of progestogens, progestins, oral contraceptives (combinations of estrogen and progesterone), Danazol (an androgenic derivative of ethisterone) and more recently GnRH agonists. These hormonal therapies are effective on pelvic pain and may induce an objective regression of lesions, but have several caveats. Estrogen may stimulate and cause proliferation of endometriotic tissue since it may be unable to respond to progesterone (Dawood et al, 1993). Progestational agents can provoke irregular bleeding along with depression, weight gain, and fluid retention. Danazol can improve symptoms in approximately 66-100% of the patients suffering from pain, but recurrence rates after up to 4 years are approximately 40% - 50%. Other drawbacks of Danazol therapy are weight gain and androgenic side effects. GnRH analogs are more potent and long acting than native GnRH, which act by removing the estrogenic stimulus for the growth of all estrogen sensitive tissues. Side effects of GnRH analogs are mainly secondary to the profound hypoestrogenemia, like decreased bone density, and recurrence rate are up to

50% after 5 years (Waller et al., 1993). Further complicating treatment is the observation that endometriotic lesions in many patients either are or become resistant to the effects of progesterone and/or progestins. (Bulun et al. 2006).

Surgical intervention can be conservative, if fertility is desired, or can lead to the removal of the uterus, tubes and ovaries in case of severe disease. In any case, even limited surgical treatment leads to a significant decrease in fertility.

Although endometriosis stands as one of the most investigated disorders of gynecology, the current understanding of pathophysiology of the disease remains elusive. According to a favored theory, endometriotic lesions develop by eutopic endometrical cells leaving their primary site, possibly by retrograde menstruation, and implant at distant sites, followed by invasion of host tissue and proliferation. Furthermore, it appears that endometriosis is an invasive and metastasizing disease. Though endometriotic cells proliferate to a certain extent, they are not neoplastic as typically found in carcinomas. Apparently, endometriotic cells become senescent, apoptotic and necrotic. Inflammatory responses that are induced or accompanied by lesion formation finally lead to fibrosis and the formation of scars.

It has been speculated whether tumor or metastasis suppressor genes (e.g. E-cadherin) are associated with endometriosis. E-cadherin is a metastasis suppressor molecule, its down-regulation or functional inactivation is a prerequisite for invasion and metastasis (Frixen et al, 1991). Zeitvogel et al. (2001) showed that E-cadherin is absent and N-cadherin is present in endometriotic cells. N-cadherin is suggested to be the path-finding molecule that allows cells to be invasive and migratory in normal development and pathological processes.

Recently, it has been demonstrated that recombinant human TNFα binding protein (rh-TBP-1) is effective in reducing the size and severity of endometriotic lesions in an experimental model of endometriosis (D'Hooghe et al. 2001). These results were the first to demonstrate that an anti-inflammatory molecule (r-hTBP-1) that targeted the

TNFα –pathway provided effective medical treatment for patients with endometriosis that did not inhibit ovulation.

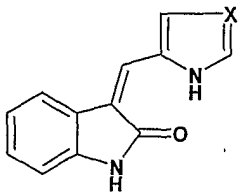
Yoshino et al. (2004) showed that mitogen-activated protein kinases (MAPKs), which are intracellular signal transducers, mediate some of the effects exerted by proinflammatory cytokines. Yoshino et al. further showed the presence of MAPks (e.g. ERK, JNK and p38) in endometriotic cells and their phosphorylation under inflammatory stimulation by IL-1β, TNFα and H_2O_2. MAPKs are serine/threonine kinases that are activated by dual phosphorylation on threonine and tyrosine residues. In mammalian cells, there are at least three separate but parallel pathways that convey information generated by extra-cellular stimuli to the MAPKs. Said pathways consist of kinase cascades leading to activation of the ERKs (extracellular regulated kinases), the JNKs (c-Jun N-terminal kinases), and the p38/CSBP kinases (Dent et al 2003).

c-Jun is a protein that forms homodimers and heterodimers (with e.g. c-Fos) to produce the transactivating complex AP-1, which is required for the activation of many genes (e.g. matrix metalloproteinases) involved in the inflammatory response.

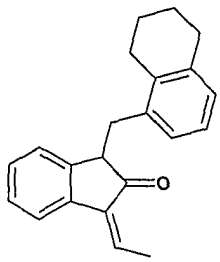
The invention described herein clearly shows the unexpected result that inhibiting JNK, by means of a JNK inhibitor, reduces endometriotic-like foci in a rat and in nude mouse experimental models. A rat model also demonstrates that such effect is obtained by inhibiting the Natural Killer cells activity associated with the disease as well as reducing several cytokines found elevated in endometriosis. These cytokines are among others, IL-6 and IL-8 that are suggested to play a key role (Barcz et al., 2000). The JNK inhibitors described herein restore the sensitivity of endometrial cells and lesions to progesterone. Furthermore, the JNK inhibitors described herein used in combination with a SPRM or progestin can prevent re-establishment of endometriosis. The reduction of endometriotic lesions using JNK inhibitors can also improve fertility rates, since the normalization of genital structure has a positive effect on the implantation rate.

Several small molecules have been proposed as modulators of the JNK pathway.

Aryl-oxindole derivatives of respectively the generic formula (A) (WO 00/35909; WO 00/35906; WO 00/35920) and formula (B) (WO 00/64872) have been developed for the treatment of neurodegenerative diseases, inflammation and solid tumors for formula (A) and for the treatment of a broad range of disorders including, neurodegenerative diseases, inflammatory and autoimmune diseases, cardiovascular and bone disorders for formula (B).

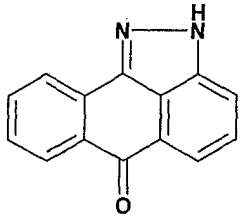


(A)



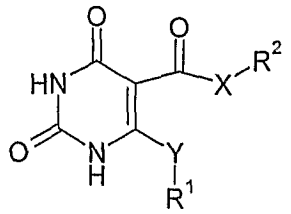
(B)

Pyrazoloanthrones derivatives of formula (C) have been reported to inhibit JNK for the treatment of neurological degenerative diseases, inflammatory and autoimmune disorders as well as cardiovascular pathologies (WO 01/12609).



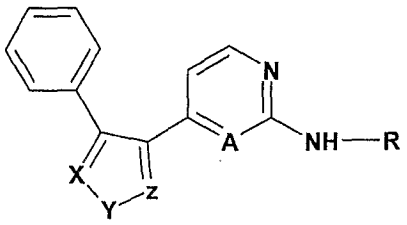
(C)

Tetrahydro-pyrimidine derivatives of formula (D) were reported to be JNK inhibitors useful in the treatment of a wide range of diseases including neurodegenerative diseases, inflammatory and autoimmune disorders, cardiac and destructive bone pathologies (WO 00/75118).



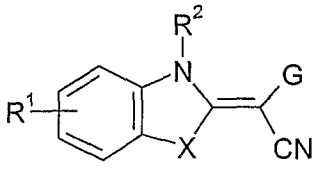
(D)

Other heterocyclic compounds of formula (E) have been proposed to inhibit protein kinases and especially c-un-N-Terminal kinases (WO 01/12621) for treating "JNK-mediated conditions" including proliferative diseases, neurodegenerative disorders, inflammatory and autoimmune disorders.



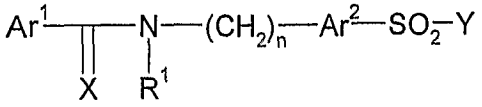
(E)

Benzazoles derivatives such as represented by formula (F) (WO 01/47920) have been described as modulators of the JNK pathway for the treatment of neuronal disorders, autoimmune diseases, cancers and cardiovascular diseases.

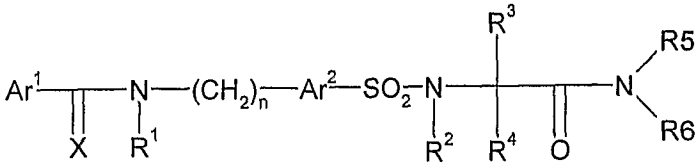


(F)

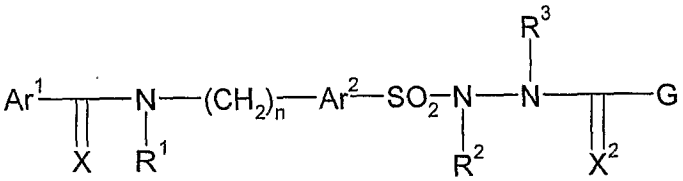
Several sulfonamide derivatives of formula (G) (WO 01/23378), sulfonyl amino acid derivatives of formula (H) (WO 01/23379) and sulfonyl hydrazide derivatives of formula (J) (WO 01/23382), were also developed to inhibit JNKs for treating neurodegenerative diseases, auto-immune disorders, cancers and cardiovascular diseases.



(G)



(H)



(J)

Summary of the invention

The present invention relates to a method of treating and/or preventing endometriosis in an individual comprising administering a therapeutically effective amount of a JNK inhibitor.

The invention further relates to a method of treating and/or preventing endometriosis by combined treatment of hormonal suppressor (e.g. GnRH antagonists, GnRH agonists, aromatase inhibitors, progesterone receptor modulators, estrogen receptor modulators) along with a JNK inhibitor.

The invention also relates to a method of treating endometriosis-related infertility in a female comprising the administration of a therapeutically effective amount of a JNK inhibitor, alone or in combination with other fertility drugs.

The invention finally relates to a pharmaceutical composition comprising a JNK inhibitor, a hormal suppressor and a pharmaceutically acceptable excipient.

Brief Description of the Drawings

Figure 1: Expression of N-cadherin and cytokeratin in endometriotic cells (12Z). Cells treated with JNK inhibitor were fixed with paraformaldehyde and stained for N-cadherin and cytokeratin. Cells were observed under fluorescent microscope (phase contrast and fluorescence pictures). Treating cells with a JNK inhibitor decreased the expression of N-cadherin. The expression of cytokeratin was not altered after treatment with the JNK inhibitor.

Figure 2: Effect of a JNK inhibitor on the growth of endometriotic-like foci in experimentally induced endometriosis in rats. The effect of the JNK inhibitor given at a dose of 10 mg/kg was not different from the vehicle. 30 mg/kg and 60mg/kg doses showed a significant regression of established endometriotic lesions.

Figure 3: Effect of JNK inhibitor on cytokines in endometriotic-like foci in the rat endometriosis model. The JNK inhibitor reduced the levels of inflammatory cytokines, IL-12, INF-γ, IL-10 and MCP-1 in the endometriotic foci.

Figure 4: Effect of JNK inhibitor on cytokines in the contralateral horn in experimentally induced endometriosis in rats. No effect of the JNK inhibitor on cytokine expression was observed.

Figure 5: Effect of JNK inhibitor on NK-cell activity in the rat endometriosis model. Treatment with a JNK inhibitor increased NK cell activity compared to the vehicle treated group.

Description of the invention

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

"C_1-C_6 -alkyl" refers to 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-butyl, n-pentyl, 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, cinnolinyl, 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.

"C_2-C_6-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.

"C_2-C_6-alkenyl aryl" refers to C_2-C_6-alkenyl groups having an aryl substituent, including 2-phenylvinyl and the like.

"C_2-C_6-alkenyl heteroaryl" refers to C_2-C_6-alkenyl groups having a heteroaryl substituent, including 2-(3-pyridinyl)vinyl and the like.

"C_2-C_6-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.

"C_2-C_6-alkynyl aryl" refers to C_2-C_6-alkynyl groups having an aryl substituent, including phenylethynyl and the like.

"C_2-C_6-alkynyl heteroaryl" refers to C_2-C_6-alkynyl groups having a heteroaryl substituent, including 2-thienylethynyl and the like.

"C_3-C_8-cycloalkyl" refers to a saturated carbocyclic group of from 3 to 8 carbon atoms having a single ring (*e.g.,* cyclohexyl) or multiple condensed rings (*e.g.,* norbornyl). Preferred cycloalkyl include cyclopentyl, cyclohexyl, norbornyl and the like.

"C_1-C_6-alkyl cycloalkyl" refers to C_1-C_6-alkyl groups having a cycloalkyl substituent, including cyclohexylmethyl, cyclopentylpropyl, and the like.

"Heterocycloalkyl" refers to a C_3-C_8-cycloalkyl group according to the definition above, in which 1 to 3 carbon atoms are replaced by hetero atoms chosen from the group consisting of O, S, NR, R being defined as hydrogen or C_1-C_6 alkyl. Preferred heterocycloalkyl include pyrrolidine, piperidine, piperazine, 1-methylpiperazine, morpholine, and the like.

"C_1-C_6-alkyl heterocycloalkyl" refers to C_1-C_6-alkyl groups having a heterocycloalkyl substituent, including 2-(1-pyrrolidinyl)ethyl, 4-morpholinylmethyl, (1-methyl-4-piperidinyl)methyl and the like.

"Carboxy" refers to the group –C(O)OH.

"C_1-C_6-alkyl carboxy" refers to C_1-C_6-alkyl groups having a carboxy substituent, including 2-carboxyethyl and the like.

"Acyl" refers to the group –C(O)R where R includes H, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", ""heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl acyl" refers to C_1-C_6-alkyl groups having an acyl substituent, including 2-acetylethyl and the like.

"Acyloxy" refers to the group –OC(O)R where R includes H, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl acyloxy" refers to C_1-C_6-alkyl groups having an acyloxy substituent, including 2-(acetyloxy)ethyl and the like.

"Alkoxy" refers to the group –O-R where R includes "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "Heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl",

"C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl alkoxy" refers to C_1-C_6-alkyl groups having an alkoxy substituent, including 2-ethoxyethyl and the like.

"Alkoxycarbonyl" refers to the group –C(O)OR where R includes "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "Heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl alkoxycarbonyl" refers to C_1-C_6-alkyl groups having an alkoxycarbonyl substituent, including 2-(benzyloxycarbonyl)ethyl and the like.

"Aminocarbonyl" refers to the group –C(O)NRR' where each R, R' includes independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "Heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl aminocarbonyl" refers to C_1-C_6-alkyl groups having an aminocarbonyl substituent, including 2-(dimethylaminocarbonyl)ethyl and the like.

"Acylamino" refers to the group –NRC(O)R' where each R, R' is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "Heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl acylamino" refers to C_1-C_6-alkyl groups having an acylamino substituent, including 2-(propionylamino)ethyl and the like.

"Ureido" refers to the group –NRC(O)NR'R" where each R, R', R" is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "Heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", and where R' and R", together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl ureido" refers to C_1-C_6-alkyl groups having an ureido substituent, including 2-(*N*'-methylureido)ethyl and the like.

"Amino" refers to the group –NRR' where each R, R' is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "Heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl amino" refers to C_1-C_6-alkyl groups having an amino substituent, including 2-(1-pyrrolidinyl)ethyl and the like.

"Cyclic amino" refers to piperazinyl, piperidinyL, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, isoindolinyl, pyrazolidinyl, pyrrolidinyl "Acyclic amino" refers to the group –NRR' 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", or "cycloalkyl", or "heterocycloalkyl" and also refers to the ammonium group -N^+RR'R" such as defined hereinafter

"Ammonium" refers to a positively charged group $-N^+RR'R''$, where each R, R',R'' is independently, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "Heterocycloalkyl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl ammonium" refers to C_1-C_6-alkyl groups having an ammonium substituent, including 2-(1-pyrrolidinyl)ethyl and the like.

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

"Sulfonyloxy" refers to a group $-OSO_2$-R wherein R is selected from H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, an $-OSO_2-CF_3$ group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonyloxy" refers to C_1-C_6-alkyl groups having a sulfonyloxy substituent, including 2-(methylsulfonyloxy)ethyl and the like.

"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_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonyl" refers to C_1-C_6-alkyl groups having a sulfonyl substituent, including 2-(methylsulfonyl)ethyl and the like.

"Sulfinyl" 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, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfinyl" refers to C_1-C_6-alkyl groups having a sulfinyl substituent, including 2-(methylsulfinyl)ethyl and the like.

"Sulfanyl" refers to groups –S-R where R includes H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, an –SO-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl". Preferred sulfanyl groups include methylsulfanyl, ethylsulfanyl, and the like.

"C_1-C_6-alkyl sulfanyl" refers to C_1-C_6-alkyl groups having a sulfanyl substituent, including 2-(ethylsulfanyl)ethyl and the like.

"Sulfonylamino" refers to a group –$NRSO_2$-R' where each R, R' includes independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonylamino" refers to C_1-C_6-alkyl groups having a sulfonylamino substituent, including 2-(ethylsulfonylamino)ethyl and the like.

"Aminosulfonyl" refers to a group $-SO_2$-NRR' where each R, R' includes independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl aminosulfonyl" refers to C_1-C_6-alkyl groups having an aminosulfonyl substituent, including 2-(cyclohexylaminosulfonyl)ethyl and the like.

"Substituted or unsubstituted": Unless otherwise constrained by the definition of the indi-vidual 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_2-C_6-alkenyl", "C_2-C_6-alkynyl", "cycloalkyl", "heterocycloalkyl", "C_1-C_6-alkyl aryl", "C_1-C_6-alkyl heteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", "amino", "ammonium", "acyl", "acyloxy", "acylamino", "aminocarbonyl", "alkoxycarbonyl", "ureido", "aryl", "heteroaryl", "sulfinyl", "sulfonyl", "alkoxy", "sulfanyl", "halogen", "carboxy", trihalomethyl, cyano, hydroxy, mercapto, nitro, and the like. Alternatively said substitution could also comprise situations where neighbouring substituents have undergone ring closure, notably when vicinal 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 that retain the desired biological activity of the below-identified compounds of formula I and exhibit minor or no undesired toxicological effects. 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 poly-galacturonic 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.

The "tautomers" of the compounds according to formula I are only those wherein R^2 and/or R^0 are hydrogen and which display the formulae (Ia) and (Ib).

"Enantiomeric excess" (ee) refers to the products that are obtained by an asymmetric synthesis, i.e. a synthesis involving non-racemic starting materials and/or reagents or a synthesis comprising at least one enantioselective step, whereby a surplus of one enantiomer in the order of at least about 52% ee is yielded.

"Aromatase Inhibitors" refers to drugs that inhibit the enzyme aromatase and by that lowers the level of the estradiol. Preferred aromatase inhibitors include by way of example anastrozole, letrozole, vorozole and exemestane.

"Estrogen receptor modulators (SERM)"refers to drugs that block the actions of estrogen by occupying the estrogen receptors on cells. SERMS also include estrogen receptor beta antagonists and estrogen receptor beta agonists. Preferred SERMs include by way of example Tamoxifen, Raloxifen.

"GnRH antagonists" refers to synthetic GnRH analogues, which are drugs that competitively block the pituitary GnRH receptor, which is located on the plasma membrane of gonadotrophs, inducing a rapid, reversible suppression of gonadotrophin secretion. Preferred GnRH antagonists include by way of example Cetrorelix, Ganirelix.

"GnRH agonists" refers to decapeptide modifications of the natural hormone GnRH, which are drugs that desensitize GnRH receptors of the pituitary gland at continued exposure, which causes an initial stimulation of the pituitary–ovarian axis, followed by a reduction in circulating serum gonadotrophin concentration and inhibition of ovarian function. Preferred GnRH agonists include by way of example Buserelin acetate, Nafarelin, Leuprolide, Triptorelin, Goserelin.

"JNK" means a protein or an isoform thereof expressed by a JNK 1, JNK 2, or JNK 3 gene (Gupta et al. 1996).

"JNK-inhibitor" refers to a compound, a peptide or a protein that inhibits c-jun amino terminal kinase (JNK) phosphorylation of a JNK targeted transcription factor. The JNK-inhibitor is an agent capable of inhibiting the activity of JNK in vitro or in vivo. Such inhibitory activity can be determined by an assay or animal model well-known in the art..

"Progesterone receptor modulators (SPRMs)": The progesterone receptor, a member of the superfamily of nuclear receptors, is the receptor for progesterone that plays a pivotal role in female reproduction. Selective progesterone receptor modulators are drugs that can have agonist, antagonist or partial (mixed) agonist/antagonist activities depending upon the site of action. A preferred SPRM includes by way of example asoprisnil.

One embodiment of the present invention is to provide a method of treating and/or preventing endometriosis in an individual comprising administering a therapeutically effective amount of a JNK inhibitor.

Another embodiment of the present invention relates to a method of treating and/or preventing endometriosis by sequential or combined treatment of a hormonal suppressor (e.g. GnRH antagonists, GnRH agonists, aromatase inhibitors, progesterone receptor modulators, estrogen receptor modulators) along with a JNK inhibitor.

Second or subsequent administrations of therapeutically effective amounts can be performed at a dosage which is the same, less than or greater than the initial or previous dose administered to the individual. Second or subsequent administrations can be administered during or prior to relapse of the endometriosis or the related symptoms. The terms "relapse" or "reoccurrence" are defined to encompass the appearance of one or more of symptoms of endometriosis.

In another embodiment, the invention relates to a method of treating endometriosis-related infertility in a female comprising the administration of a therapeutically effective amount of a JNK inhibitor, alone or in combination with other fertility drugs.

In a further embodiment, the sequential or combined treatment regimen minimizes the disease by suppressing endocrine-dependent cells.

Another embodiment of the present invention consists of a pharmaceutical composition comprising a JNK inhibitor, a hormal suppressor (e.g. GnRH antagonists, GnRH agonists, aromatase inhibitors, progesterone receptor modulators, estrogen receptor modulators) and a pharmaceutically acceptable excipient.

Another embodiment of the present invention consists of the use of a JNK inhibitor in the manufacture of a medicament for the treatment and/or prevention of endometriosis.

The term "preventing", as used herein, should be understood as partially or totally preventing, inhibiting, alleviating, or reversing one or more symptoms or cause(s) of endometriosis.

A proposed model for progression of endometriotic disease predicts that lesions progress from benign inflammatory lesions responsive to endocrine intervention to partially or completely hormonally unresponsive lesions that involve upregulated survival pathways in addition to inflammatory pathways.

Therefore, in one embodiment, the JNK inhibitor may interfere with survival pathways in endometriosis.

Another embodiment of the invention relates to the use of a JNK inhibitor together with a hormal suppressor (e.g. GnRH antagonists, GnRH agonists, aromatase inhibitors, progesterone receptor modulators, estrogen receptor modulators) and a pharmaceutically acceptable carrier in the manufacture of a medicament for the treatment and/or prevention of endometriosis.

The use of a JNK inhibitor together with a hormal suppressor (e.g. GnRH antagonists, GnRH agonists, aromatase inhibitors, progesterone receptor modulators, estrogen receptor modulators) can be a sequential or a combined use of the JNK inhibitor and the hormal suppressor.

Another embodiment of the invention, relates to the use of a JNK inhibitor, alone or in combination with other drugs, in the manufacture of a medicament for the treatment of endometriosis-related infertility.

In particular, when endometriosis-related infertility is intended to be treated or cured, biologically active human chorionic gonadotrophin (hCG), luteinizing hormone (LH) or follicle stimulating hormone (FSH), either in a natural highly purified or in a recombinant form, can be administered. Such molecules and methods of their production have been described in the European Patent Applications EP 160,699, EP 211,894 and EP 322,438.

The pharmaceutical compositions of the present invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous,

intramuscular and intranasal. 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 JNK inhibitor 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 nonaqueous 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 pepper-mint, 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 JNK inhibitor 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 5 of *Remington's Pharmaceutical Sciences*, 20th Edition, 2000, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein by 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*.

The definition of "pharmaceutically acceptable" is meant to encompass any carrier, which does not interfere with effectiveness of the biological activity of the active ingredient and that is not toxic to the host to which it is administered. For example, for parenteral administration, JNK inhibitor may be formulated in a unit dosage form for injection in vehicles such as saline, dextrose solution, serum albumin and Ringer's solution.

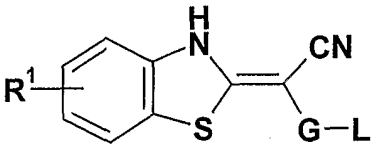
For parenteral (e.g. intravenous, subcutaneous, intramuscular) administration, JNK inhibitors can be formulated as a solution, suspension, emulsion or lyophilized powder in association with a pharmaceutically acceptable parenteral vehicle (e.g. water, saline, dextrose solution) and additives that maintain isotonicity (e.g. mannitol) or chemical stability (e.g. preservatives and buffers). The formulation is sterilized by commonly used techniques.

The therapeutically effective amounts of a JNK inhibitor will be a function of many variables, including the type of inhibitor, the affinity of the inhibitor for JNK, any residual cytotoxic activity exhibited by the JNK inhibitor, the route of administration or the clinical condition of the patient.

A "therapeutically effective amount" is such that when administered, the JNK inhibitor results in inhibition of the biological activity of JNK. The dosage administered, as single or multiple doses, to an individual will vary depending upon a variety of factor,

including JNK inhibitor pharmacokinetic properties, the route of administration, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired. Adjustment and manipulation of established dosage ranges are well within the ability of those skilled, as well as *in vitro* and *in vivo* methods of determining the inhibition of JNK in an individual.

The JNK inhibitors may be of formula (I)



(I)

Said compounds are disclosed in WO 01/47920 (Applied Research Systems ARS Holding NV) in which benzazoles derivatives of formula (A) are described in particular for the treatment of neuronal disorders, autoimmune diseases, cancer and cardiovascular diseases:

In the compounds according to formula (I):

G is an unsubstituted or substituted pyrimidinyl group.

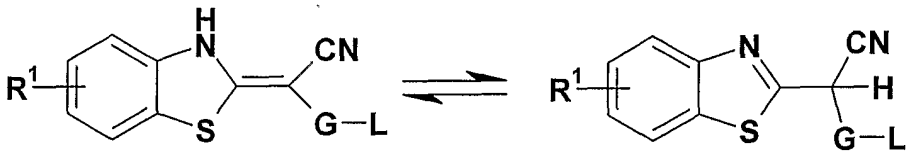
L is an unsubstituted or substituted C_1-C_6-alkoxy, or an amino group, or an unsubstituted or a substituted 3-8 membered heterocycloalkyl, containing at least one heteroatom selected from N, O, S (e.g. a piperazine, a piperidine, a morpholine, a pyrrolidine).

R^1 is selected from the group comprising or consisting of hydrogen, sulfonyl, amino, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl or C_1-C_6-alkoxy, unsubstituted or substituted aryl (e.g. phenyl), halogen, cyano or hydroxy.

Preferably R^1 is H or C_1-C_3 alkyl (e.g. a methyl or ethyl group).

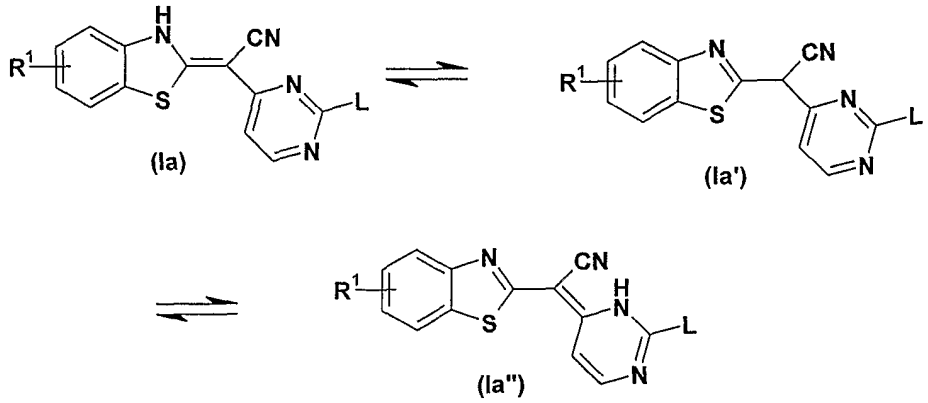
Formula (I) also comprises its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof. Preferred pharmaceutically acceptable salts of the formula (I) are acid addition salts formed with pharmaceutically acceptable acids like hydrochloride, hydrobromide, sulfate or bisulfate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzenesulfonate, and *para*-toluenesulfonate salts.

More specifically, the benzothiazole acetonitriles of formula (I) comprise the tautomeric forms, e.g. the below ones:



(I) (I')

A specific embodiment of the present invention consists in benzothiazole acetonitriles of formula (Ia) in its tautomeric forms, e.g. the below ones:



(Ia) (Ia') (Ia")

R^1 and L are as defined for formula (I).

According to a specific embodiment, the moiety L is an amino group of the formula $-NR^3R^4$ wherein R^3 and R^4 are each independently from each other H, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, unsubstituted or substituted C_1-C_6-alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted saturated or unsaturated 3-8-membered cycloalkyl, unsubstituted or substituted 3-8-membered heterocycloalkyl, (wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl groups may be fused with 1-2 further cycloalkyl, heterocycloalkyl, aryl or heteroaryl group), unsubstituted or substituted C_1-C_6-alkyl aryl, unsubstituted or substituted C_1-C_6-alkyl heteroaryl, unsubstituted or substituted C_2-C_6-alkenyl aryl, unsubstituted or substituted C_2-C_6-alkenyl heteroaryl, unsubstituted or substituted C_2-C_6-alkynyl aryl, unsubstituted or substituted C_2-C_6-alkynyl heteroaryl, unsubstituted or substituted C_1-C_6-alkyl cycloalkyl, unsubstituted or substituted C_1-C_6-alkyl heterocycloalkyl, unsubstituted or substituted C_2-C_6-alkenyl cycloalkyl, unsubstituted or substituted C_2-C_6-alkenyl heterocycloalkyl, unsubstituted or substituted C_2-C_6-alkynyl cycloalkyl, unsubstituted or substituted C_2-C_6-alkynyl heterocycloalkyl.

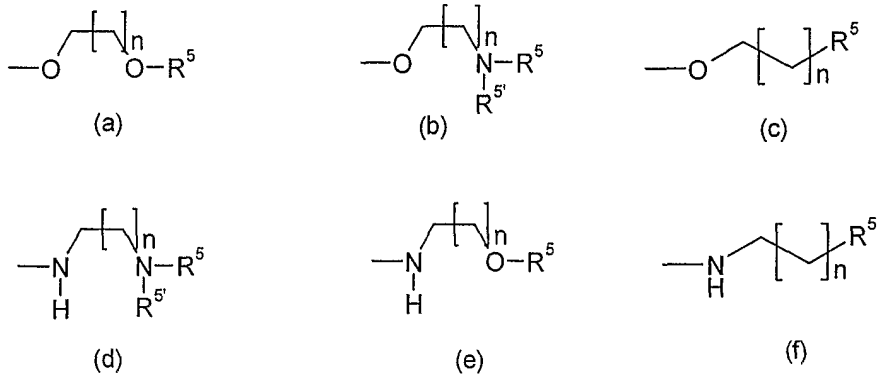
Alternatively, R^3 and R^4 may form a ring together with the nitrogen to which they are attached.

In a specific embodiment, R^3 is hydrogen or a methyl or ethyl or propyl group and R^4 is selected from the group consisting of unsubstituted or substituted (C_1-C_6)-alkyl, unsubstituted or substituted C_1-C_6 alkyl-aryl, unsubstituted or substituted C_1-C_6-alkyl-heteroaryl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl or heteroaryl and unsubstituted or substituted 4-8 membered saturated or unsaturated cycloalkyl.

In a further specific embodiment, R^3 and R^4 form a substituted or unsubstituted piperazine or a piperidine or a morpholine or a pyrrolidine ring together with the nitrogen to which they are bound, whereby said optional substituent is selected from the group

consisting of unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, unsubstituted or substituted C_1-C_6-alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted saturated or unsaturated 3-8-membered cycloalkyl, unsubstituted or substituted 3-8-membered heterocycloalkyl, (wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl groups may be fused with 1-2 further cycloalkyl, heterocycloalkyl, aryl or heteroaryl group), unsubstituted or substituted C_1-C_6-alkyl aryl, unsubstituted or substituted C_1-C_6-alkyl heteroaryl, unsubstituted or substituted C_2-C_6-alkenyl aryl, unsubstituted or substituted C_2-C_6-alkenyl heteroaryl, unsubstituted or substituted C_2-C_6-alkynyl aryl, unsubstituted or substituted C_2-C_6-alkynyl heteroaryl, unsubstituted or substituted C_1-C_6-alkyl cycloalkyl, unsubstituted or substituted C_1-C_6-alkyl heterocycloalkyl, unsubstituted or substituted C_2-C_6-alkenyl cycloalkyl, unsubstituted or substituted C_2-C_6-alkenyl heterocycloalkyl, unsubstituted or substituted C_2-C_6-alkynyl cycloalkyl, unsubstituted or substituted C_2-C_6-alkynyl heterocycloalkyl.

In a specific embodiment L is selected from:



wherein n is 1 to 3, preferably 1 or 2.

R^5 and $R^{5'}$ are independently selected from each other from the group consisting of H, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted aryl or substituted

or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_6 alkyl-aryl and substituted or unsubstituted C_1-C_6-alkyl-heteroaryl.

Compounds wherein L is moiety (d) are particularly preferred.

Specific examples of compounds of formula (I) include the following:

1,3-benzothiazol-2-yl(2,6-dimethoxy-4-pyrimidinyl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(1H-imidazol-5-yl)ethyl]amino}-4-pyrimidinyl)acetonitrile

1,3-benzothiazol-2-yl[2-(1-piperazinyl)-4-pyrimidinyl]acetonitrile

1,3-benzothiazol-2-yl[2-(4-benzyl-1-piperidinyl)-4-pyrimidinyl]acetonitrile

1,3-benzothiazol-2-yl[2-(4-methyl-1-piperazinyl)-4-pyrimidinyl]acetonitrile

1,3-benzothiazol-2-yl[2-(4-morpholinyl)-4-pyrimidinyl]acetonitrile

1,3-benzothiazol-2-yl[2-(methylamino)-4-pyrimidinyl]acetonitrile

1,3-benzothiazol-2-yl(2-{4-[2-(4-morpholinyl)ethyl]-1-piperazinyl}-4-pyrimidinyl)-acetonitrile

1,3-benzothiazol-2-yl{2-[4-(benzyloxy)-1-piperidinyl]-4-pyrimidinyl}acetonitrile

1,3-benzothiazol-2-yl[2-(4-hydroxy-1-piperidinyl)-4-pyrimidinyl]acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(dimethylamino)ethyl]amino}-4-pyrimidinyl)acetonitrile

1,3-benzothiazol-2-yl[2-(dimethylamino)-4-pyrimidinyl]acetonitrile

1,3-benzothiazol-2-yl{2-[(2-methoxyethyl)amino]-4-pyrimidinyl}acetonitrile

1,3-benzothiazol-2-yl{2-[(2-hydroxyethyl)amino]-4-pyrimidinyl}acetonitrile

1,3-benzothiazol-2-yl[2-(propylamino)-4-pyrimidinyl]acetonitrile

1,3-benzothiazol-2-yl(2-{[3-(1H-imidazol-1-yl)propyl]amino}-4-pyrimidinyl)acetonitrile

1,3-benzothiazol-2-yl[2-(1-pyrrolidinyl)-4-pyrimidinyl]acetonitrile

1,3-benzothiazol-2-yl{2-[(2-phenylethyl)amino]-4-pyrimidinyl}acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(2-pyridinyl)ethyl]amino}-4-pyrimidinyl)acetonitrile

1,3-benzothiazol-2-yl{2-[(2-pyridinylmethyl)amino]-4-pyrimidinyl}acetonitrile

1,3-benzothiazol-2-yl{2-[4-(1H-1,2,3-benzotriazol-1-yl)-1-piperidinyl]-4-pyrimidinyl}acetonitrile

1,3-benzothiazol-2-yl{2-[4-(2-pyrazinyl)-1-piperazinyl]-4-pyrimidinyl}acetonitrile

1,3-benzothiazol-2-yl{2-[4-(2-pyrimidinyl)-1-piperazinyl]-4-pyrimidinyl}acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(3-pyridinyl)ethyl]amino}-4-pyrimidinyl)acetonitrile

1,3-benzothiazol-2-yl(5-bromo-2-{[2-(dimethylamino)ethyl]amino}-4-pyrimidinyl)-acetonitrile

1,3-benzothiazol-2-yl{2-[(2-morpholin-4-ylethyl)amino]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl[2-(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)-acetonitrile

1,3-benzothiazol-2-yl(2-{methyl[3-(methylamino)propyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-4-yl)-acetonitrile

1,3-benzothiazol-2-yl{2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(1-methyl-1H-imidazol-4-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(1H-indol-3-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(4-hydroxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

tert-butyl ({4-[1,3-benzothiazol-2-yl(cyano)methyl]pyrimidin-2-yl}amino)acetate

{2-[(3-aminopropyl)amino]pyrimidin-4-yl}(1,3-benzothiazol-2-yl)acetonitrile

{2-[(2-aminoethyl)amino]pyrimidin-4-yl}(1,3-benzothiazol-2-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[3-(dimethylamino)propyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl{2-[(2-piperidin-1-ylethyl)amino]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(1-methyl-1H-imidazol-5-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl[2-(benzylamino)pyrimidin-4-yl]acetonitrile

isopropyl 3-({4-[1,3-benzothiazol-2-yl(cyano)methyl]pyrimidin-2-yl}amino)propanoate

1,3-benzothiazol-2-yl{2-[(3-hydroxypropyl)amino]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl{2-[(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl{2-[(pyridin-4-ylmethyl)amino]pyrimidin-4-yl}acetonitrile

tert-butyl 4-[2-({4-[1,3-benzothiazol-2-yl(cyano)methyl]pyrimidin-2-yl}amino)-ethyl]phenylcarbamate

(2-{[2-(4-aminophenyl)ethyl]amino}pyrimidin-4-yl)(1,3-benzothiazol-2-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(3,4-dimethoxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(3-methoxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(2-fluorophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl[2-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl{2-[(2-hydroxy-2-phenylethyl)amino]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl{2-[(2-{[3-(trifluoromethyl)pyridin-2-yl]amino}ethyl)amino]-pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(3-chlorophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(3,4-dichlorophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(4-methoxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(4-methylphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(3-fluorophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(4-phenoxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(2-phenoxyphenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(4-bromophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(4-fluorophenyl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl{2-[(2-[1,1'-biphenyl]-4-ylethyl)amino]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl{2-[(2-{4-[hydroxy(oxido)amino]phenyl}ethyl)amino]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl(2-{[2-(1H-1,2,4-triazol-1-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl(2-{[3-(1H-pyrazol-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

4-[2-({4-[1,3-benzothiazol-2-yl(cyano)methyl]pyrimidin-2-yl}amino)ethyl]benzenesulfonamide

{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}[5-(trifluoromethyl)-1,3-benzothiazol-2-yl]acetonitrile

1,3-benzothiazol-2-yl{2-[(1H-tetrazol-5-ylmethyl)amino]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl[2-(benzyloxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl{2-[(4-pyridin-3-ylbenzyl)oxy]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl[2-(pyridin-4-ylmethoxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl[2-(pyridin-2-ylmethoxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl[2-(3-pyridin-2-ylpropoxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl{2-[(4-methoxybenzyl)oxy]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl[2-(pyridin-3-ylmethoxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl{2-[2-(4-methoxyphenyl)ethoxy]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl[2-([1,1'-biphenyl]-3-ylmethoxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl{2-[(3,4,5-trimethoxybenzyl)oxy]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl{2-[(3,4-dichlorobenzyl)oxy]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl[2-({3-[(dimethylamino)methyl]benzyl}oxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl{2-[(1-oxidopyridin-3-yl)methoxy]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl(2-{[4-(morpholin-4-ylmethyl)benzyl]oxy}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl{2-[(4-pyridin-2-ylbenzyl)oxy]pyrimidin-4-yl}acetonitrile

1,3-benzothiazol-2-yl(2-{[4-(piperidin-1-ylmethyl)benzyl]oxy}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl[2-(4-methoxyphenoxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl[2-(4-butoxyphenoxy)pyrimidin-4-yl]acetonitrile

{2-[4-(4-acetylpiperazin-1-yl)phenoxy]pyrimidin-4-yl}(1,3-benzothiazol-2-yl)acetonitrile

[2-(4-methoxyphenoxy)pyrimidin-4-yl][5-(trifluoromethyl)-1,3-benzothiazol-2-yl]acetonitrile

N-[2-({4-[1,3-benzothiazol-2-yl(cyano)methyl]pyrimidin-2-yl}amino)ethyl]-4-chlorobenzamide

1,3-benzothiazol-2-yl(2-methoxy-4-pyrimidinyl)acetonitrile

1,3-benzothiazol-2-yl[2-({4-[(4-methylpiperazin-1-yl)methyl]benzyl}oxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl[2-({4-[(4-benzyl-piperazin-1-yl)methyl]-benzyl}oxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl(2-{[4-(piperazin-1-ylmethyl)benzyl]oxy}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl[2-({4-[(4-formylpiperazin-1-yl)methyl]benzyl}oxy)pyrimidin-4-yl]acetonitrile

[2-({4-[(4-acetylpiperazin-1-yl)methyl]benzyl}oxy)pyrimidin-4-yl](1,3-benzothiazol-2-yl)acetonitrile

(3H-Benzothiazol-2-ylidene)-{2-[4-(4-[1,2,4]oxadiazol-3-ylmethyl-piperazin-1-ylmethyl)-benzyloxy]-pyrimidin-4-yl}-acetonitrile

4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazine-1-carboxylic acid methyl ester

2-[4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazin-1-yl]-acetamide

(2-{4-[4-(2-Amino-acetyl)-piperazin-1-ylmethyl]-benzyloxy}-pyrimidin-4-yl)-(3H-benzothiazol-2-ylidene)-acetonitrile

[4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazin-1-yl]-acetic acid methyl ester

(3H-Benzothiazol-2-ylidene)-(2-{4-[4-(2-methoxy-ethyl)-piperazin-1-ylmethyl]-benzyloxy}-pyrimidin-4-yl)-acetonitrile

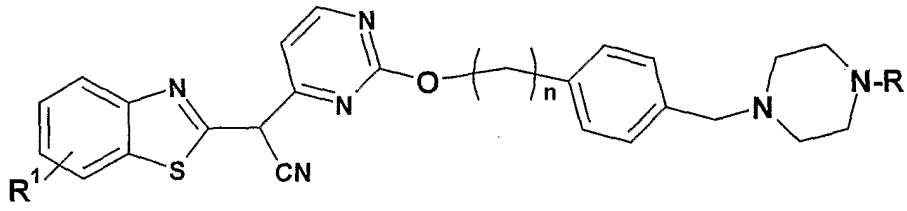
4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazine-1-carboxylic acid dimethylamide

(3H-Benzothiazol-2-ylidene)-{2-[4-(4-ethyl-piperazin-1-ylmethyl)-benzyloxy]-pyrimidin-4-yl}-acetonitrile

(3H-Benzothiazol-2-ylidene)-(2-{4-[4-(2-hydroxy-ethyl)-piperazin-1-ylmethyl]-benzyloxy}-pyrimidin-4-yl)-acetonitrile

The compounds of formula (I) may be obtained according to methods described in WO 01/47920.

In a further embodiment, the compounds of formula (I), are of sub-structure (II) and corresponding tautomers thereof.



(II)

wherein R in formula (II) 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-alkyl aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_6-alkyl heteroaryl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-

alkenyl aryl, substituted or unsubstituted C_2-C_6-alkenyl heteroaryl, substituted or unsubstituted C_2-C_6-alkynyl, substituted or unsubstituted C_2-C_6-alkynyl aryl, substituted or unsubstituted C_2-C_6-alkynyl heteroaryl, substituted or unsubstituted C_3-C_8-cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted C_1-C_6-alkyl cycloalkyl, substituted or unsubstituted C_1-C_6-alkyl heterocycloalkyl, substituted or unsubstituted C_1-C_6-alkyl carboxy, acyl, substituted or unsubstituted C_1-C_6-alkyl acyl, acyloxy, substituted or unsubstituted C_1-C_6-alkyl acyloxy, substituted or unsubstituted C_1-C_6-alkyl alkoxy, alkoxycarbonyl, substituted or unsubstituted C_1-C_6-alkyl alkoxycarbonyl, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkyl aminocarbonyl, acylamino, substituted or unsubstituted C_1-C_6-alkyl acylamino, ureido, substituted or unsubstituted C_1-C_6-alkyl ureido, amino, substituted or unsubstituted C_1-C_6-alkyl amino, sulfonyloxy, substituted or unsubstituted C_1-C_6-alkyl sulfonyloxy, sulfonyl, substituted or unsubstituted C_1-C_6-alkyl sulfonyl, sulfinyl, substituted or unsubstituted C_1-C_6-alkyl sulfinyl, sulfanyl, substituted or unsubstituted C_1-C_6-alkyl sulfanyl, sulfonylamino, substituted or unsubstituted C_1-C_6-alkyl sulfonylamino.

R^1 is selected from the group comprising or consisting of H, halogen, cyano, nitro, amino, substituted or unsubstituted C_1-C_6-alkyl, in particular C_1-C_3 alkyl, like methyl or ethyl or $-CF_3$, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, substituted or unsubstituted C_1-C_6-alkyl-aryl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_6-alkyl-heteroaryl, $-C(O)-OR^2$, $-C(O)-R^2$, $-C(O)-NR^2R^{2'}$, $-(SO_2)R^2$, with

R^2 and $R^{2'}$ being independently selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted C_1-C_6-alkyl aryl, unsubstituted or substituted C_1-C_6-alkyl heteroaryl. Preferably R^1 is H n is an integer from 0 to 3, more preferred is 1.

Specific piperazine benzothiazole derivatives according to the present invention are selected from the following group:

1,3-benzothiazol-2-yl[2-({4-[(4-methylpiperazin-1-yl)methyl]benzyl}oxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl[2-({4-[(4-benzyl-piperazin-1-yl)methyl]-benzyl}oxy)pyrimidin-4-yl]acetonitrile

1,3-benzothiazol-2-yl(2-{[4-(piperazin-1-ylmethyl)benzyl]oxy}pyrimidin-4-yl)acetonitrile

1,3-benzothiazol-2-yl[2-({4-[(4-formylpiperazin-1-yl)methyl]benzyl}oxy)pyrimidin-4-yl]acetonitrile

[2-({4-[(4-acetylpiperazin-1-yl)methyl]benzyl}oxy)pyrimidin-4-yl](1,3-benzothiazol-2-yl)acetonitrile

(3H-Benzothiazol-2-ylidene)-{2-[4-(4-[1,2,4]oxadiazol-3-ylmethyl-piperazin-1-ylmethyl)-benzyloxy]-pyrimidin-4-yl}-acetonitrile

4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazine-1-carboxylic acid methyl ester

2-[4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazin-1-yl]-acetamide

(2-{4-[4-(2-Amino-acetyl)-piperazin-1-ylmethyl]-benzyloxy}-pyrimidin-4-yl)-(3H-benzothiazol-2-ylidene)-acetonitrile

[4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazin-1-yl]-acetic acid methyl ester

(3H-Benzothiazol-2-ylidene)-(2-{4-[4-(2-methoxy-ethyl)-piperazin-1-ylmethyl]-benzyloxy}-pyrimidin-4-yl)-acetonitrile

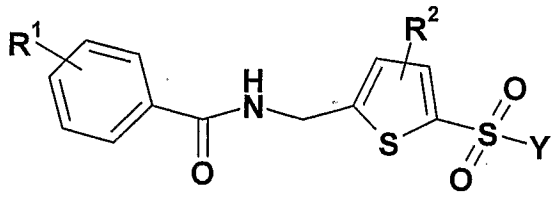
4-(4-{4-[(3H-Benzothiazol-2-ylidene)-cyano-methyl]-pyrimidin-2-yloxymethyl}-benzyl)-piperazine-1-carboxylic acid dimethylamide

(3H-Benzothiazol-2-ylidene)-{2-[4-(4-ethyl-piperazin-1-ylmethyl)-benzyloxy]-pyrimidin-4-yl}-acetonitrile

(3H-Benzothiazol-2-ylidene)-(2-{4-[4-(2-hydroxy-ethyl)-piperazin-1-ylmethyl]-benzyloxy}-pyrimidin-4-yl)-acetonitrile.

The compounds of formula (II) may be obtained according to the methods described in WO 03/091249.

In a further embodiment the JNK inhibitors may have the formula (III):



(III)

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

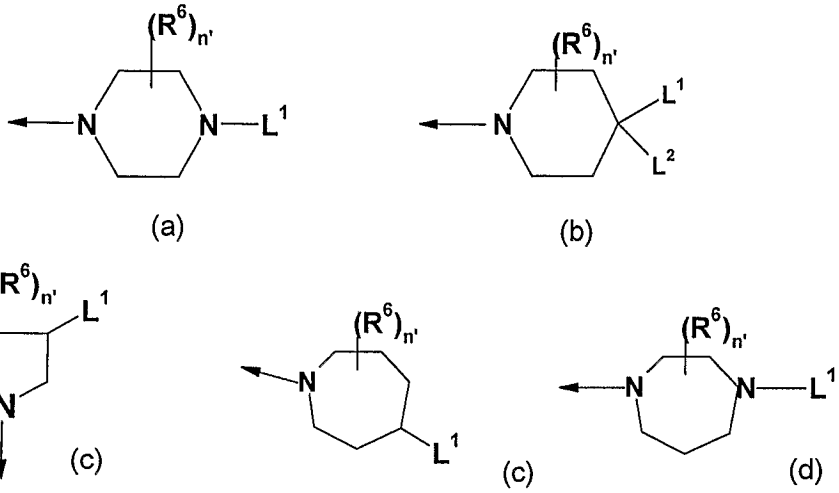
R^1 is selected from the group comprising or consisting of hydrogen, unsubstituted or a substituted C_1-C_6-alkoxy, unsubstituted or a substituted C_1-C_6-alkyl, unsubstituted or a substituted C_2-C_6-alkenyl, unsubstituted or a substituted C_2-C_6-alkynyl, amino, sulfanyl, sulfinyl, sulfonyl, sulfonyloxy, sulfonamide, acylamino, aminocarbonyl, unsubstituted or a substituted C_1-C_6 alkoxycarbonyl, unsubstituted or a substituted aryl, unsubstituted or a substituted heteroaryl, carboxy, cyano, halogen, hydroxy, nitro, hydrazide.

More specifically, R^1 is selected from the group consisting of hydrogen, halogen (e.g. chlorine), C_1-C_6 alkyl (e.g. methyl or ethyl) or C_1-C_6 alkoxy (e.g. methoxy or ethoxy). Most preferred is halogen, in particular chlorine.

R^2 is selected from the group comprising or consisting of hydrogen, $COOR^3$, -$CONR^3R^{3'}$, OH, a C_1-C_4 alkyl substituted with an OH or amino group, a hydrazido carbonyl group, a sulfate, a sulfonate, an amine or an ammonium salt. Thereby, R^3, $R^{3'}$ are

independently selected from the group consisting of H, C_1-C_6-alkyl, C_2-C_6-alkenyl, aryl, heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl.

According to one embodiment the cyclic amines Y have either of the general formulae (a) to (d):



Thereby, L^1 and L^2 are independently selected from each other from the group consisting of unsubstituted or a substituted C_1-C_6-alkyl, unsubstituted or a substituted C_2-C_6-alkenyl, unsubstituted or a substituted C_2-C_6-alkynyl, unsubstituted or a substituted C_4-C_8-cycloalkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl.

Alternatively, L^1 and L^2 are independently selected from the group consisting of unsubstituted or a substituted aryl, unsubstituted or a substituted heteroaryl, unsubstituted or a substituted aryl-C_1-C_6-alkyl, unsubstituted or a substituted 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, -$SO_2NR^{3'}R^3$.

Alternatively, L^1 and L^2 taken together may form a 4-8-membered, unsubstituted or a substituted saturated cyclic alkyl or heteroalkyl ring.

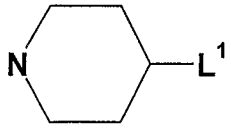
R^3, $R^{3'}$ are independently selected from the group consisting of H, unsubstituted or a substituted C_1-C_6-alkyl, unsubstituted or a substituted C_2-C_6-alkenyl, unsubstituted or a substituted aryl, unsubstituted or a substituted heteroaryl, unsubstituted or a substituted aryl-C_1-C_6-alkyl, unsubstituted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

R^6 is selected from the group consisting of hydrogen, unsubstituted or a substituted C_1-C_6-alkyl, 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. In one embodiment R^6 is hydrogen.

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

In a more specific embodiment L^1 is $-NHR^3$; where R^3 is a straight or branched C_4-C_{12}-alkyl, preferably a C_6-C_{12}-alkyl, optionally substituted with a cyclohexyl group or a benzyl group.

In an even more specific embodiment Y is a piperidine group



L^1 is $-NHR^3$; where R^3 is a straight or branched C_4-C_{12}-alkyl, preferably a C_8-C_{12}-alkyl, or a benzyl group.

Specific examples of compounds of formula (III) 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-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 acid

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 acid

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

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

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

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

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

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

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

5-{[(3-methoxybenzoyl)amino]methyl}-2-[(4-{3-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thiophene-3-carboxylic acid

5-{[(3-methoxybenzoyl)amino]methyl}-2-{[4-(octylamino)piperidin-1-yl]sulfonyl}thiophene-3-carboxylic acid

N-(2-hydroxyethyl)-5-{[(3-methoxybenzoyl)amino]methyl}-2-[(4-{3-[(trifluoro-methyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thiophene-3-carboxamide

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

5-{[(3-methoxybenzoyl)amino]methyl}-2-[(4-{3-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thiophene-3-carboxamide

N-[2-(dimethylamino)ethyl]-5-{[(3-methoxybenzoyl)amino]methyl}-2-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thiophene-3-carboxamide

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

N-({5-[(4-{[(1R)-1-cyclohexylethyl]amino}azepan-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

methyl [{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetate

tert-butyl [{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetate

[{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-thienyl)sulfonyl]-4-piperidinyl}(hexyl)amino]acetic acid

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

3-methoxy-N-[(5-{[3-(octylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

3-methoxy-N-[(5-{[3-(pentylamino)pyrrolidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

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

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

N-{[5-({3-[(2-cyclohexylethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

N-({5-[(3-{[(1R)-1-cyclohexylethyl]amino}pyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide

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

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

N-{[5-({3-[(cyclohexylmethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

N-{[5-({3-[(1-adamantylmethyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

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

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

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

N-{[5-({3-[(2-ethylhexyl)amino]pyrrolidin-1-yl}sulfonyl)thien-2-yl]methyl}-3-methoxybenzamide

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

N-{[5-({4-[(4-butoxybenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-4-chlorobenzamide

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

N-{[5-({4-[(4-tert-butylbenzyl)amino]-1-piperidinyl}sulfonyl)-2-thienyl]methyl}-4-chlorobenzamide

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

N-[(5-{[4-(hexylamino)-1-piperidinyl]sulfonyl}-2-thienyl)methyl]-2-hydroxybenzamide

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

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

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

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

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

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

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

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

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

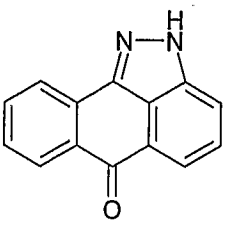
N-({5-{[4-(hexylamino)piperidin-1-yl]sulfonyl}-4-[hydroxy(phenyl)methyl]thien-2-yl}methyl)-3-methoxybenzamide

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

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

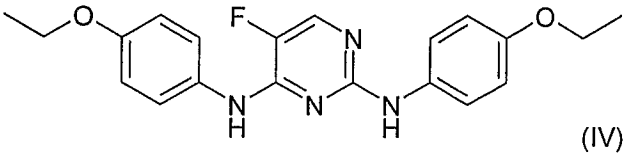
The compounds of formula (III) may be obtained according to the methods described in any of WO 01/23378, WO 02/28856 and WO 02/26733.

In a further embodiment the JNK inhibitors may be a pyrazoloanthrone derivative as shown in formula (C) (WO 01/12609):



(C)

In a further embodiment the JNK inhibitors may have the formula (IV) (WO 03/018022):



(IV) .

The present invention will now be illustrated by the example, which is not intended to be limiting in any way.

Examples

Example 1: Models for Endometriosis

The effect of the JNK inhibitor was evaluated in both in vitro and in vivo models of endometriosis. The efficacy of the drug treatment in inhibiting endometriosis was tested in two in vivo models, i) nude mouse model and ii) the rat model and an in vitro proliferative organ culture model.

Example 1.1: N-cadherin Expression

For in vitro studies, human endometriotic cells (12Z) were used (Zeitvogel et al 2001). These cells are invasive and express N-cadherin, whereas less invasive cells have lower levels of N-cadherin. These cells were treated with the JNK inhibitor and cells were fixed with paraformaldehyde. Fixed cells were stained for N-cadherin and cytokeratin using specific antibodies against these proteins, followed by second antibody conjugated to Alexafluor (a fluorochrome). Cells were observed under fluorescent microscope and both

phase contrast and fluorescent pictures were taken. Fig.1 represents the expression patterns of cytokeratin and N-cadherin in these cells. Treating cells with the JNK inhibitor decreased the expression of N-cadherin (Fig.1), showing that this pathway is involved in the regulation of N-cadherin expression and invasive activity of endometriosis. On the other hand, expression of cytokeratin, a marker for epithelial cells was not altered following the treatment with the compound (Fig. 1). This shows that only endometriotic cells are affected by treatment with the JNK inhibitor, whereas epithelial cells are not affected. Thus, by blocking the JNK pathway, the invasive properties associated with endometriosis can be specifically inhibited and thus be very useful for treating endometriosis.

Example 1.2: Nude Mouse Model

Human endometrial tissue was injected in ovarectomized nude mice to establish the disease (Bruner-Tran et al 2002). In brief, endometrial biopsies obtained from normal volunteers or from endometriotic patients were cut into small pieces and cultured in the presence of estradiol for 24h. Treated tissues, were injected either subcutaenously or intraperitoneally into ovarectomized nude mice with estradiol implant. Within 2-4 days of injection, ectopic endometriotic lesions developed in animals. Treatment with either progesterone or a JNK inhibitor was started 10-12 days following the injection of tissue. The compound was administered at a dose of 10mg/kg and 30mg/kg/animal for 30 days. Earlier work using this model has established that progesterone treatment prevents disease progression, hence this was used as control. Following the completion of treatment, animals were sacrificed, lesions developed from the transplanted tissue found in both subcutaneous and intraperitoneal sites, were measured (both size and number).

Table 1 below, illustrates the results of studies carried out as described above. The JNK inhibitor at a dose of 30mg/kg was effective in regressing the established disease in 50% animals compared to progesterone treatment. The mean lesion size was also reduced

by 20% by the treatment. In another experiment conducted with TBP, about 60% reduction in number of animals having the disease was observed compared to the positive control, progesterone, without any effect on lesion size. These results are significant, since the model measures the growth/regression of human endometrial tissue and thus has a direct relevance for treating the human disease.

Table 1: Effects of JNK inhibitors (a JNK inhibitor of formula I) and protein immunomodulatory agents on regression of endometriotic lesions in the nude mouse xenograft model.

Treatment	**Lesion (% Progesterone)** Compared to progesterone treated group	**Lesion size**
JNK inhibitor 30 mg/kg x 30 days	50 % Decrease	20 % Decrease
TBP-1 (control) 5 mg/kg x 30 days	60 % Decrease	No change

In another experiment in nude mice, human endometrial tissue was obtained from endometriotic patients, and cultured in the presence of either estradiol alone, estradiol plus medroxy progesterone acetate (MPA) or JNK inhibitor for 24 h. Treated tisses were then injected either subcutaneously or intraperitoneally into ovarectomized mice with estradiol implant. Within 2-4 days of injection, ectopic endometriotic lesions developed in animals. At 10-12 days following injection of tissue, treatment was begun with either MPA alone, JNK inhibitor alone or MPA plus JNK inhibitor. The JNK inhibitor was administered at a dose of 30/mg/kg/animal for 30 days. Following the completion of treatment, animals were sacrificed, lesions developed from the transplanted tissue found in both subcutaneous and intraperitoneal sites were measured in both size and number. Treatment with a combination of MPA and JNK inhibitor of formula 1 led to a reduction in the lesion load of approximately 50% with a reduction in lesion size of about 15 to 30% as compared to the lesion load and size of those treated with estradiol alone. These results indicate that the combination of a JNK inhibitor of formula 1 in combination with a progestin would be effective in treating and/or preventing endometriosis.

Example 1.3: Rat Model

Endometriosis was induced in rats as described earlier (D'Antonio et al 2000). In brief, autologous uterine horn fragment was transplanted onto the inner surface of the abdominal wall in rat. Three weeks following transplantation, the size and the viability of the engrafted tissue was measured. One week after the confirmation of the tissue attachment, treatments were started. The control group received the vehicle only. The JNK inhibitor was administered orally (po) at doses of 10mg/kg and 30 mg/kg per day. Treatment with JNK inhibitor was conducted for nine days, animals were anaesthetized 2hr following the last treatment and blood samples were collected. Surface area of the endometriosis-like foci was measured, endometriotic-like foci flushed with PBS and contralateral uterine flushing was also collected for measuring cytokine. The endometriotic-

like foci and spleen was removed for histology and for NK cell activity measurement respectively. In this model, the effect of the JNK inhibitor at 10mg/kg dose was not different from the vehicle, but at 30 mg/kg and 60mg/kg a significant regression of established endometriotic lesions was observed (Fig. 2). Treatment with antide (for comparison) showed about 85% regression (data not shown).

Example 1.4: Rat Model / Determination of Cytokine Levels

Of additional significance from these recent studies are modifications in cytokine levels measured in either the endometriotic foci or in the contralateral uterine horn without any lesion. The effect of the JNK inhibitor on the cytokine levels was determined in the rat model (see Example 1.3). The results demonstrate that treatment with the JNK inhibitor reduced the levels of inflammatory cytokines, IL-12, INF-γ, IL-10 and MCP-1 in the endometriotic foci (Fig. 3). These cytokines have been previously reported to be elevated in peritoneal fluid of women with disease. In the contralateral horn, the JNK inhibitor was without effect on the cytokine expression (Fig. 4). In addition, inhibitor treatment increased NK cell activity compared to the vehicle treated group (Fig. 5). A reduced lymphocyte cytolytic activity has been observed in women with endometriosis. Therefore, these results suggest that an increase in the NK cell cytolytic activity due to the JNK inhibitor treatment may contribute to the elimination of ectopic endometrium. Further, these results with JNK inhibitors suggest that the effects of the inhibitor may treat the diseased tissue without affecting portions of the uterus or peritoneal cavity without disease.

The immune system of the rat in this model is intact, suggesting that if molecules had as a primary mechanism to affect only an immune-modulated pathway of the host, that the effects of the molecules in this model should have been stronger than observed in nude mice. In fact, these results from nude mouse and rat models suggest an important activity of the molecule directly on the endometriotic tissue or in immune cell populations that remain in nude mice. Another important distinction of the rat model is that intact myometrial and endometrial tissues are surgically resected into experimental animals. Taken together, results from these two model systems show that kinase inhibitors which target JNK pathway are involved in endometriosis and can be effective agents for treatment of disease.

Example 1.5: Proliferative Organ Culture Model

Normal endometrial tissues were acquired just prior to ovulation by biopsy from a donor population (no history of endometriosis) and from women with surgically confirmed endometriosis. Informed consent was obtained prior to biopsy and the use of human tissues was approved by Vanderbilt University's Institutional Review Board and Committee for the Protection of Human Subjects.

Endometrial biopsies were dissected into small cubes (~1x1 mm^3) and 8-10 pieces of tissue per treatment group were suspended in tissue culture inserts. Organ cultures were maintained a total of 72 hrs at 37°C in DME/F-12 media with serum supplements. Tissue treatments included 17β-estradiol (E), E plus progesterone (P), or E plus medroxy progesterone acetate (MPA) with and without the JNK inhibitor. Cultures were maintained for 24 hours in E only until the initiation of experimental conditions. JNK inhibitor was used at a concentration of 5 or 15 μM and MPA was used at a concentration of 50, 100 or 250 μM.

Media was collected from organ cultures and secreted proteins quantified using the Coomassie Plus Protein Assay (Pierce) and 20μg total protein subjected to 10% SDS-PAGE. Proteins were transferred to PVDF membrane and blocked in PBS with 10% non-fat milk and 0.05% Tween-20. Blots were incubated overnight at 4°C in PBS/Milk/Tween with a primary antibody recognizing human MMP-3, which is a marker for endometrial tissue, washed and incubated with secondary antibody for one hour. Proteins were visualized by chemiluminesence (Amersham) and autoradiography. As a negative control, identical blots were incubated without a primary antibody.

Results showed that the normal human endometrial cultures were sensitive to MPA treatment, in contrast to endometrial cultures obtained from endometriosis patients, which failed to regress with MPA alone. When a JNK inhibitor of formula 1 was combined with MPA treatment, the sensitivity to MPA was restored in the cultures obtained from endometriosis patients and maintained in the cultures obtained from normal volunteers.

These results indicate that co-administration of a progestin with a JNK inhibitor of formula 1 would treat and prevent the re-establishment of endometriosis.

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WO 01/12621

WO 01/12609

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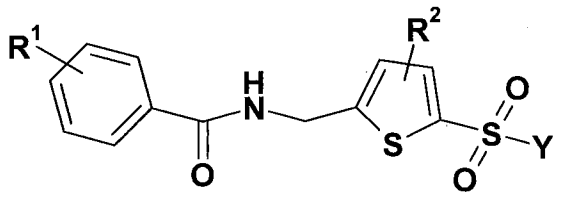
Claims

1. Use of a JNK inhibitor of formula (III)



(III)

as well as its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment and/or prevention of endometriosis wherein

Y is a 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 (III) thus providing the sulfonamide;

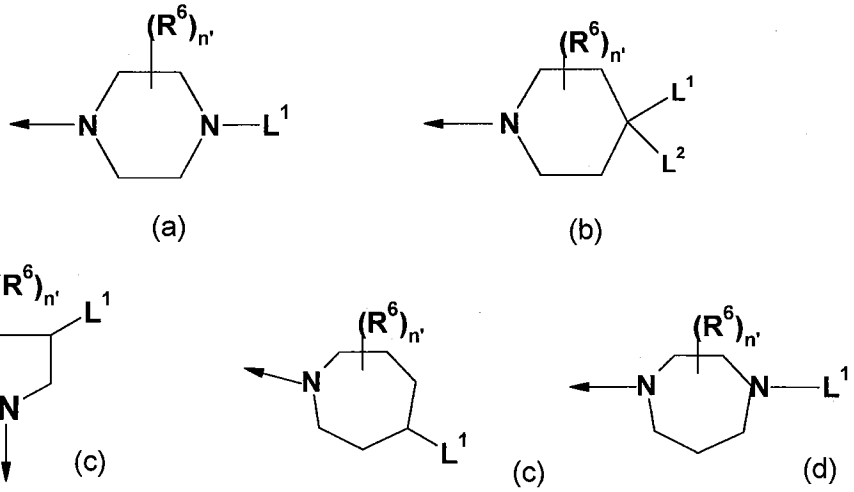
R^1 is selected from the group consisting of hydrogen, C_1-C_6-alkoxy, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, amino, sulfanyl, sulfinyl, sulfonyl, sulfonyloxy, sulfonamide, acylamino, aminocarbonyl, C_1-C_6 alkoxycarbonyl, aryl, heteroaryl, carboxy, cyano, halogen, hydroxy, nitro and hydrazide;

R^2 is selected from the group consisting of hydrogen, $COOR^3$, $-CONR^3R^{3'}$, OH, a C_1-C_4 alkyl substituted with an OH or amino group, a hydrazido carbonyl group, a sulfate, a sulfonate, an amine and an ammonium salt;

with R^3, $R^{3'}$ being substituents independently selected from the group consisting of H, C_1-C_6-alkyl, C_2-C_6-alkenyl, aryl, heteroaryl, aryl-C_1-C_6-alkyl, and heteroaryl-C_1-C_6-alkyl

2. The use of the JNK inhibitor of Formula (III) according to claim 1, wherein R^1 is selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl and C_1-C_6 alkoxy.

3. The use of the JNK inhibitor of Formula (III) according to claim 1, wherein Y is either of the cyclic amines having the general formulae:



whereby, L^1 and L^2 are independently selected from each other from the group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_4-C_8-cycloalkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L^1 and L^2 are independently selected from the group consisting of aryl, 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, and -$SO_2NR^{3'}R^3$,

with R^3, $R^{3'}$ being substituents independently selected from the group consisting of H, C_1-C_6-alkyl, C_2-C_6-alkenyl, aryl, heteroaryl, aryl-C_1-C_6-alkyl, and heteroaryl-C_1-C_6-alkyl;

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

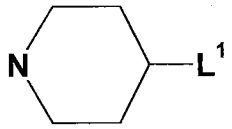
R^6 is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo (=O), and

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

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

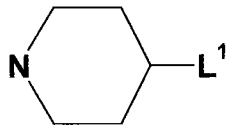
5. The use of JNK inhibitor of Formula (III) according to any one of claims 3 to 4, wherein L^1 is $-NHR^3$; where R^3 is a straight or branched C_4-C_{12}-alkyl, preferably a C_6-C_{12}-alkyl, optionally substituted with a cyclohexyl group or a benzyl group.

6. The use of JNK inhibitor of Formula (III) according to claim 1, wherein Y is a piperidine group



L^1 is $-NHR^3$; where R^3 is a straight or branched C_4-C_{12}-alkyl, preferably a C_8-C_{12}-alkyl, or a benzyl group.

7. The use of JNK inhibitor of Formula (III) according to claim 3, wherein Y is a piperidine group



L^1 is $-NHR^3$; where R^3 is a straight or branched C_4-C_{12}-alkyl, preferably a C_8-C_{12}-alkyl, or a benzyl group.

8. The use of JNK inhibitor of Formula (III) according to any one of the above claims, wherein the JNK inhibitor is selected from the group consisting of:

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

9. A pharmaceutical composition comprising a JNK inhibitor of Formula (III) according to claim 1, a hormal suppressor and a pharmaceutically acceptable excipient.

10. The pharmaceutical composition according to claim 9, wherein said hormal suppressor is selected from the group consisting of a GnRH antagonist, GnRH agonist, aromatase inhibitor, progesterone receptor modulator and an estrogen receptor modulator.