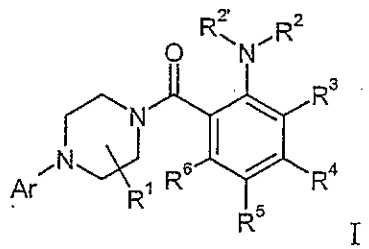
1- (2-AMINO-BENZOL) -PIPERAZINE DERIVATIVES AS GLYCINE UPTAKE INHIBITORS FOR THE TREATMENT OF PSYCHOSES

The present invention relates to compounds of the general formula I



I

In a first aspect, there is provided a compound of the general formula I

wherein

Ar is unsubstituted or substituted aryl or 6-membered heteroaryl, containing one, two or three nitrogen atoms, and wherein the aryl and the heteroaryl groups are substituted by one or more substituents selected from the group consisting of hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

R^1 is hydrogen or (C_1-C_6)-alkyl;

R^2 and $R^{2'}$ are independently from each other hydrogen, $(CR_2)_n$-hydroxy for R being hydrogen or $C_1-C_6)$-alkyl, or are (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_1-C_6)-alkyl substituted by halogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl, $(CH_2)_n$-heterocycloalkyl, $(CH_2)_n$-O-(C_1-C_6)-alkyl or $(CH_2)_n$-aryl or

R^2 and $R^{2'}$ form together with the N atom to which they are attach a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O, which rings are unsubstituted or substituted by $(CH_2)_n$-hydroxy, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $(CH_2)_n$-O-(C_1-C_6)-alkyl, or form together with the N atom a 5-membered heteroaryl group, optionnally containing in addition to the N atom one, two or three further nitrogen atoms and wherein the heteroaryl group is optionally substituted by (C_1-C_6)-alkyl;

R^3, R^4 and R^6 are independently from each other hydrogen, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy;

R^5 is NO_2, CN, $C(O)R^9$, S-(C_1-C_6)-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other hydrogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or (C_1-C_6)-alkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy or NR^7R^8;

R^{10} is (C_1-C_6)-alkyl, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or NR^7R^8;

R^{11} and R^{12} are independently from each other hydrogen, $C(O)$-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, or form together with the N-atom a 5-membered heteroaryl group optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, (C_1-C_6)-alkyl or $(CH_2)_n(C_3-C_6)$-cycloalkyl;

n is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof,

with the proviso that

1-[5-(aminosulfonyl)-2-(4-morpholinyl)benzoyl]-4-phenyl-piperazine,

1-(4-methoxyphenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,

1-[2-(4-morpholinyl)-5-nitrobenzoyl]-4-[2-nitro-4-(trifluoromethyl)phenyl]-piperazine,

1-(4-methoxyphenyl)-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,

1-[2-[4-(2-hydroxyethyl)-1-piperazinyl]-5-nitrobenzoyl]-4-(4-methoxyphenyl)-piperazine,

1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-piperidinyl)benzoyl]-piperazine,

1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,

1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperidinyl)-5-nitrobenzoyl]-piperazine,

1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine,

1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,

1-[5-[[methyl(phenylmethyl)amino]sulfonyl]-2-(4-morpholinyl)benzoyl]-4-(4-nitrophenyl)-piperazine and
1-(4-acetyl-2-fluorophenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]- piperazine, are excluded.

The compound 1-[5-(aminosulfonyl)-2-(4-morpholinyl)benzoyl]-4-phenyl-piperazine has been described specifically in US 4,244,871, which possess tyrosine-paralyzing activity, and the other compounds mentioned above are commercially available products.

Disclosed herein are compounds of general formula I, pharmaceutical composition containing them and their use in the treatment of neurological and neuropsychiatric disorders. It has surprisingly been found that the compounds of general formula I may be good inhibitors of the glycine transporter I (GlyT-1), and that they have a good selectively to glycine transporter 2(GlyT-2) inhibitors.

Schizophrenia is a progressive and devastating neurological disease characterized by episodic positive symptoms such as delusions, hallucinations, thought disorders and psychosis and persistent negative symptoms such as flattened affect, impaired attention and social withdrawal, and cognitive impairments (Lewis DA and Lieberman JA, *Neuron, 28:325-33, 2000*). For decades research has focused on the "dopaminergic hyperactivity" hypothesis which has led to therapeutic interventions involving blockade of the dopaminergic system (Vandenberg RJ and Aubrey KR., *Exp. Opin. Ther. Targets, 5(4): 507-518, 2001*; Nakazato A and Okuyama S, et al., *Exp. Opin. Ther. Patents, 10(1): 75-98, 2000*). This pharmacological approach poorly address negative and cognitive symptoms which are the best redictors of functional outcome (Sharma T., *Br.J. Psychiatry, 174(suppl. 28): 44-51, 1999).*

A complementary model of schizophrenia was proposed in the mid-1960' based upon the psychotomimetic action caused by the blockade of the glutamate system by compounds like phencyclidine (PCP) and related agents (ketamine) which are non-competitive NMDA receptor antagonists. Interestingly in healthy volunteers, PCP-induced psychotomimetic action incorporates positive and negative symptoms as well as cognitive dysfunction, thus closely resembling schizophrenia in patients (Javitt DC et al., *Biol. Psychiatry, 45: 668-679,* 1999). Furthermore transgenic mice expressing reduced levels of the NMDAR1 subunit displays behavioral abnormalities similar to those observed in pharmacologically induced models of schizophrenia, supporting a model in which reduced NMDA receptor activity results in schizophrenia-like behavior (Mohn AR et al., *Cell, 98: 427-236, 1999).*

Glutamate neurotransmission, in particular NMDA receptor activity, plays a critical role in synaptic plasticity, learning and memory, such as the NMDA receptors

appears to serve as a graded switch for gating the threshold of synaptic plasticity and memory formation (Wiley, NY; Bliss TV and Collingridge GL, *Nature, 361: 31-39,* 1993). Transgenic mice overexpressing the NMDA NR2B subunit exhibit enhanced synaptic plasticity and superior ability in learning and memory (Tang JP et al., *Natur, 401- 63-69, 1999*).

Thus, if a glutamate deficit is implicate in the pathophysiology of schizophrenia, enhancing glutamate transmission, in particular via NMDA receptor activation, would be predicted to produce both anti-psychotic and cognitive enhancing effects.

The amino acid glycine is known to have at least two important functions in the CNS. It acts as an inhibitory amino acid, binding to strychnine sensitive glycine receptors, and it also influences excitatory activity, acting as an essential co-agonist with glutamate for N-methyl-D-aspartate (NMDA) receptor function. While glutamate is released in an activity-dependent manner from synaptic terminals, glycine is apparently present at a more constant level and seems to modulate/control the receptor for its response to glutamate.

One of the most effective ways to control synaptic concentrations of neurotransmitter is to influence their re-uptake at the synapses. Neurotransmitter transporters by removing neurotransmitters from the extracellular space, can control their extracellular lifetime and thereby modulate the magnitude of the synaptic transmission (Gainetdinov RR et al, *Trends in Pharm. Sci., 23(8): 367-373, 2002*).

Glycine transporters, which form part of the sodium and chloride family of neurotransmitter transporters, play an important role in the termination of post-synaptic glycinergic actions and maintenance of low extracellular glycine concentration by re-uptake of glycine into presynaptic nerve terminals and surrounding fine glial processes.

Two distinct glycine transporter genes have been cloned (GlyT-1 and GlyT-2) from mammalian brain, which give rise to two transporters with ~50 % amino acid sequence homology. GlyT-1 presents four isoforms arising from alternative splicing and alternative promoter usage (1a, 1b, 1c and 1d). Only two of these isoforms have been found in rodent brain (GlyT-1a and GlyT-1b). GlyT-2 also presents some degree of heterogeneity. Two GlyT-2 isoforms (2a and 2b) have been identified in rodent brains. GlyT-1 is known to be located in CNS and in peripheral tissues, whereas GlyT-2 is specific to the CNS. GlyT-1 has a predominantly glial distribution and is found not only in areas corresponding to strychnine sensitive glycine receptors but also outside these areas, where it has been postulated to be involved in modulation of NMDA receptor function (Lopez-Corcuera B et al., *Mol. Mem. Biol., 18: 13-20, 2001*). Thus, one strategy to enhance NMDA receptor activity is to elevate the glycine concentration in the local microenvironment of synaptic NMDA receptors by inhibition of GlyT-1 transporter

(Bergereon R. et al., *Proc. Natl. Acad. Sci. USA, 95: 15730-15734*, 1998; Chen L. et al., *J. Neurophysiol., 89(2): 691-703*, 2003).

Glycine transporters inhibitors are suitable for the treatment of neurological and neuropsychiatric disorders. The majority of diseases states implicated are psychoses, schizophrenia (Armer RE and Miller DJ, *Exp. Opin. Ther. Patents, 11 (4): 563-572, 2001)*, psychotic mood disorders such as severe major depressive disorder, mood disorders associated with psychotic disorders such as acute mania or depression, associated with bipolar disorders and mood disorders, associated with schizophrenia, (Pralong ET et al., *Prog. Neurobiol., 67: 173-202, 2002*), autistic disorders (Carlsson ML, *J. Neural Trans,. 105: 525-535, 1998*), cognitive disorders such as dementias, including age related dementia and senile dementia of the Alzheimer type, memory disorders in a mammal, including a human, attention deficit disorders and pain (Armer RE and Miller DJ, *Exp. Opin. Ther. Patents, 11 (4): 563-572, 2001*).

Thus, increasing activation of NMDA receptors via GlyT-1 inhibition may lead to agents that treat psychosis, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

Disclosed herein are the compounds of formula I per se, the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to activation of NMDA receptors via Glyt-1 inhibition, their manufacture, medicaments based on the disclosed compound and their production as well as the use of compounds of formula I in the control or prevention of illnesses such as psychoses, disfunction in memory and learning, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

The preferred indications using the compounds are schizophrenia, cognitive impairment and Alzheimer's disease.

Also disclosed herein are racemic mixtures, all their corresponding enantiomers and/or optical isomers.

As used herein, the term "alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups with 1 - 4 carbon atoms.

The term "alkenyl" denotes an unsaturated straight- or branched-chain group containing from 2 to 6 carbon atoms. Preferred alkenyl group is allyl.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "aryl" denotes a monovalent cyclic aromatic hydrocarbon radical consisting of one or more fused rings in which at least one ring is aromatic in nature, for example phenyl or naphthyl.

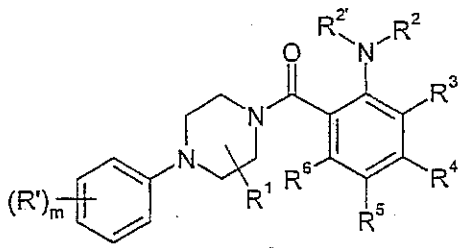
The term "6-membered heteroaryl containing one, two or three nitrogen atoms" denotes a monovalent aromatic carbocyclic radical, for example pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl or triazinyl.

The term "5-membered heteroaryl group optionally containing in addition to the N atom one, two or three further nitrogen atoms" denotes a monovalent aromatic carbocyclic radical, for example pyrrolyl, 2,5-dihydro-pyrrol-1-yl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl.

The term "heterocycloalkyl" denotes a non aromatic hydrocarbon radical, for example azepanyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidinyl; pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

Preferred compounds of formula I are those of formula I-1



I-1

wherein

R' is hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

m is 0, 1, 2 or 3;

R^1 is hydrogen or (C_1-C_6)-alkyl;

R^2 and $R^{2'}$ are independently from each other hydrogen, $(CR_2)_n$-hydroxy for R being hydrogen or $C_1-C_6)$-alkyl, or are (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_1-C_6)-alkyl substituted by halogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl, $(CH_2)_n$-heterocycloalkyl, $(CH_2)_n$-O-(C_1-C_6)-alkyl or $(CH_2)_n$-aryl;

R^3, R^4 and R^6 are independently from each other hydrogen, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy;

R^5 is NO_2, CN, $C(O)R^9$, S-(C_1-C_6)-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other hydrogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or (C_1-C_6)-alkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy or NR^7R^8;

R^{10} is (C_1-C_6)-alkyl, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or NR^7R^8;

R^{11} and R^{12} are independently from each other hydrogen, $C(O)$-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, or form together with the N-atom a 5-membered heteroaryl group optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, (C_1-C_6)-alkyl or $(CH_2)_n(C_3-C_6)$-cycloalkyl;

n is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

The following compounds of formula I-1 are preferred:

1-(4-{4-[2-(cyclopropylmethyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone,

1-{4-[4-(2-cyclohexylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,

1-{4-[4-(2-diethylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,

1-{3-fluoro-4-[4-(2-isobutylamino-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,

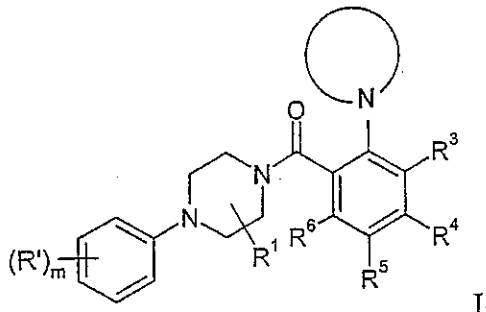
1-{4-[4-(2-cyclobutylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,

1-{4-[4-(2-cyclobutylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,

1-{4-[4-(2-cyclopentylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone or

1-(4-{4-[2-(allyl-methyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone.

Further preferred are compounds of formula I-2



I-2

wherein

R' is hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

m is 0, 1, 2 or 3;

R^1 is hydrogen or (C_1-C_6)-alkyl;



is a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O, which rings are unsubstituted or substituted by $(CH_2)_n$-hydroxy, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $(CH_2)_n$-O-(C_1-C_6)-alkyl, or form together with the N atom a 5-membered heteroaryl group, optionnally containing in addition to the N atom one, two or three further nitrogen atoms and wherein the heteroaryl group is optionally substituted by (C_1-C_6)-alkyl;

R^3, R^4 and R^6 are independently from each other hydrogen, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy;

R^5 is NO_2, CN, $C(O)R^9$, S-$(C_1$-$C_6)$-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other hydrogen, $(CH_2)_n$-$(C_3$-$C_6)$-cycloalkyl or $(C_1$-$C_6)$-alkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, $(C_1$-$C_6)$-alkoxy or NR^7R^8;

R^{10} is $(C_1$-$C_6)$-alkyl, $(CH_2)_n$-$(C_3$-$C_6)$-cycloalkyl or NR^7R^8;

R^{11} and R^{12} are independently from each other hydrogen, $C(O)$-$(C_1$-$C_6)$-alkyl, SO_2-$(C_1$-$C_6)$-alkyl, or form together with the N-atom a 5-membered heteroaryl group optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, $(C_1$-$C_6)$-alkyl or $(CH_2)_n(C_3$-$C_6)$-cycloalkyl;

n is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

The following compounds of formula I-2 are preferred:

1-{4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,

1-{3-fluoro-4-[4-(5-nitro-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,

1-{3-fluoro-4-[4-(5-nitro-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,

1-{4-[4-(2-azepan-1-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,

1-(3-fluoro-4-{4-[2-(2-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,

1-(3-fluoro-4-{4-[2-(4-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,

1-(3-fluoro-4-{4-[2-(3-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,

1-(3-fluoro-4-{4-[2-(2-methyl-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,

1-(4-{4-[2-(2,5-dihydro-pyrrol-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone,

1-{3-fluoro-4-[4-(5-nitro-2-thiomorpholin-4-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,

1-(3-fluoro-4-{4-[2-(3-hydroxy-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,

1-{4-[4-(2-azepan-1-yl-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,

1-{3-fluoro-4-[4-(5-methanesulfonyl-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,

N-methyl-4-pyrrolidin-1-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,

N-methyl-4-morpholin-4-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,

3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide,

1-(3-fluoro-4-{4-[2-(3-hydroxymethyl-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,

2-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile,

3-fluoro-4-[4-(5-methanesulfonyl-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-benzonitrile,

2-fluoro-4-[4-(5-methanesulfonyl-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-benzonitrile,

[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-piperidin-1-yl-phenyl)-methanone,

[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-piperidin-1-yl-phenyl)-methanone,

3-[4-(4-cyano-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide,

3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide,

3-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide,

3-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide,

3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

3-[4-(4-cyano-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

N-methyl-4-piperidin-1-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,

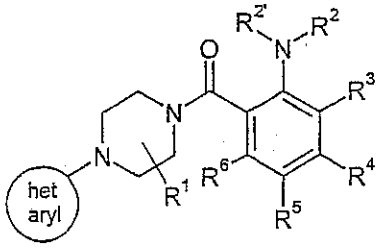
3-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

3-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

3-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide or

3-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide.

Further preferred are compounds of formula I-3



I-3

wherein

hetaryl is a 6-membered heteroaryl, containing one, two or three nitrogen atoms, optionally substituted by one or more substituents selected from the group consisting of hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

R^1 is hydrogen or (C_1-C_6)-alkyl;

R^2 and $R^{2'}$ are independently from each other hydrogen, $(CR_2)_n$-hydroxy for R being hydrogen or $C_1-C_6)$-alkyl, or are (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_1-C_6)-alkyl substituted by halogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl, $(CH_2)_n$-heterocycloalkyl, $(CH_2)_n$-O-(C_1-C_6)-alkyl or $(CH_2)_n$-aryl or

R^3, R^4 and R^6 are independently from each other hydrogen, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy;

R^5 is NO_2, CN, $C(O)R^9$, S-(C_1-C_6)-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other hydrogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or (C_1-C_6)-alkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy or NR^7R^8;

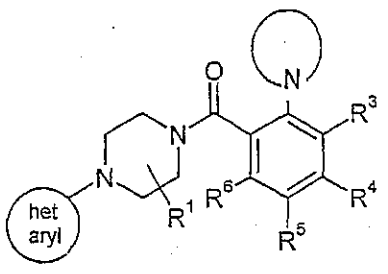
R^{10} is (C_1-C_6)-alkyl, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or NR^7R^8;

R^{11} and R^{12} are independently from each other hydrogen, C(O)-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, or form together with the N-atom a 5-membered heteroaryl group optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, (C_1-C_6)-alkyl or $(CH_2)_n(C_3-C_6)$-cycloalkyl;

n is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

Further preferred are compounds of formula I-4

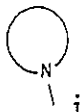


I-4

wherein

hetaryl is a 6-membered heteroaryl, containing one, two or three nitrogen atoms, optionally substituted by one or more substituents selected from the group consisting of hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

R^1 is hydrogen or (C_1-C_6)-alkyl;



is a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O, which rings are unsubstituted or substituted by $(CH_2)_n$-hydroxy, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $(CH_2)_n$-O-(C_1-C_6)-alkyl, or form together with the N atom a 5-membered heteroaryl group, optionnally containing in addition to the N atom one, two or three further nitrogen atoms and wherein the heteroaryl group is optionally substituted by (C_1-C_6)-alkyl;

R^3, R^4 and R^6 are independently from each other hydrogen, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy;

R^5 is NO_2, CN, $C(O)R^9$, S-(C_1-C_6)-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other hydrogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or (C_1-C_6)-alkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy or NR^7R^8;

R^{10} is (C_1-C_6)-alkyl, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or NR^7R^8;

R^{11} and R^{12} are independently from each other hydrogen, C(O)-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, or form together with the N-atom a 5-membered heteroaryl group optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, (C_1-C_6)-alkyl or $(CH_2)_n(C_3-C_6)$-cycloalkyl;

n is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

The following compounds of formula I-4 are preferred:

3-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide

(2-morpholin-4-yl-5-nitro-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

[4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

6-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-nicotinonitrile

[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

(2-morpholin-4-yl-5-nitro-phenyl)-[4-(4-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

(2-morpholin-4-yl-5-nitro-phenyl)-[4-(6-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

[4-(5-bromo-pyrimidin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

[4-(6-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(2-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone

6-[4-(5-methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-nicotinonitrile

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

[4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone

[4-(5-chloro-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-methanone

[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-methyl-pyridin-3-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-methyl-pyridin-2-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

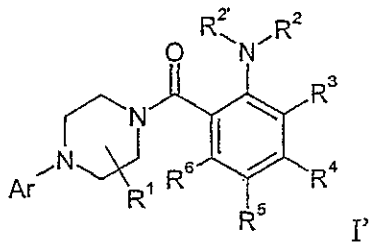
(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(2-trifluoromethyl-pyrimidin-5-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyridazin-3-yl)-piperazin-1-yl]-methanone

[4-(4-dimethylamino-[1,3,5]triazin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone or

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-(5'-trifluoromethyl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone.

In a second aspect, there is provided compounds of formula



I'

wherein

Ar is unsubstituted or substituted aryl or 6-membered heteroaryl, containing one, two or three nitrogen atoms, and wherein the aryl and the heteroaryl groups are substituted by one or more substituents selected from the group consisting of hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy,
(C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

R^1 is hydrogen or (C_1-C_6)-alkyl;

R^2 and $R^{2'}$ are independently from each other hydrogen, hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-alkenyl, (C_2-C_6)-alkyl substituted by halogen, (C_3-C_6)-cycloalkyl, heterocycloalkyl, (C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl-heterocycloalkyl, (C_1-C_6)-alkyl-C(O)-R^9, (C_1-C_6)-alkyl-CN, (C_2-C_6)-alkyl-O-R^{13}, (C_2-C_6)-alkyl-NR^7R^8, aryl or 6-membered heteroaryl containing one, two or three nitrogen atoms, (C_1-C_6)-alkyl-aryl or (C_1-C_6)-alkyl-5 or-6-membered heteroaryl containing one, two or three heteroatoms, selected from the group consisting of oxygen, sulphur or nitrogen, wherein aryl, heterocycloalkyl and heteroaryl are unsubstituted or substituted by one or more substituents selected from the group consisting of hydroxy, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy; or
R^2 and $R^{2'}$ form together with the N atom to which they are attach a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O, which rings are unsubstituted or substituted by hydroxy, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkyl-O-R^{13}, or form together with the N atom a 5-membered heteroaryl group, optionnally containing in addition to the N atom one, two or three further nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen or (C_3-C_6)-cycloalkyl;

R^3, R^4 and R^6 are independently from each other hydrogen, hydroxy, halogen, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy or NR^7R^8;

R^5 is NO_2, CN, C(O)R^9, S-(C_1-C_6)-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other hydrogen, (C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl, or (C_3-C_6)-cycloalkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy or NR^7R^8;

R^{10} is (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl or NR^7R^8;

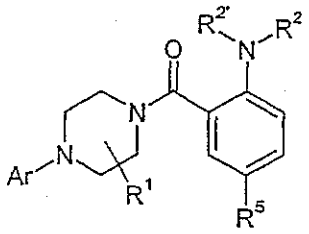
R^{11} and R^{12} are independently from each other hydrogen, C(O)-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, or form together with the N-atom a 5-membered heteroaryl

group optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, (C_1-C_6)-alkyl,
(C_1-C_6)-alkyl substituted by halogen or (C_3-C_6)-cycloalkyl;

R^{13} is hydrogen, (C_1-C_6)-alkyl or (C_3-C_6)-cycloalkyl;

and pharmaceutically acceptable acid addition salts thereof,
with the proviso that
1-[5-(aminosulfonyl)-2-(4-morpholinyl)benzoyl]-4-phenyl-piperazine,
1-(4-methoxyphenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[2-(4-morpholinyl)-5-nitrobenzoyl]-4-[2-nitro-4-(trifluoromethyl)phenyl]-piperazine,
1-(4-methoxyphenyl)-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-[4-(2-hydroxyethyl)-1-piperazinyl]-5-nitrobenzoyl]-4-(4-methoxyphenyl)-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-piperidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperidinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[5-[[methyl(phenylmethyl)amino]sulfonyl]-2-(4-morpholinyl)benzoyl]-4-(4-nitrophenyl)-piperazine and
1-(4-acetyl-2-fluorophenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]- piperazine,
are excluded.

One embodiment are compounds of formula Ia



Ia

wherein

Ar is unsubstituted or substituted phenyl or 6-membered heteroaryl, containing one or two nitrogen atoms, and wherein the phenyl and the heteroaryl groups are optionally substituted by one or two substituents selected from the group consisting of halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

R^1 is hydrogen or (C_1-C_6)-alkyl;

R^2 and $R^{2'}$ are independently from each other hydrogen, hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-alkenyl, (C_3-C_6)-cycloalkyl, heterocycloalkyl, (C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl-aryl, (C_2-C_6)-alkyl-O-R^{13}, or

R^2 and $R^{2'}$ form together with the N atom to which they are attach a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O, which rings are unsubstituted or substituted by hydroxy, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkyl-O-R^{13}, or form together with the N atom a 5-membered heteroaryl group optionnally containing in addition to the N atom one or two nitrogen atoms;

R^5 is NO_2, CN, $C(O)R^9$, S-(C_1-C_6)-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other hydrogen, (C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl or form together with the N atom to which they are attach a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of oxygen;

R^9 is (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy or NR^7R^8;

R^{10} is (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl or NR^7R^8;

R^{11} and R^{12} are independently from each other SO_2-(C_1-C_6)-alkyl, or form together with the N-atom a 5-membered heteroaryl group containing in addition to the N atom one, two or three nitrogen atoms;

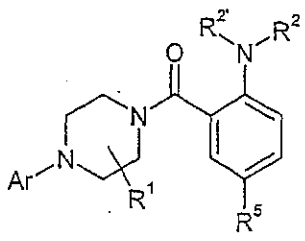
R^{13} is hydrogen or (C_1-C_6)-alkyl;

and pharmaceutically acceptable acid addition salts thereof,

with the proviso that

1-[5-(aminosulfonyl)-2-(4-morpholinyl)benzoyl]-4-phenyl-piperazine,
1-(4-methoxyphenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[2-(4-morpholinyl)-5-nitrobenzoyl]-4-[2-nitro-4-(trifluoromethyl)phenyl]-piperazine,
1-(4-methoxyphenyl)-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-[4-(2-hydroxyethyl)-1-piperazinyl]-5-nitrobenzoyl]-4-(4-methoxyphenyl)-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-piperidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperidinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[5-[[methyl(phenylmethyl)amino]sulfonyl]-2-(4-morpholinyl)benzoyl]-4-(4-nitrophenyl)-piperazine and
1-(4-acetyl-2-fluorophenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]- piperazine,
are excluded.

Another embodiment are those compounds of formula Ia, wherein



Ia

wherein

Ar is unsubstituted or substituted phenyl, pyridyl or pyrimidinyl, optionally substituted by one or two substituents selected from the group consisting of halogen, NO_2, CN, methyl, CF_3, methoxy, OCF_3, NH_2, $C(O)CH_3$, $C(O)OCH_3$, $C(O)OCH_2CH_3$,

SO_2NH_2 or SO_2CH_3;

R^1 is hydrogen or methyl;

R^2 and $R^{2'}$ are independently from each other hydrogen, hydroxy, (C_1-C_6)-alkyl, $-CH_2CH=CH_2$, $-CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, cyclopropyl, cyclopentyl, cyclohexyl, tetrahydropyranyl, $-CH_2$-cyclopropyl, $(CH_2)_2OCH_3$, benzyl, or

R^2 and $R^{2'}$ form together with the N atom to which they are attach a heterocycloalkyl ring, selected from the group consisting of morpholinyl, thiomorpholinyl, azetidinyl, pyrrolidinyl, piperidinyl or azepanyl, which rings are unsusbtituted or substituted by hydroxy, methyl, methoxy, ethoxy, CH_2OH, or form together with the N atom a 5-membered heteroaryl ring, selected from the group consisting of imidazolyl, triazolyl or di-hydro-pyrrolyl;

R^5 is NO_2, CN, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)CH_3$, $-SCH_3$, $-SO_2-(C_1-C_6)$-alkyl, $-SO_2-NH-(C_1-C_6)$-alkyl, $-SO_2-N-[(C_1-C_6)\text{-alkyl}]_2$, $-SO_2NH_2$, $-NHSO_2CH_3$, $-SO_2-NHCH_2$-cycloalkyl, $-SO_2-CH_2$-cycloalkyl, $-SO_2$-pyrrolidin-1-yl, $-SO_2$-morpholidin-1-yl, imidazolyl or tetrazolyl;

and pharmaceutically acceptable acid addition salts thereof,
with the proviso that
1-[5-(aminosulfonyl)-2-(4-morpholinyl)benzoyl]-4-phenyl-piperazine,
1-(4-methoxyphenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[2-(4-morpholinyl)-5-nitrobenzoyl]-4-[2-nitro-4-(trifluoromethyl)phenyl]-piperazine,
1-[2-[4-(2-hydroxyethyl)-1-piperazinyl]-5-nitrobenzoyl]-4-(4-methoxyphenyl)-piperazine and
1-(4-acetyl-2-fluorophenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]- piperazine,
are excluded.

Still another embodiment are compounds, wherein R^2 and $R^{2'}$ form together with the N atom to which they are attach a morpholine ring, for example the following compounds:
1-{4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
N-methyl-4-morpholin-4-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-

benzenesulfonamide or
2-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile.

Another embodiment are compounds, wherein R^2 and $R^{2'}$ form together with the N atom to which they are attach a pyrrolidin- or 2,5-dihydropyrrol ring, which are optionally substituted by methyl or CH_2OH, for example the following compounds:
1-{3-fluoro-4-[4-(5-nitro-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
1-(3-fluoro-4-{4-[2-(2-methyl-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
1-(4-{4-[2-(2,5-dihydro-pyrrol-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone,
1-{3-fluoro-4-[4-(5-methanesulfonyl-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
N-methyl-4-pyrrolidin-1-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide or
1-(3-fluoro-4-{4-[2-(3-hydroxymethyl-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone.

Still another embodiment are further those compounds, wherein R^2 and $R^{2'}$ form together with the N atom to which they are attach a piperidine ring, which is optionally substituted by methyl or hydroxy, for example the following compounds:
1-{3-fluoro-4-[4-(5-nitro-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
1-(3-fluoro-4-{4-[2-(2-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
1-(3-fluoro-4-{4-[2-(4-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
1-(3-fluoro-4-{4-[2-(3-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone or
1-(3-fluoro-4-{4-[2-(3-hydroxy-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone.

An embodiment of the invention are further those compounds, wherein R^2 and $R^{2'}$ form together with the N atom to which they are attach a azepane ring, for example the following compounds:
1-{4-[4-(2-azepan-1-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone or

1-{4-[4-(2-azepan-1-yl-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone.

Compounds of the invention are further those, wherein R^2 and $R^{2'}$ form together with the N atom to which they are attach a thiomorpholine ring, for example the following compound:

1-{3-fluoro-4-[4-(5-nitro-2-thiomorpholin-4-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone.

A further embodiment of the invention are further those compounds, wherein R^2 or $R^{2'}$ is CH_2-cycloalkyl or cycloalkyl, for example the following compounds:

1-(4-{4-[2-(cyclopropylmethyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone,

1-{4-[4-(2-cyclohexylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,

1-{4-[4-(2-cyclobutylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone or

1-{4-[4-(2-cyclopentylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone.

An embodiment of the invention are further those compounds, wherein one of R^2 or $R^{2'}$ is $(C_1$-$C_6)$-alkyl, and the other is hydrogen or both of R^2 or $R^{2'}$ are $(C_1$-$C_6)$-alkyl, for example the following compounds:

1-{3-fluoro-4-[4-(2-isopropylamino-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,

1-{3-fluoro-4-[4-(2-isobutylamino-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,

1-{3-fluoro-4-[4-(2-tert.-butylamino-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone or

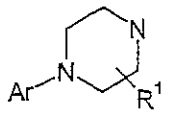
1-{4-[4-(2-diethylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone.

Compounds of the invention are further those, wherein one of R^2 or $R^{2'}$ is $(C_2$-$C_6)$-alkenyl, and the other is $(C_1$-$C_6)$-alkyl, for example the following compound:

1-(4-{4-[2-(allyl-methyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone.

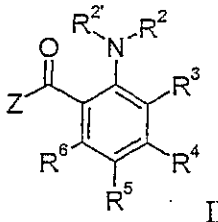
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below. In a third aspect, there is provided processes for preparation of compounds of formula I and their pharmaceutically acceptable salts, which process comprises

a) reacting a compound of formula



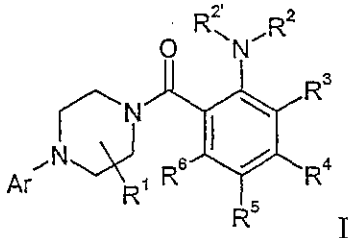
II

with a compound of formula



III

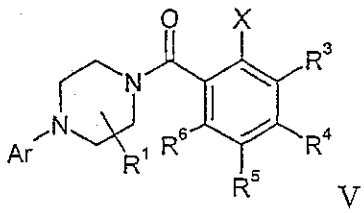
to a compound of formula



I

wherein Z is OH or halogen and the other substituents are as defined above, or

b) reacting a compound of formula

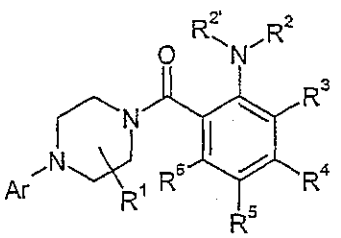


V

with a compound of formula

$R^2R^{2'}NH$

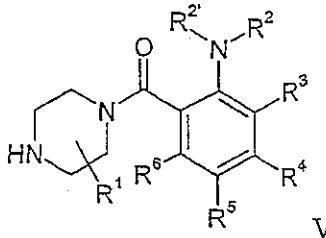
to a compound of formula



I

wherein X is halogen and the other substituents are as defined above,

c) reacting a compound of formula

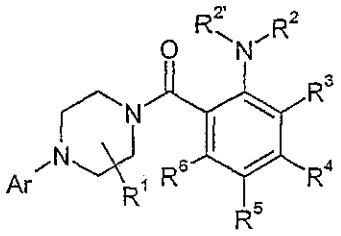


VII

with a compound of formula

ArX

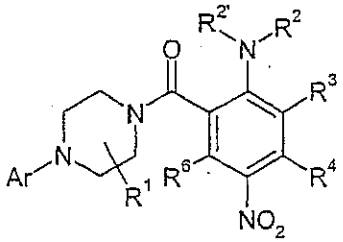
to a compound of formula



I

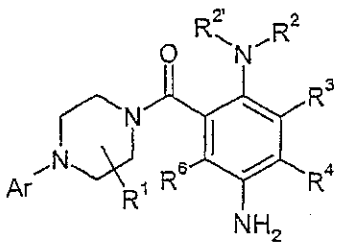
wherein X is halogen and the other substituents are as defined above,

d) reacting a compound of formula



IA

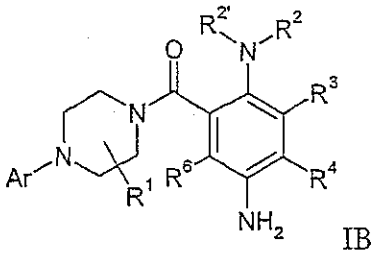
with hydrogen on Pd/C
to a compound of formula



IB

wherein the substituents are as defined above,

e) reacting a compound of formula

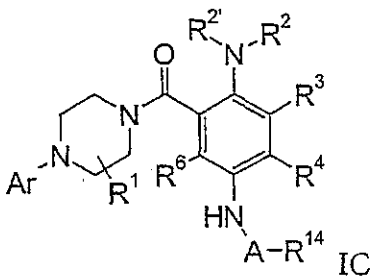


IB

with a compound of formula

$R^{14}AX$

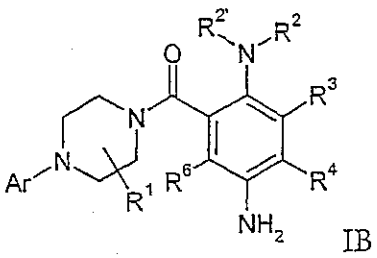
to a compound of formula



IC

wherein X is halogen, A is –C(O)- or $–SO_2$-, R^{14} is (C_1-C_6)-alkyl and the other substituents are as defined above,

f) reacting a compound of formula

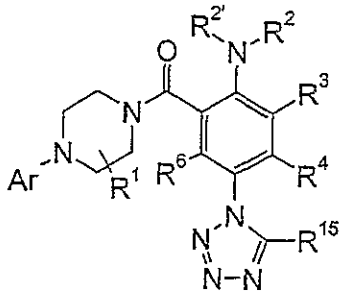


IB

with a compound of formula

$R^{15}C(OEt)_3$

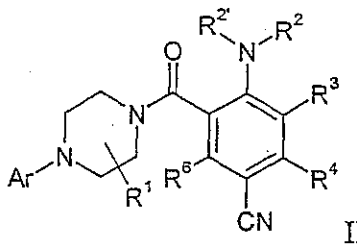
to a compound of formula



ID

wherein R^{15} is hydrogen, halogen, $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl substituted by halogen or $(C_3\text{-}C_6)$-cycloalkyl and the other substituents are as defined above,

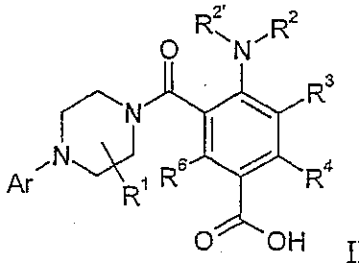
g) reacting a compound of formula



IE

with a base

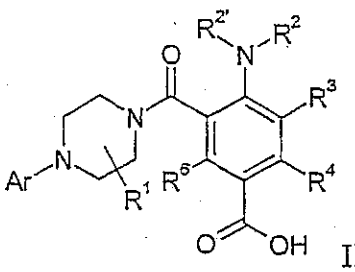
to a compound of formula



IF

wherein the substituents are as defined above,

h) reacting a compound of formula

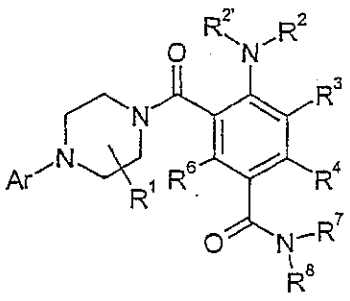


IF

with a compound of formula

R^7R^8NH

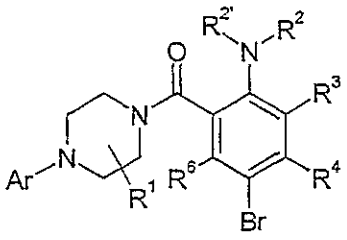
to a compound of formula



IG

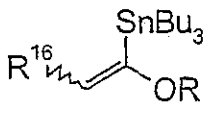
wherein the substituents are as defined above,

i) reacting a compound of formula



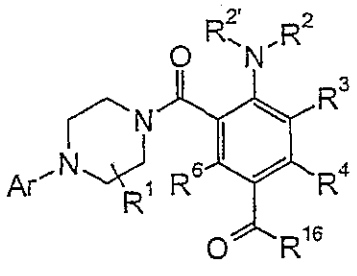
X

with a compound of formula



XI

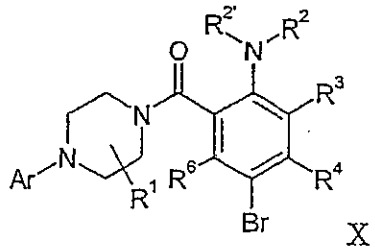
to a compound of formula



IH

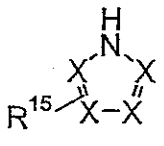
wherein R is (C_1-C_6)-alkyl, R^{16} is (C_1-C_6)-alkyl or (C_3-C_6)-cycloalkyl and the other substituents are as defined above,

j) reacting a compound of formula



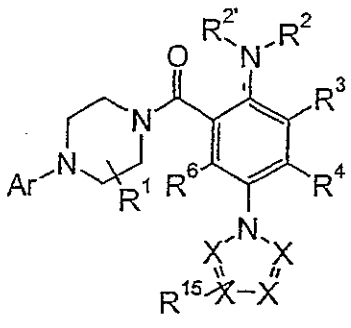
X

with a compound of formula



XII

to a compound of formula



II

wherein X is CH or N and the heteroaryl ring is selected from the group consisting of imidazole, pyrazole or triazole, R^{15} is hydrogen, halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen or (C_3-C_6)-cycloalkyl and the other substituents are as defined above,

and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

In a fourth aspect, there is provided a medicament containing one or more compounds as defined above or containing

1-(4-methoxyphenyl)-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine

1-(4-methoxyphenyl)-4-[2- (4-morpholinyl)-5-nitrobenzoyl]-piperazine,

1-[2- (4-morpholinyl)-5-nitrobenzoyl]-4- [2-nitro-4- (trifluoromethyl) phenyl] - piperazine,

1-(4-methoxyphenyl)-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-[4-(2-hydroxyethyl)-1-piperazinyl]-5-nitrobenzoyl]-4- (4-methoxyphenyl)-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-piperidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl) phenyl]-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-l-piperidinyl)-5-nitrobenzoyl]- piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-l-piperazinyl)-5-nitrobenzoyl]- piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-morpholinyl)-5-nitrobenzoyl]- piperazine,
1-[5-[[methyl(phenylmethyl)amino]sulfonyl-2-(4-morpholinyl)benzoyl]-4-(4-nitrophenyl)-piperazine,
1-(4-acetyl-2-fluorophenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
l-{4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-l-yl]-3-fluoro-phenyl}-ethanone and
[4-(4-methoxy-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone.
and pharmaceutically acceptable excipients.

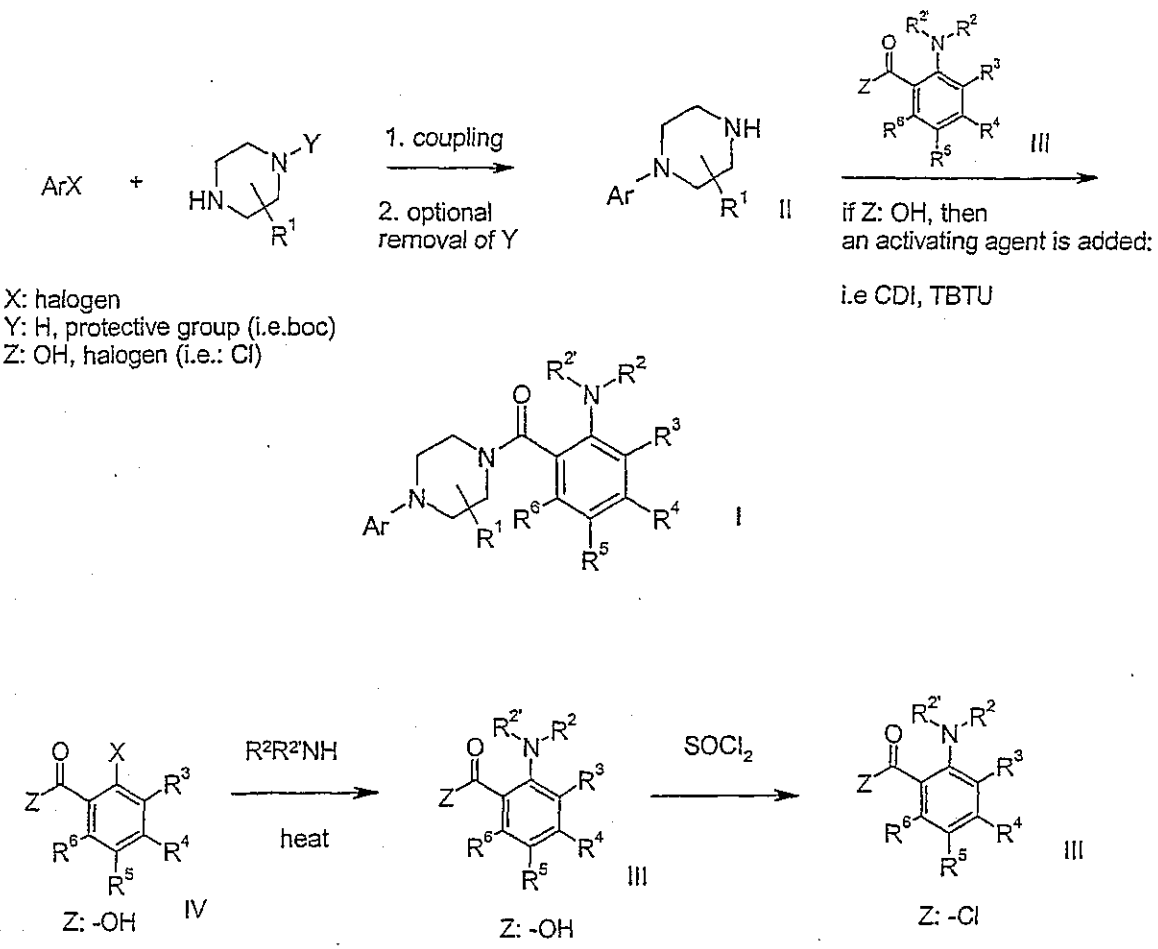
In a fifth aspect, there is provided the use of a compound as defined in the first aspect and of
1-(4-methoxyphenyl)-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine
1-(4-methoxyphenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[2-(4-morpholinyl)-5-nitrobenzoyl]-4-[2-bitro-4-(trifluoromethyl)phenyl]-piperazine,
1-(4-methoxyphenyl)-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-[4-(2-hydroxyethyl)-1-piperazinyl]-5-bitrobenzoyl]-4-(4-methoxyphenyl)-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-piperidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperidinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[5-[[methyl(phenylmethyl)amino]sulfonyl]-2-(4-morpholinyl)benzoyl]-4-(4-nitrophenyl)-piperazine,
1-(4-acetyl-2-fluorophenyl)-4-[2-(4-morphonlinyl)-5-nitrobenzoyl]-piperazine,
1-{4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and
[4-(4-methoxy-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

for manufacture of medicaments for the treatment of psychoses, pain, neurodegenerative disfunction in memory and learning, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

The compounds of formula I may be prepared in accordance with process variants a) to j) and with the following schemes 1 to 6.

The starting material is commercially available or may be prepared in accordance with known methods.

Scheme I

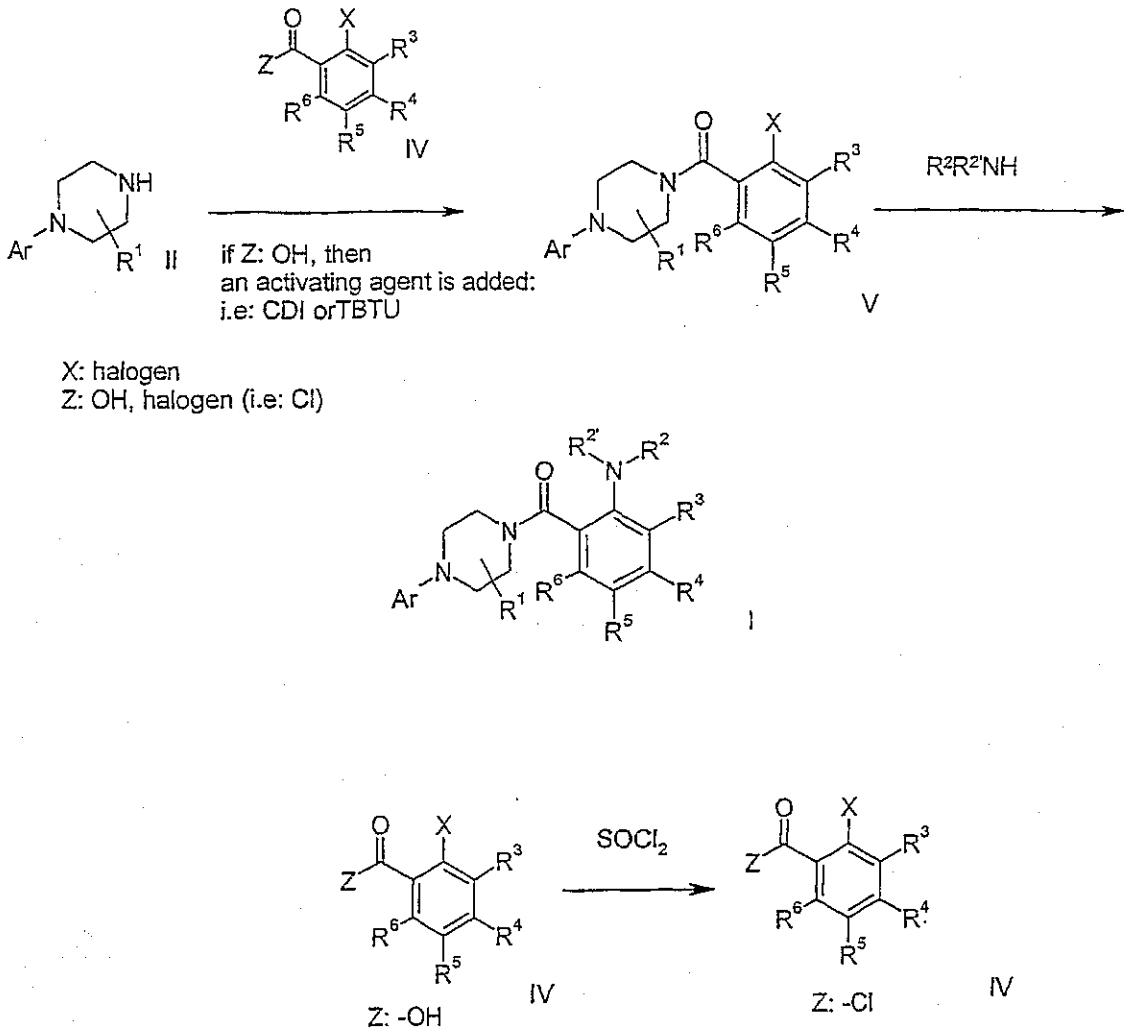


Compounds of general formula I can be prepared by reacting of a piperazine of formula II with a compound of formula III (Z: Cl) or III (Z: OH) in the presence of an activating agent like CDI (N,N-carbonyldiimidazole) or TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate).

A compound of formula III (Z: Cl) can be prepared from a compound of formula III (Z: OH) in the presence of an activating agent like thionylchloride. In turn the acid of formula III (Z: OH) can be prepared by heating a mixture of an acid of formula IV and an amino derivative of formula $R^2R^{2'}NH$.

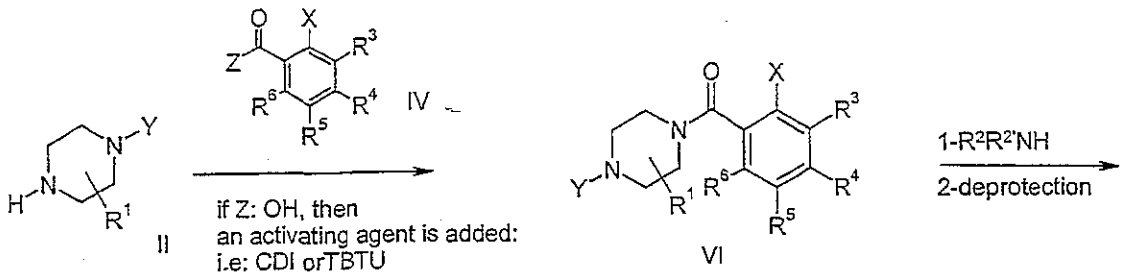
The piperazine of formula II can be prepared by heating of a corresponding piperazine with ArX or by reacting of a N-protected piperazine with ArX in the presence of palladium catalyst followed by cleavage of the protective group. The protective group is typically tert-butoxycarbonyl (Boc).

Scheme 2

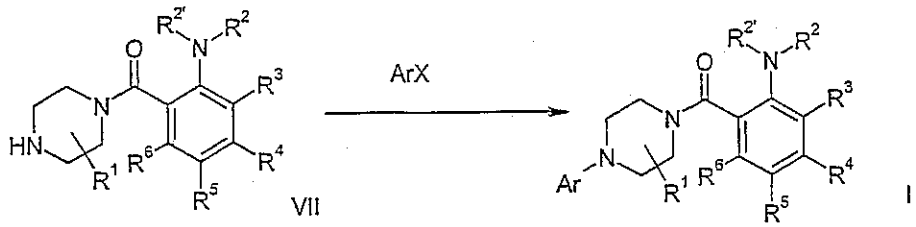


Aternatively, compounds of general formula I can be prepared by reaction of a derivative of formula V with a corresponding amine of formula $R^2R^{2'}NH$. Compounds of formula V can be prepared by reacting of derivatives of formula II with compounds of formula IV (Z: Cl) or with compounds of formula IV(Z: OH) in the presence of an activating agent like CDI (N-carbonyldiimidazole) or TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate).

Scheme 3

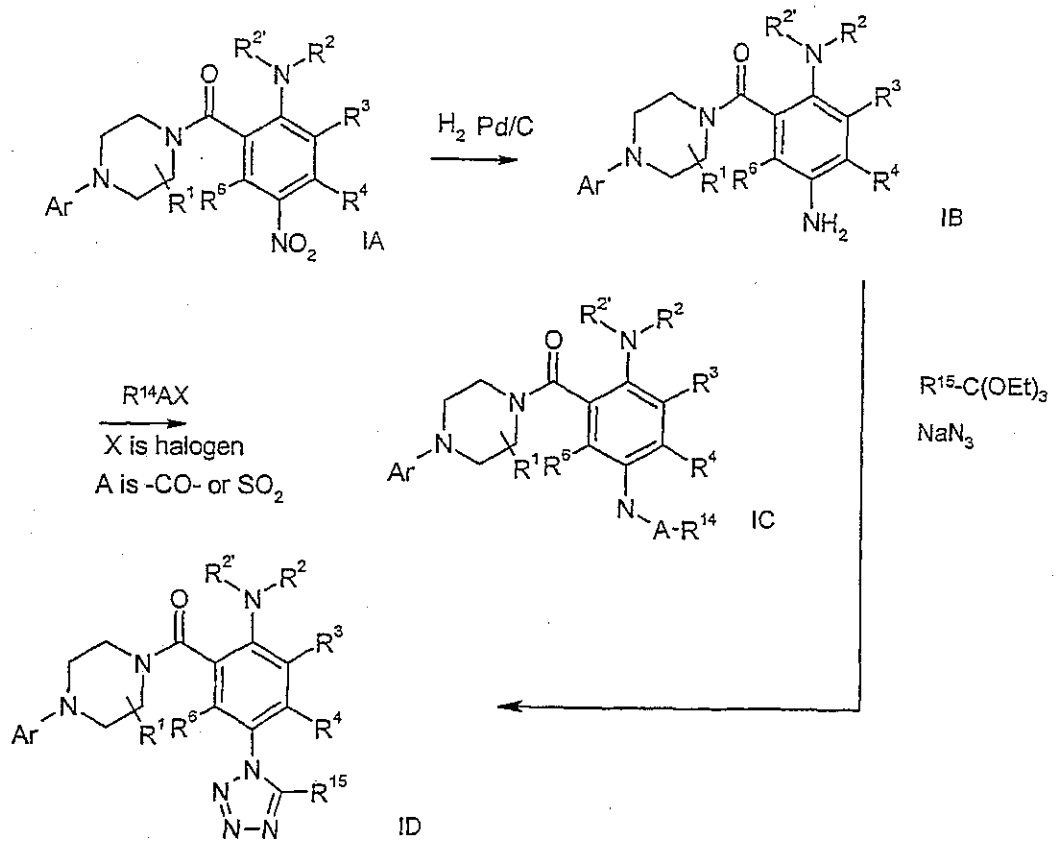


X: halogen
Y: H, protective group (i.e.boc)
Z: OH, halogen (i.e: Cl)



Aternatively, compounds of general formula I can be prepared by reaction of a compound of formula VII with ArX. A compound of formula VII can be prepared by reacting of a
N-protected derivative of formula VI with an amine of formula $R^2R^{2'}NH$, followed by cleavage of the protective group. The protective group is typically tert-butoxycarbonyl (Boc). In turn, a compound of formula VI can be prepared by reacting of a piperazine of formula II with a compound of formula IV (Z: Cl) or with a compound of formula IV (Z: OH) in the presence of an activating agent like CDI (N-carbonyldiimidazole) or TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate).

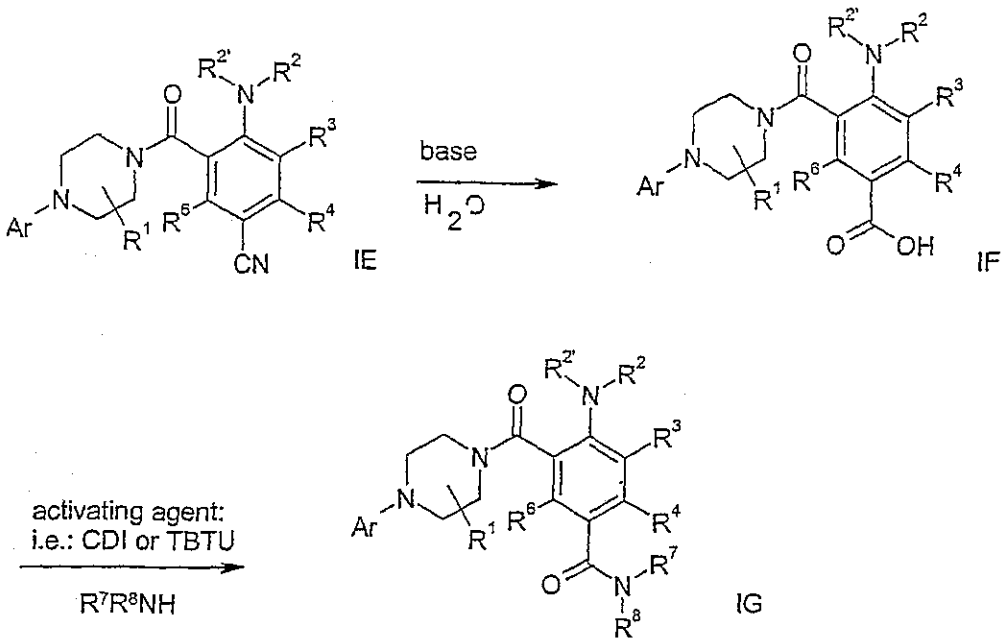
Scheme 4



Compounds of formula IC (A is –CO-) and IC (A is -SO_2-) can be prepared respectively by carbonylation or sulfonylation of a corresponding amino derivative IB in the presence of a compound of formula $R^{14}AX$. In turn, a compound of formula IB can be prepared by hydrogenation of a compound of formula IA.

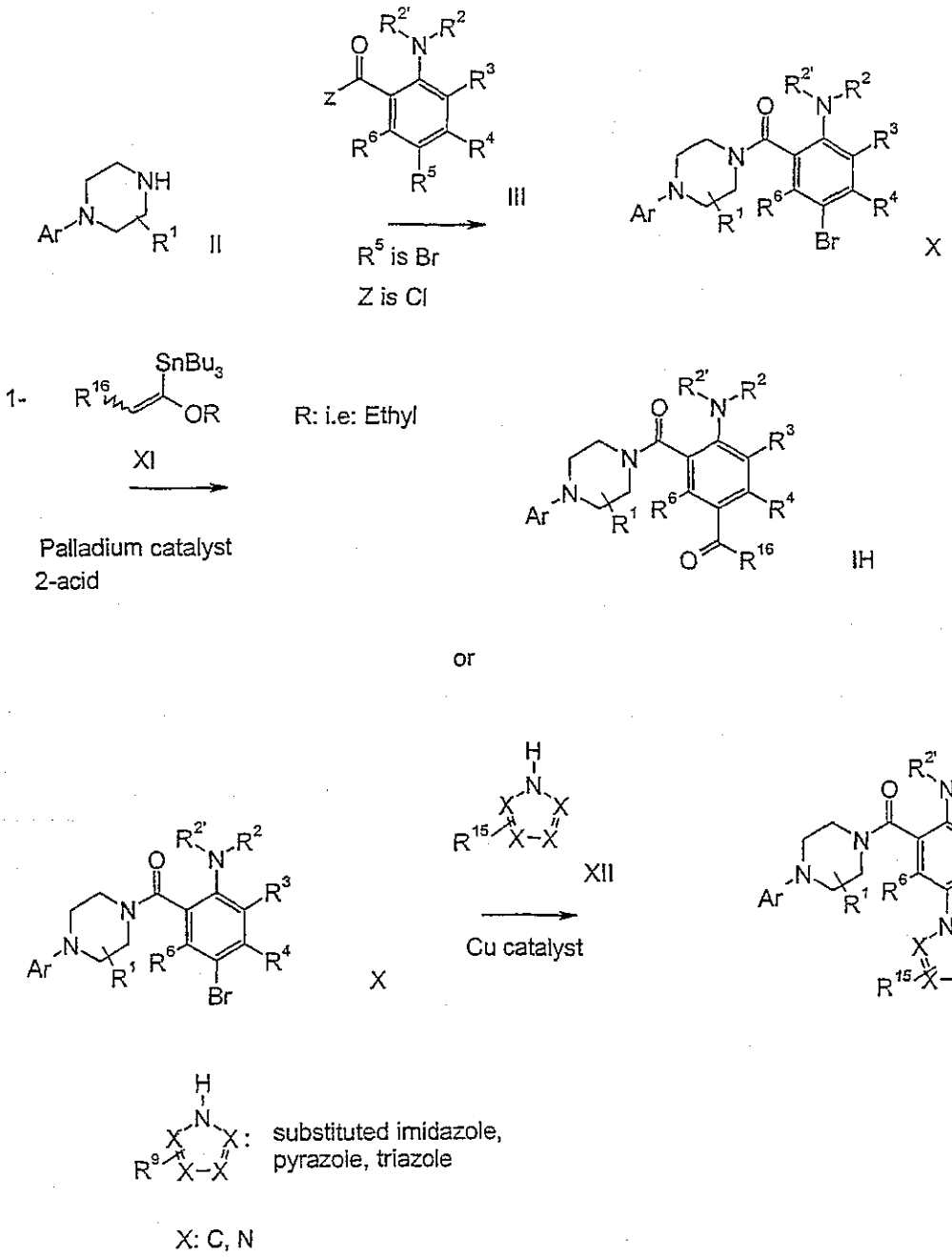
Heterocyclic compounds of formula ID can be prepared by reaction of a compound of formula IB with a substituted triethyl orthoformate derivative of formula R^{15}-$C(OEt)_3$ in the presence of sodium azide.

Scheme 5



Compounds of formula IG can be prepared by reaction of an acid derivative of formula IF with an amine of formula R^7R^8NH in the presence of an activating agent like CDI (N-carbonyldiimidazole) or TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate). A compound of formula IF can be prepared by hydrolysis of a compound of formula IE in the presence of base like sodium hydroxide.

Scheme 6



A compound of formula IH can be prepared by reacting under Stille conditions with an aryl-bromo derivative of formula X and with a corresponding vinyl stannane of formula XI in the presence of a palladium catalyst like dichlorobis(triphenylphosphine) palladium(II). A compound of formula I I can be prepared by reacting of a compound of formula X with a compound of formula XII in the presence of a Cu catalyst like CuI. A compound of formula X can be prepared by coupling an acid chloride III with a piperazine derivative of formula II.

The acid addition salts of the basic compounds of formula I may be converted to the corresponding free bases by treatment with at least a stoichiometric equivalent of a suitable base such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention are good inhibitors of the glycine transporter I (GlyT-1).

The compounds were investigated in accordance with the test given hereinafter.

Solutions and materials

DMEM complete medium: Nutrient mixture F-12 (Gibco Life-technologies), fetal bovine serum (FBS) 5 %, (Gibco life technologies), Penicillin/Streptomycin1 % (Gibco life technologies), Hygromycin 0.6 mg/ml (Gibco life technologies), Glutamine 1 mM Gibco life technologies)

Uptake buffer (UB): 150 mM NaCl, 10 mM Hepes-Tris, pH 7.4, 1 mM $CaCl_2$, 2.5 mM KCl, 2.5 mM $MgSO_4$, 10 mM (+) D-glucose.
Flp-in™-CHO (Invitrogen Cat n° R758-07)cells stably transfected with mGlyT1b cDNA.

Glycine uptake inhibition assay (mGlyT-1b)

On day 1 mammalian cells, (Flp-in™-CHO), transfected with mGlyT-1b cDNA , were plated at the density of 40,000 cells/well in complete F-12 medium, without hygromycin in 96-well culture plates. On day 2, the medium was aspirated and the cells were washed twice with uptake buffer (UB). The cells were then incubated for 20 min at 22°C with either (i) no potential competitor, (ii) 10 mM non-radioactive glycine , (iii) a concentration of a potential inhibitor. A range of concentrations of the potential inhibitor was used to generate data for calculating the concentration of inhibitor resulting in 50 % of the effect (e.g. IC_{50}, the concentration of the competitor inhibiting glycine uptake of 50 %). A solution was then immediately added containing [^{3}H]-glycine 60 nM (11-16 Ci/mmol) and 25 µM non-radioactive glycine. The plates were incubated with gentle shaking and the reaction was stopped by aspiration of the mixture and washing (three times) with ice-cold UB. The cells were lysed with scintillation liquid, shaken 3 hours and the radioactivity in the cells was counted using a scintillation counter.

The compounds in the above table show an IC_{50} (µM) at mGlyT-1 < 0.02 (µM)

Example No.	IC_{50} (μM)	Example No.	IC_{50} (μM)
1	0.015	131	0.008
4	0.013	133	0.009
6	0.01	175	0.0097
11	0.015	176	0.02
16	0.012	186	0.015
18	0.0025	216	0.012
19	0.003	217	0.016
20	0.0021	219	0.017
21	0.0023	220	0.019
27	0.0012	233	0.016
28	0.0033	234	0.01
35	0.006	235	0.0065
36	0.014	236	0.004
37	0.007	245	0.018
38	0.008	246	0.011
41	0.014	247	0.014
42	0.0035	248	0.01
43	0.009	250	0.015
45	0.019	251	0.019
76	0.019	263	0.01
83	0.019	264	0.012

129	0.005		

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose,corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are however usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of schizophrenia, cognitive impairment and Alzheimer's disease.

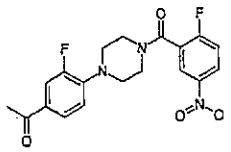
The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

The following examples illustrate the present invention without limiting it. All temperatures are given in degree Celsius.

The following abbreviations were used in the examples:
RT: room temperature;
n-Boc-piperazine: tert-Butyl 1-piperazinecarboxylate,
oxone®: (potassium peroxymonosulfate) $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$,
EtOAc: ethyl acetate;
THF: tetrahydrofuran;
TBTU: 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate;
DIPEA: diisopropylethylamine,
DMF: N,N-dimetyhylformamide

Example A

1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone



A solution of 2-Fluoro-5-nitro-benzoyl chloride (CAS: 7304-32-7; Feng, Y.; Burgess, K.; Chem.Europ.J.; EN; 5; 11; 1999; 3261 – 3272) (0.054 g, 0.261 mmol) in dioxane (1ml) was treated with triethylamine (0.073 ml, 0.522 mmol) and then with a solution of 1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (CAS: 189763-57-3; WO9714690) (58 mg, 0.261 mmol) in dioxane (1 ml). The mixture was stirred at room temperature for 30 minutes. The solvent was removed in vacuo. The crude oil was taken in water. The aqueous layer was extracted 3 times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude gum was purified on silicagel (eluent: heptane/ethylacetate 0%-20% (10 minutes) to provide the title compound (69 mg, 68%) as a light yellow solid, MS (m/e): 390.2 (MH^+, 100%)

Example 1

1-{4-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone (known compound, RN 310415)

A solution of 1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone (0.065 g, 0.167 mmol) in morpholine (0.29 ml) was heated for 30 minutes at 100 ^{0}C then cooled to room temperature and diluted with water. The resulting solid was filtered and dried to provide the title compound (71 mg, 93%) as a yellow solid, MS (m/e): 457.3 ($M+H^+$, 100%)

According to the procedure described for the synthesis of Example 1 further derivatives have been synthesised and comprise Examples 179,180, 189, 190, 191, 196, 197, 198 in Table 1.

Example 2

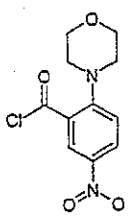
1-{4-[4-(2-Ethylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone

A mixture of 27.4 mg (0.07 mmol) 1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone, 91 ul (0.091 mmol) of a 1N solution of ethylamine in DMF and 30 ul (0.175 mmol) DIPEA in 2 ml THF was heated to 80 °C for 16 h. After evaporation of the volatiles the residue was taken up in 2 ml methanol / formic acid 6/1 and subjected to preparative HPLC purification on reversed phase eluting with an acetonitrile / water gradient to yield after evaporation of the product fractions 20.2 mg (70%) of the title compound. MS (m/e): 415.2 (MH^+, 100%)

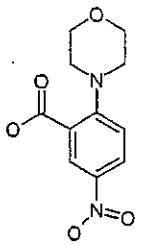
According to the procedure described for the synthesis of Example 2 further derivatives have been synthesised from 1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and amines and comprise Examples 2-45 in Table 1.

Example B

2-Morpholin-4-yl-5-nitro-benzoyl chloride

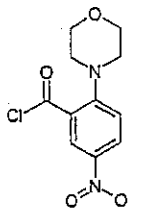


step 1: 2-Morpholin-4-yl-5-nitro-benzoic acid



To a solution of 2-Fluoro-5-nitrobenzoic acid (4.86 g, 26.2 mmol) in dioxane (50 ml) was added morpholine (11.5 ml). The mixture was stirred at room temperature for 2 hours. The solvent was removed in vacuo. The residue was dissolved in water and the mixture was acidified with HCl 2N. The solid was filtered, washed with water and dried to provide the title compound (6.2 g, 93%) as a yellow solid, MS (m/e): 251.2 (M-H, 100%).

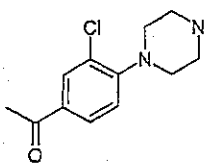
Step 2: 2-Morpholin-4-yl-5-nitro-benzoyl chloride



To a suspension of 2-Morpholin-4-yl-5-nitro-benzoic acid (4.0 g, 16 mmol) in toluene were added 2 drops of DMF and thionylchloride (5.7 ml, 79.3 mmol). The mixture was heated to 80°C for 50 minutes. The solvent was removed in vacuo, and the resulting solid was stirred in ether, filtered and dried to provide the title compound (4.0 g, 93%) as a yellow solid.

Example C

1-(3-Chloro-4-piperazin-1-yl-phenyl)-ethanone



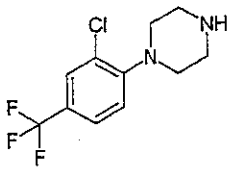
A mixture of 5.0 g (29 mmol) 3-Chloro-4-fluoroacetophenon and 12.5 g (145 mmol) piperazine in 10 ml N,N-dimethyl-acetamide was heated to 120 °C for 23 h. All volatiles were removed under vacuum and the residue was purified by flash column

chromatography on silica eluting with a mixture of DCM / methanol / 5% NH_3 aq. to yield 3.47 g (50 %) of the title compound as yellow amorphous solid.

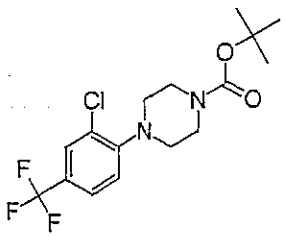
1-H-NMR (300 MHz, $CDCl_3$) δ= 7.96 (d, J_1=8.4 Hz, J_2=2.1 Hz, H-2, 1H), 7.82 (dd, J_1=8.4 Hz, J_2=2.1 Hz, H-6, 1H), 7.04 (d, J_1=8.4 Hz, H-5, 1H), 3.03 (m, 4H, piperazine), 2.88 (m, 4H, piperazine), 2.55 (s, 3H, COMe).
MS (m/e): 239.2 (MH^+, 100%)

Example D

1-(2-Chloro-4-trifluoromethyl-phenyl)-piperazine

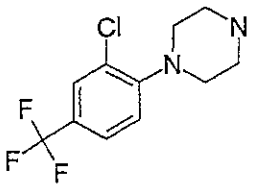


step 1: 4-(2-Chloro-4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester



A mixture of 0.5 g (1.6 mmol) of 3-chloro-4-iodobenzotrifluoride 0.7 g (3.8 mmol), N-Boc-piperazine, 41 mg (0.04 mmol) Tris(dibenzylideneacetone)dipalladium chloroform complex, 0.44 g (4.43 mmol) sodium-*t*-butoxide and 48 mg (0.16 mmol) tri-o-tolylphosphine in 6 ml dioxane was heated overnight at 100 °C. The solution was allowed to cool to room temperature, taken up in ether (30ml) and washed with brine (25ml). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude oil was chromatographed over on silica gel: Eluent: Heptane-AcOEt 0-10% over 15min to provide the title compound (0.06g, 10%) as a brown oil, MS (m/e): 365.1 (MH^+, 100%).

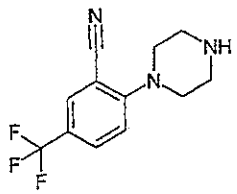
Step 2: 1-(2-Chloro-4-trifluoromethyl-phenyl)-piperazine



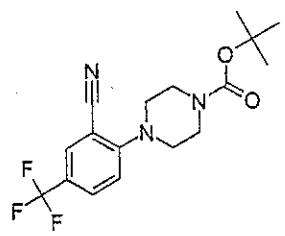
A solution of 4-(2-Chloro-4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (60 mg, 0.164 mmol) in $MeCl_2$ (0.8 ml) was treated with trifluoroacetic acid (63µl), heated up to 40°C and stirred for 4h. The solvent was removed in vacuo. The residue was dissolved in water and basified with NaOH 1N. The aqueous layer was extracted twice with $MeCl_2$. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in vacuo to provide the title compound (20 mg, 46%) as a yellow oil, MS (m/e): 265.0 (MH^+, 100%).

Example E

2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile

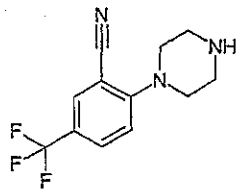


step 1: 4-(2-Cyano-4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester



Title compound was prepared according to the procedure described in example G from N-Boc-piperazine and 2-Chloro-5-trifluoromethylbenzonitrile (CAS: 328-87-0)(15% yield, yellow oil, MS (m/e): 373.1 ($M+NH4^+$, 100%).

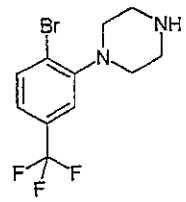
Step 2: 2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile



Title compound was prepared according to procedure described in example D/ step2, (82% yield, yellow oil, MS (m/e): 256.0 ($M+H^+$, 100%).

Example F

1-(2-Bromo-5-trifluoromethyl-phenyl)-piperazine

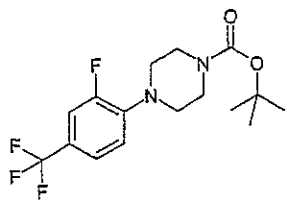


A mixture of 2 g (8 mmol)1-Bromo-2-fluoro-4-trifluoromethyl-benzene and 2.13 g (25 mmol) piperazine in 2 ml N,N-dimethylacetamide was heated to 100 °C for 2 h and subsequently all volatiles were removed under vacuum. The residue was purified by flash column chromatography on silica eluting with DCM / methanol / 1% NH3 aq. to yield 0.765 g (37 %) of the title compound as colourless oil.

1-H-NMR (300 MHz, $CDCl_3$) δ= 7.81 (d, J = 8 Hz, 1H, H-4), 7.30 (m, 2H, H-3 / H-6), 3.2-3.5 (s, br, 1H, NH), 2.93 (m, 4H, piperazine) 2.86 (m, 4H, piperazine).
MS (m/e): 309.1 (MH^+, 100%)

Example G

4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester



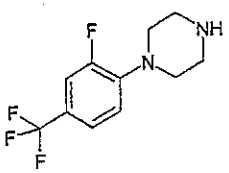
A mixture of 5 g (20 mmol) 1-Bromo-2-fluoro-4-trifluoromethyl-benzene , 4.6 g (24.7 mmol) n-Boc-piperazine, 106 mg (0.1 mmol) Tris(dibenzylideneacetone)dipalladium chloroform complex 2.77 g (28.8 mmol) sodium-*t*-butoxide and 144 mg (0.4 mmol) 2-

(Dicyclohexylphosphino)biphenyl in 50 ml toluene was heated for 16 h at 80 °C. After cooling to room temperature the mixture was treated with 15 g Isolute HM-N and all volatiles were removed under vacuum. The residue was purified on silica eluting with a gradient of heptane / EtOAc to yield after evaporation 4.54 g (63%) of the title compound as white amorphous solid.

1-H-NMR (300 MHz, $CDCl_3$) δ= 7.50 (d, J = 12 Hz, 1H, H-3), 7.48 (d, J = 8 Hz, 1H, H-5), 7.2 (dd, J_1 = 8 Hz, J_2 = 8 Hz, 1H, H-6), 3.49 (m, 4H, piperazine), 3.08 (m, 4H, piperazine).
MS (m/e): 349.2 (MH^+, 100%)

Example H

1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine

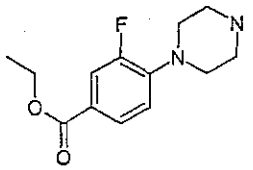


A mixture of 3.11 g (9 mmol) 4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester in 20 ml dioxane was treated with 8.93 ml 4N HCl in dioxane for 2 h at 80 °C. The mixture was concentrated and treated with 20 ml water, 20 ml 2M Na_2CO_3 and extracted with 50 ml EtOAc. The organic phase was washed with 30 ml saturated NaCl. All aqueous phases were combined and extracted with 50 ml EtOAc. The combined organic phases were dried with MgSO4 and evaporated to yield 2.1 g (95 %) of the title compound as brownish crystals.

1-H-NMR (300 MHz, $CDCl_3$) δ= 7.50 (d, J = 13.3 Hz, 1H, H-3), 7.45 (d, J = 8.8 Hz, 1H, H-5), 7.16 (dd, J_1 = 8.8 Hz, J_2 = 8.8 Hz, 1H, H-6), 3.5-3.2 (s, br, 1H, NH), 3.04 (m, 4H, piperazine), 2.87 (m, 4H, piperazine).
MS (m/e): 249.2 (MH^+, 100%)

Example I

3-Fluoro-4-piperazin-1-yl-benzoic acid ethyl ester



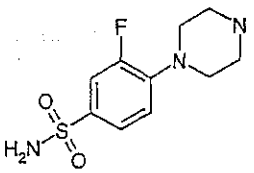
A mixture of 5 g (27 mmol)3,4-Difluoro-benzoic acid ethyl ester and 11.56 g (134 mmol) piperazine in 15 ml N,N-dimethylacetamide was heated to 120 °C for 1.5 h and subsequently all volatiles were removed under vacuum. The residue was purified by flash column chromatography on silica eluting with DCM / methanol to yield 6.19 g (91 %) of the title compound as white amorphous solid.

1-H-NMR (300 MHz, DMSO-d6) δ= 7.69(dd, J_1= 8.4 Hz, J_2=1.9 Hz, 1H, H-6), 7.57(dd, J_1=12.1Hz, J_2=2.0Hz, 1H, H-2), 7.07(dd, J_1=8.7 Hz, J_2=8.7 Hz, 1H, H-5), 4.26(q, J_1=7.1 Hz, 2H, O-CH_2), 3.06(m, 4H, piperazine), 2.83(m, 4H, piperazine), 1.30(t, J_1=7.1Hz, 3H, CH_3).

MS (m/e): 253.2 (MH^+, 100%)

Example J

3-Fluoro-4-piperazin-1-yl-benzenesulfonamide



A mixture of 0.5 g (3 mmol) 3,4-Difluoro-benzenesulfonamide and 1.15 g (13 mmol) piperazine in 2.3 ml water was heated to 110 °C for 3 h and subsequently the precipitate was filtered off and washed with water and toluene. The residue was dried under high vacuum to yield 0.578 g (86 %) of the title compound as white crystals.

1-H-NMR (300 MHz, DMSO-d6) δ= 7.53 (dd, J_1=8.6 Hz, J_2=2Hz, 1H, H-6), 7.48(dd, J_1=15 Hz, J_2=2 Hz, 1H, H-2), 7.2-7.4(s, br, 2H, NH_2), 7.13(dd, J_1=8.6 Hz, J_2=8.6 Hz 1H, H-5), 3.2-3.5(s, br, 1H, NH), 3.03(m, 4H, piperazine), 2.83(m, 4H, piperazine).

MS (m/e): 260.0 (MH^+, 100%)

Example 46

[4-(2-Chloro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

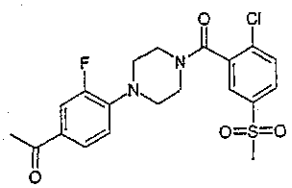
A mixture of 18.9 mg (0.07 mmol) 2-Morpholin-4-yl-5-nitro-benzoyl chloride, 16.5 mg (0.084 mmol) 1-(2-Chloro-phenyl)-piperazine and 34 ul (0.245 mmol) NEt_3 in 2 ml DCM was stirred at room temperature for 16 h. After evaporation of the volatiles the residue was taken up in 2 ml CH_3CN/MeOH/HCOOH 2/2/1 and subjected to preparative HPLC purification on reversed phase eluting with an acetonitrile / water gradient to yield after evaporation of the product fractions 23.2 mg (77%) of the title compound.

MS (m/e): 431.2 (MH^+, 100%)

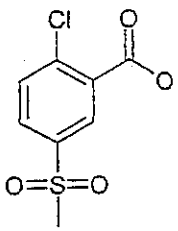
According to the procedure described for the synthesis of Example 46 further derivatives have been synthesised from 2-morpholin-4-yl-5-nitro-benzoyl chloride and piperazine derivatives and comprise Examples 46-74, 177, 184, 185, 186,187,188, 192, 200, 201 in Table 1.

Example K

1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone



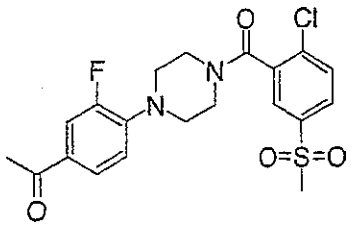
step 1: 2-Chloro-5-methanesulfonyl-benzoic acid



A solution of 2-Chloro-5-(methylthio)benzoic acid (CAS: 51546-12-4; 2.5 g, 11.8 mmol) was dissolved in methanol (50 ml) and cooled to 0°C. Oxone (21.9 g, 35.5 mmol) was added portionwise within 5 minutes. The mixture was stirred at 0°C for 30 minutes and then at room temperature for 22 hours. The mixture was filtered. The filtrate was poured onto water (200 ml). The aqueous layer was extracted with dichloromethane (5x50 ml). The combined extracts were dried over Na_2SO_4, filtered and the solvent was removed in

vacuo. The solid was stirred in ether (30 ml), filtered and dried to provide the title compound (1.96 g, 70%) as a beige solid, MS (m/e): 232.9 ($M-H^+$, 100%).

Step 2: 1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone



To a solution of 2-Chloro-5-methanesulfonyl-benzoic acid (200 mg, 0.852 mmol) in DMF (3 ml) was added dropwise 1,1'-Carbonyldiimidazole (142 mg, 0.852 mmol). When the CO_2 evolution ceased, the mixture was heated to 50 °C for 15 minutes. The mixture was cooled to room temperature. 1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (189 mg, 0.852 mmol) was added portionwise. The mixture was stirred at room temperature for 1 hour. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate. The solution was washed twice with water, dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude oil was purified on silica gel (Heptane/AcOEt 0%-50% (15 minutes) to provide the title compound (185 mg, 49 %) as a white solid, MS (m/e): 439.1 ($M+H^+$, 100%).

Example 75

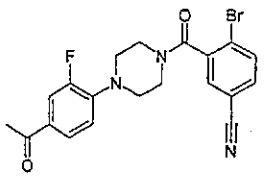
1-(3-Fluoro-4-{4-[5-methanesulfonyl-2-(2-methyl-pyrrolidin-1-yl)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone

A mixture of 30.7 mg (0.7 mmol) 1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone, 30 ul (0.175 mmol) DIPEA and 91 ul (0.91 mmol) of a 1M solution of 2-Methyl-pyrrolidine in DMF was heated to 100 °C for 24 h. After removal of THF 2 ml dioxane, 180 ul of a 1M solution of 2-Methyl-pyrrolidine in DMF and 30 ul (0.175 mmol) DIPEA were added and the mixture was heated to 120 °C for 16 h. After evaporation of all volatiles the residue was taken up in 1 ml MeOH / formic acid 6 / 1 and subjected to reversed phase HPLC purification eluting with an acetonitrile / water gradient to yield after evaporation of the product fractions 4.7 mg (14 %) of the title compound. MS (m/e): 488.2 (MH^+, 100%)

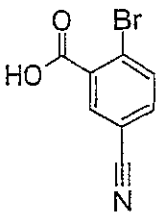
According to the procedure described for the synthesis of Example 75 further derivatives have been synthesised from 1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and amines and comprise Examples 75-89 in Table 1.

Example L

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile

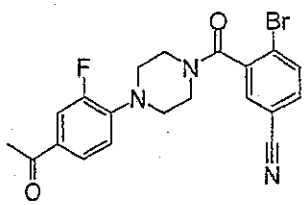


step 1: 2-bromo-5-cyano-benzoic acid



To a suspension of copper (II) bromide (1.6 g, 7.1 mmol) in acetonitrile (30 ml) was added dropwise tert-butylnitrite (1.15 ml, 8.63 mmol) at 0 °C within 2 minutes. 2-Amino-5-cyano-benzoic acid (CAS: 99767-45-0; WO9518097) (1.0 g, 6.17 mmol) was added portionwise within 10 minutes at 0 °C. The mixture was stirred at 0 °C for 2 hours and then at room temperature overnight. Half of the solvent was removed in vacuo. The residue was taken in HCl 1N (15 ml) and ethyl acetate (30 ml). The organic layer was extracted with NaOH 1N (3x10 ml). The aqueous layer was acidified with HCl 2N. The resulting solid was filtered, washed with water and dried (high vacum, 50 °C) to provide the title compound (0.92 g, 66%) as a yellow solid.

Step 2: 3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo benzonitrile



Title compound was prepared according to procedure described in example K/ step2 from 1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone and 2-bromo-5-cyano-benzoic acid , (49% yield, white solid, MS (m/e): 430 (M^+, 100%).

Example 90

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-azepan-1-yl-benzonitrile

A mixture of 30.1 mg (0.7 mmol) 3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile, 30 ul (0.175 mmol) DIPEA and 91 ul (0.91 mmol) of a 1M solution of azepane in DMF was heated to 100 °C for 24 h. After removal of THF 2 ml dioxane, 180 ul of a 1M solution of azepane in DMF and 30 ul (0.175 mmol) DIPEA were added and the mixture was heated to 120 °C for 16 h. After evaporation of all volatiles the residue was taken up in 1 ml MeOH / formic acid 6 / 1 and subjected to reversed phase HPLC purification eluting with an acetonitrile / water gradient to yield after evaporation of the product fractions 9.3 mg (30 %) of the title compound. MS (m/e): 449.2 (MH^+, 100%)

According to the procedure described for the synthesis of Example 90 further derivatives have been synthesised from 3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and amines and comprise Examples 90-103 in Table 1.

Example 104

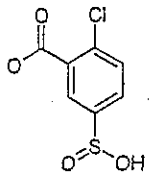
3-Chloro-4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzonitrile

A mixture of 40.6 mg (0.15 mmol) 2-Morpholin-4-yl-5-nitro-benzoyl chloride, 39.9 mg (0.18 mmol) 3-Chloro-4-piperazin-1-yl-benzonitrile (WO9625414) and 62.5 ul (0.45 mmol) NEt_3 in 1 ml DCM was stirred at room temperature for 16 h. After evaporation of the volatiles the residue was taken up in 1 ml CH_3CN/DMF/HCOOH 3/5/2 and subjected to preparative HPLC purification on reversed phase eluting with an acetonitrile / water gradient to yield after evaporation of the product fractions 4.9 mg (8 %) of the title compound.
MS (m/e): 456.2 (MH^+, 100%)

According to the procedure described for the synthesis of Example 104 further derivatives have been synthesised from 2-Morpholin-4-yl-5-nitro-benzoyl chloride and piperazine derivatives and comprise Examples 104-122 in Table 1.

Example M

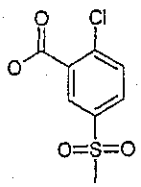
2-Chloro-5-sulfino-benzoic acid



A solution of 33.59 g (267 mmol) sodium sulfite in 100 ml water at 0 °C is treated with 21.2 g (89 mmol) 2-Chloro-5-fluorosulfonyl-benzoic acid and 26.6 ml of a 10M aqueous NaOH solution (267 mmol). The mixture was allowed to stirr for 3 h at room temperature, acidified with HCl conc. (pH = 4) and water was removed under vacuum. Methanol was added, the precipitate filtered off and the filtrate concentrated. Methanol and diethylether were added and the precipitate was filtered off washed with ether and dried to yield 15 g (76.5%) of the title compound as white gum. MS (m/e): 219.1 (MH^-, 100%)

Example N

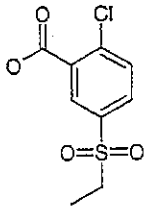
2-Chloro-5-methanesulfonyl-benzoic acid



A mixture of 1 g (4 mmol) 2-Chloro-5-sulfino-benzoic acid in 20 ml Methanol and 20 ml water was treated with 10N NaOH to pH = 9 before adding 1.7 g (12 mmol) Methyliodide. The mixture was heated for 48 h to 80 °C with occasional addition of NaOH to maintain pH = 9. After removal of all volatiles HCl conc. was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried with $MgSO_4$ and evaporated to dryness. The residue was taken up in methanol and subjected to reversed phase HPLC purification eluting with an acetonitrile / water gradient to yield after evaporation of the product fractions 323 mg (34 %) of the title compound. MS (m/e): 233.0 (MH^-, 100%).

Example O

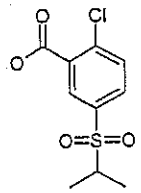
2-Chloro-5-ethanesulfonyl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 2-Chloro-5-methanesulfonyl-benzoic acid from 2-Chloro-5-sulfino-benzoic acid and ethyl iodide in 20 ml ethanol / 20 ml water and obtained in 27% yield. MS (m/e): 247.1 (MH^-, 100%).

Example P

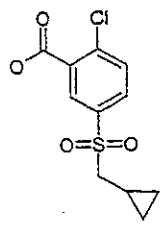
2-Chloro-5-(propane-2-sulfonyl)-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 2-Chloro-5-methanesulfonyl-benzoic acid from 2-Chloro-5-sulfino-benzoic acid and 2-iodopropane in 20 ml isopropanol/ 20 ml water and obtained in 42% yield. MS (m/e): 261.1 (MH^-, 100%).

Example Q

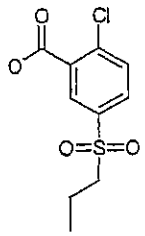
2-Chloro-5-cyclopropylmethanesulfonyl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 2-Chloro-5-methanesulfonyl-benzoic acid from 2-Chloro-5-sulfino-benzoic acid and Bromomethyl-cyclopropane (+catalytic amount I_2) in 20 ml cyclopropyl methanol/ 20 ml water and obtained in 8% yield. MS (m/e): 273.1 (MH^-, 100%).

Example R

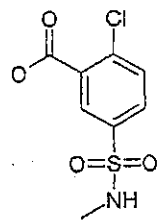
2-Chloro-5-(propane-1-sulfonyl)-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 2-Chloro-5-methanesulfonyl-benzoic acid from 2-Chloro-5-sulfino-benzoic acid and 1-iodopropane in 20 ml propanol/ 20 ml water and obtained in 3% yield. MS (m/e): 261.1 (MH^-, 100%).

Example S

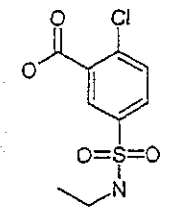
2-Chloro-5-methylsulfamoyl-benzoic acid



A mixture of 1 g (4 mmol) 2-Chloro-5-sulfino-benzoic acid and 0.62 g (20 mmol) Methylamine in 10 ml dioxane was stirred for 3 h at room temperature. After evaporation of the volatiles 15 ml 5N HCl was added and the mixture was extracted 3x with ethylacetate. The solvent was removed under vacuum to yield 0.724 g (72 %) of the title compound as amorphous white solid. MS (m/e): 248.1 (MH^-, 100%).

Example T

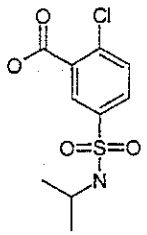
2-Chloro-5-ethylsulfamoyl-benzoic acid



The title compound was synthesised according to the procedure described for 2-Chloro-5-methylsulfamoyl-benzoic acid from 2-Chloro-5-sulfino-benzoic acid and ethylamine and obtained in 78 % yield. MS (m/e): 262.2 (MH^-, 100%).

Example U

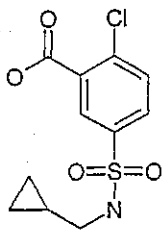
2-Chloro-5-isopropylsulfamoyl-benzoic acid



The title compound was synthesised according to the procedure described for 2-Chloro-5-methylsulfamoyl-benzoic acid from 2-Chloro-5-sulfino-benzoic acid and isopropylamine and obtained in 74 % yield. MS (m/e): 276.1 (MH^-, 100%).

Example V

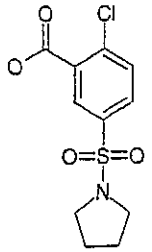
2-Chloro-5-(cyclopropylmethyl-sulfamoyl)-benzoic acid



The title compound was synthesised according to the procedure described for 2-Chloro-5-methylsulfamoyl-benzoic acid from 2-Chloro-5-sulfino-benzoic acid and cyclopropylmethylamine and obtained in 81 % yield. MS (m/e): 288.0 (MH^-, 100%).

Example W

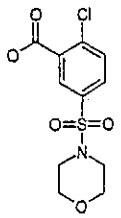
2-Chloro-5-(pyrrolidine-1-sulfonyl)-benzoic acid



The title compound was synthesised according to the procedure described for 2-Chloro-5-methylsulfamoyl-benzoic acid from 2-Chloro-5-sulfino-benzoic acid and pyrrolidine and obtained in 91 % yield. MS (m/e): 288.0 (MH^-, 100%).

Example X

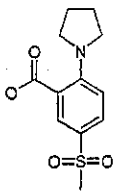
2-Chloro-5-(morpholine-4-sulfonyl)-benzoic acid



The title compound was synthesised according to the procedure described for 2-Chloro-5-methylsulfamoyl-benzoic acid from 2-Chloro-5-sulfino-benzoic acid and morpholine and obtained in 100 % yield. MS (m/e): 304.0 (MH^-, 100%).

Example Y

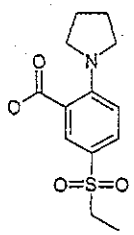
5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid



A mixture of 163.8 mg (0.7 mmol) 2-Chloro-5-methanesulfonyl-benzoic acid in 2 ml pyrrolidine was heated for 16 h to 100 °C. After evaporation of all volatiles the residue was taken up in 2 ml methanol/formic acid 3/1 and subjected to reversed phase HPLC purification eluting with an acetonitrile / water gradient to yield after evaporation of the product fractions 143.4 mg (77 %) of the title compound. MS (m/e): 268.1 (MH^-, 100%).

Example Z

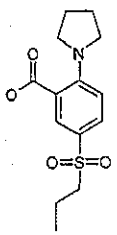
5-Ethanesulfonyl-2-pyrrolidin-1-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-(ethane-2-sulfonyl)-benzoic acid and pyrrolidine and obtained in 73 % yield. MS (m/e): 282.2 (MH^-, 100%).

Example AA

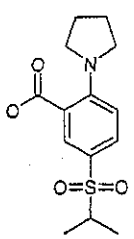
5-(Propane-1-sulfonyl)-2-pyrrolidin-1-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-(propane-2-sulfonyl)-benzoic acid and pyrrolidine and obtained in 63 % yield. MS (m/e): 296.2 (MH^-, 100%).

Example AB

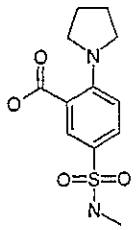
5-(Propane-2-sulfonyl)-2-pyrrolidin-1-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-(propane-2-sulfonyl)-benzoic acid and pyrrolidine and obtained in 72 % yield. MS (m/e): 296.2 (MH^-, 100%).

Example AC

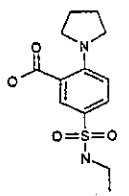
5-Methylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-methylsulfamoyl-benzoic acid and pyrrolidine and obtained in 45 % yield. MS (m/e): 283.1 (MH^-, 100%).

Example AD

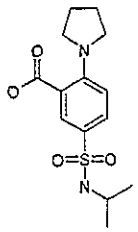
5-Ethylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-ethylsulfamoyl-benzoic acid and pyrrolidine and obtained in 43 % yield. MS (m/e): 202.2 (MH^-, 100%).

Example AE

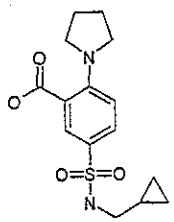
5-Isopropylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-isopropylsulfamoyl-benzoic acid and pyrrolidine and obtained in 40 % yield. MS (m/e): 311.2 (MH^-, 100%).

Example AF

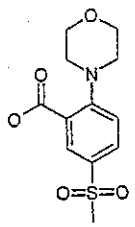
5-(Cyclopropylmethyl-sulfamoyl)-2-pyrrolidin-1-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-(cyclopropylmethyl-sulfamoyl)-benzoic acid and pyrrolidine and obtained in 38 % yield. MS (m/e): 323.2 (MH^-, 100%).

Example AG

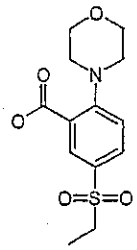
5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-(methane-2-sulfonyl)-benzoic acid and morpholine and obtained in 80 % yield. MS (m/e): 284.1 (MH^-, 100%).

Example AH

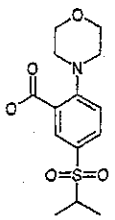
5-Ethanesulfonyl-2-morpholin-4-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-(ethane-2-sulfonyl)-benzoic acid and morpholine and obtained in 77 % yield. MS (m/e): 298.2 (MH^-, 100%).

Example AI

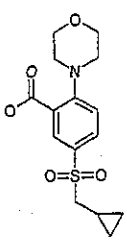
2-Morpholin-4-yl-5-(propane-2-sulfonyl)-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-(isopropane-2-sulfonyl)-benzoic acid and morpholine and obtained in 53 % yield. MS (m/e): 312.1 (MH^-, 100%).

Example AJ

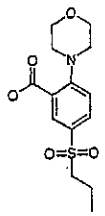
5-Cyclopropylmethanesulfonyl-2-morpholin-4-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-cyclopropylmethanesulfonyl-benzoic acid and morpholine and obtained in 27 % yield. MS (m/e): 324.2 (MH^-, 100%).

Example AK

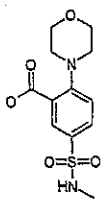
2-Morpholin-4-yl-5-(propane-1-sulfonyl)-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-(propane-2-sulfonyl)-benzoic acid and morpholine and obtained in 62 % yield. MS (m/e): 312.2 (MH^-, 100%).

Example AL

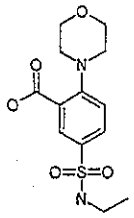
5-Methylsulfamoyl-2-morpholin-4-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-methylsulfamoyl-benzoic acid and morpholine and obtained in 40 % yield. MS (m/e): 299.2 (MH^-, 100%).

Example AM

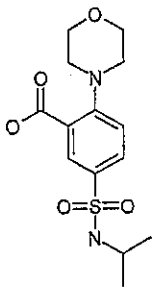
5-Ethylsulfamoyl-2-morpholin-4-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-ethylsulfamoyl-benzoic acid and morpholine and obtained in 42 % yield. MS (m/e): 313.2 (MH^-, 100%).

Example AN

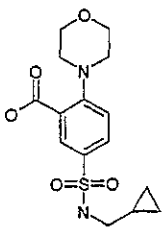
5-Isopropylsulfamoyl-2-morpholin-4-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-isopropylsulfamoyl-benzoic acid and morpholine and obtained in 38 % yield. MS (m/e): 327.2 (MH^-, 100%).

Example AO

5-(Cyclopropylmethyl-sulfamoyl)-2-morpholin-4-yl-benzoic acid

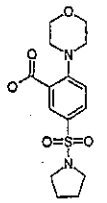


The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-

(cyclopropylmethyl-sulfamoyl)-benzoic acid and morpholine and obtained in 33 % yield. MS (m/e): 339.2 (MH^-, 100%).

Example AP

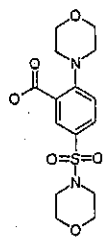
2-Morpholin-4-yl-5-(pyrrolidine-1-sulfonyl)-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-(pyrrolidine-1-sulfonyl)-benzoic acid and morpholine and obtained in 34 % yield. MS (m/e): 339.2 (MH^-, 100%).

Example AQ

5-(Morpholine-4-sulfonyl)-2-morpholin-4-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid from 2-Chloro-5-(morpholine-1-sulfonyl)-benzoic acid and morpholine and obtained in 22 % yield. MS (m/e): 355.2 (MH^-, 100%).

Example 123

4-Fluoro-2-[4-(5-methanesulfonyl-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-benzonitrile

A mixture of 13.6 mg (0.05 mmol) 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid, 15.7 mg (0.06 mmol) 2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460), 17.9 mg (0.06 mmol) TBTU and 43 ul (0.25 mmol) DIPEA in 1 ml DMF was stirred

for 16 h at room temperature. After addition of 100ul formic acid the mixture was subjected to preparative HPLC purification on reversed phase eluting with an acetonitrile / water gradient to yield after evaporation of the product fractions 10.6 mg (33%) of the title compound. MS (m/e): 457.2 (MH^+, 100%)

According to the procedure described for the synthesis of Example 123 further derivatives have been synthesised from acid derivatives and piperazine derivatives and comprise Examples 123-173 in Table 1.

Example 174

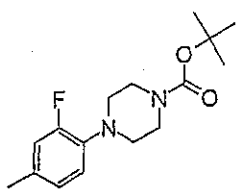
1-(4-{4-[2-(4-Methyl-piperazin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone

A stirred mixture of 150 mg (0.39 mmol) 1-{3-fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone, 200 mg (2.0 mmol) 1-methylpiperazine in 4 ml THF was heated to 80 °C for 1h. Water was added to the reaction mixture, the precipitate isolated, dried and purified by flash-chromatography on silica gel with heptane/AcOEt as eluent. The title compound was obtained as a light yellow powder, MS (m/e): 471.2 (MH^+, 100%).

According to the procedure described for the synthesis of Example 174 further derivatives have been synthesised from 1-{3-fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and amines and comprise Examples 174 to 176 in Table 1.

Example AR

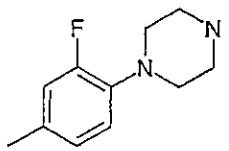
4-(2-Fluoro-4-methyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester



Title compound was prepared according to the procedure described in example G from N-Boc-piperazine and 4-bromo-3-fluorotoluene (40% yield, yellow oil, MS (m/e): 295.2 (M+H+, 100%).

Example AS

1-(2-Fluoro-4-methyl-phenyl)-piperazine



Title compound was prepared according to procedure described in example D/ step 2, (99% yield, yellow oil, MS (m/e): 195.3 ($M+H^+$, 100%).

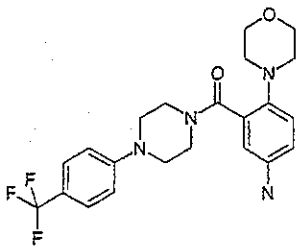
Example 177

[4-(2-Fluoro-4-methyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

Title compound was prepared according to procedure described in example 46 from 1-(2-Fluoro-4-methyl-phenyl)-piperazine and 2-morpholin-4-yl-5-nitro-benzoyl chloride (70% yield, yellow oil, MS (m/e): 429.2 ($M+H^+$, 100%).

Example AT

(5-Amino-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone



To a solution of (2-Morpholin-4-yl-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (preparation described in example 57, 150 mg, 0.323 mmol) in methanol (3 ml) was added Pd/C 10 % (6. 9 mg) . The mixture was stirred under an atmospheric pressure of hydrogen at room temperature for 1 hour. Catalyst was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed over silicagel (Eluent: Heptane/Ethylacetate (0-100% in 20 minutes)) to provide the title compound (111 mg, 79% yield) as a yellow solid, MS (m/e): 435.2 ($M+H^+$, 100%).

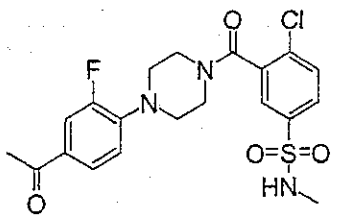
Example 178

(2-Morpholin-4-yl-5-tetrazol-1-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

A suspension of (5-Amino-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (50 mg, 0.115 mmol) in Acetic acid (1 ml) was heated to 75°C under nitrogen and then triethylorthoformate (36.76 ul, 0.34 mmol) was slowly added. After 1 hour, sodium azide (22.4 mg, 0.34 mmol) was added portionwise and the reaction mixture was stirred at 75°C for 1h30. The reaction mixture was cooled to room temperature, diluted with water and basified with 1N NaOH solution. The aqueous phase was extracted with ethyl acetate. The organic phases were combined, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was chromatographed on silica gel: Eluent: Heptane/Ethylacetate 0% to 60% (10 minutes) to provide the title compound (29 mg, 52%) as yellow solid, MS (m/e): 488.2 ($M+H^+$, 100%)

Example AU

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-chloro-N-methyl-benzenesulfonamide



The title compound was prepared according to the procedure described for example K/ step2 from 1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone and 2-Chloro-5-methylsulfamoyl-benzoic acid (CAS: 68901-09-7; BE 620741) (69%, light yellow foam, MS (m/e): 452.1 (M-H, 100%)

Example 179

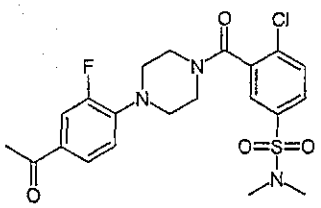
3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide

The title compound was prepared according to the procedure described for example 1 from 3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-chloro-N-methyl-

benzenesulfonamide and morpholine (58%, light yellow solid, MS (m/e): 503.1 (M-H, 100%)

Example AV

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-chloro-N,N-dimethyl-benzenesulfonamide



The title compound was prepared according to the procedure described for example K/ step2 from 1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone and 2-Chloro-5-dimethylsulfamoyl-benzoic acid (CAS: 37088-27-0; BE 620741) (64%, light yellow foam, MS (m/e): 468.1 ($M+H^+$, 100%)

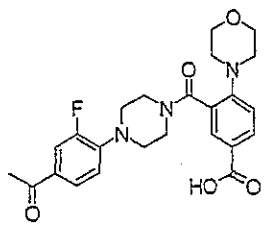
Example 180

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N,N-dimethyl-4-morpholin-4-yl-benzenesulfonamide

The title compound was prepared according to the procedure described for example 1 from 3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-chloro-N,N-dimethyl-benzenesulfonamide and morpholine (60%, light yellow solid, MS (m/e): 519.2 (M+H, 100%)

Example AW

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzoic acid



A suspension of 3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzonitrile (example 196, 469 mg, 1.07 mmol) in ethanol (6 ml) and NaOH 2N (6

ml) was heated to 85°C for 17 hours. The reaction mixture was cooled to room temperature, diluted with water and acidified with 2N HCl. The resulting solid was filtered, washed with water and dried to provide the title compound (0.47 g, 96%) as an orange solid.

Example 181

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzamide

The title compound was prepared according to the procedure described for example K/step2 from 3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzoic acid and ammonia (10%, white solid, MS (m/e): 455.2 (M+H, 100%)

Example 182

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzamide

The title compound was prepared according to the procedure described for example K/step2 from 3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzoic acid and methylamine (43%, white solid, MS (m/e): 469.3 (M+H, 100%)

Example 183

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N,N-dimethyl-4-morpholin-4-yl-benzamide

The title compound was prepared according to the procedure described for example K/step2 from 3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzoic acid and dimethylamine (44%, yellow solid, MS (m/e): 483.2 (M+H, 100%)

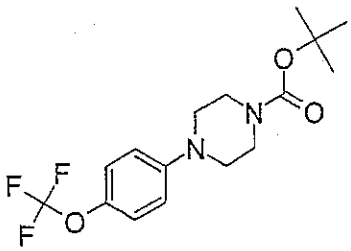
Example 184

[4-(2-Chloro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

The title compound was prepared according to the procedure described for example 46 from 1-(2-Chloro-4-trifluoromethyl-phenyl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride (74%, yellow solid, MS (m/e): 499.2 (M+H, 100%)

Example AX

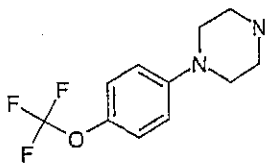
4-(4-Trifluoromethoxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester



To a mixture of cesium carbonate (1.88 g, 5.7 mmol), palladium(II)acetate (46.1 mg, 0.205 mmol), rac-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (192 mg, 0.31 mmol), tert-Butyl-1-piperazine carboxylate (928mg, 4.93 mmol) and 1-Bromo-4-(trifluoromethoxy)benzene (1g, 4.11 mmol) was added degazed toluene (10 ml). The mixture was heated to 100°C for 4 hours. The mixture was cool to room temperature, diluted with ethylacetate, filtered and the solvent was removed in vacuo. The crude oil was chromatographed over silica gel: eluent: heptane/ethylacetate 0-10% over 20 minutes to provide the title compound (180 mg, 13%) as a yellow solid, MS (m/e): 347.4 (M+H, 100%).

Example AY

1-(4-Trifluoromethoxy-phenyl)-piperazine



The title compound was prepared according to the procedure described for example D step 2 from 4-(4-trifluoromethoxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (44%, brown oil, MS (m/e): 247.1(M+H, 100%)

Example 185

(2-Morpholin-4-yl-5-nitro-phenyl)-[4-(4-trifluoromethoxy-phenyl)-piperazin-1-yl]-methanone

The title compound was prepared according to the procedure described for example 46 from 1-(4-Trifluoromethoxy-phenyl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride (74%%, yellow solid, MS (m/e): 481.2(M+H, 100%)

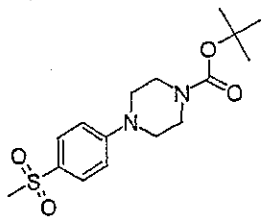
Example 186

2-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile

The title compound was prepared according to the procedure described for example 46 from 2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile and 2-Morpholin-4-yl-5-nitro-benzoyl chloride (69%, yellow solid, MS (m/e): 490.2 (M+H, 100%)

Example AZ

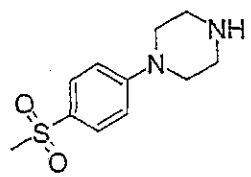
4-(4-Methanesulfonyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester



The title compound was prepared according to the procedure described for example AX from 4-bromophenyl methyl sulfone and N-Boc-piperazine (31%, white solid, MS (m/e): 241.2(M-Boc, 100%)

Example BA

1-(4-Methanesulfonyl-phenyl)-piperazine



The title compound was prepared according to the procedure described for example D step 2 from 4-(4-Methanesulfonyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (99%, brown solid, MS (m/e): 241.2(M+H, 100%)

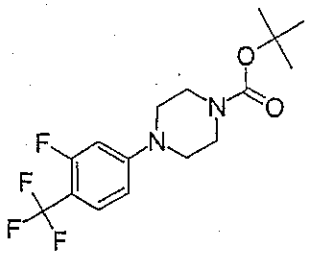
Example 187

[4-(4-Methanesulfonyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

The title compound was prepared according to the procedure described for example 46 from 1-(4-Methanesulfonyl-phenyl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride (76%, yellow solid, MS (m/e): 475.1 (M+H, 100%)

Example BB

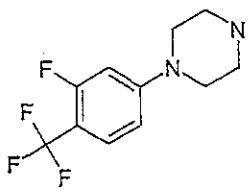
4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester



To a mixture of sodium tert-butoxide (0.68 g, 6.9 mmol), palladium(II)acetate (11 mg, 0.05 mmol), 2-(di-t-butylphosphino)biphenyl (149 mg, 0.49 mmol), tert-Butyl-1-piperazine carboxylate (1.1 g, 5.9 mmol) and 4-chloro-2-fluorobenzotrifluoride (1 g, 4.94 mmol) was added degazed toluene (10 ml). The mixture was heated to 80 °C overnight. The mixture was cool to room temperature, diluted with ether, filtered and the filtrate was concentrated in vacuo. The residue was chromatographed over silica gel: eluent: Heptane/Ethylacetate 0-10% over 15 minutes to provide the title compound (1.05 g, 61%) as a white solid, MS (m/e): 349.2 (M+H, 100%).

Example BC

1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine



The title compound was prepared according to the procedure described for example D step 2 from 4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (98%, brown solid, MS (m/e): 249.2(M+H, 100%)

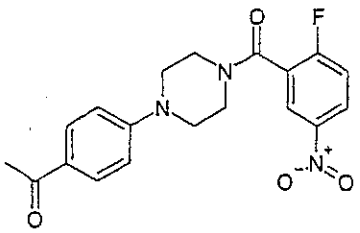
Example 188

[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

The title compound was prepared according to the procedure described for example 46 from 1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride (62%, yellow solid, MS (m/e): 483.2 (M+H, 100%)

Example BD

1-{4-[4-(2-Fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone



The title compound was prepared according to the procedure described for example K step 2 from 4'-piperazino-acetophenone and 2-fluoro-5-nitrobenzoic acid (16%, yellow solid, MS (m/e): 372.1 (M+H, 100%)

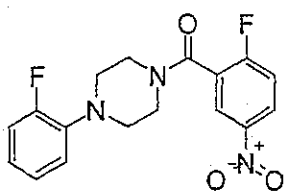
Example 189

1-{4-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone

The title compound was prepared according to the procedure described for example 1 from 1-{4-[4-(2-Fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and morpholine (85%, yellow solid, MS (m/e): 439.3 (M+H, 100%)

Example BE

(2-Fluoro-5-nitro-phenyl)-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone



The title compound was prepared according to the procedure described for example 46 from 2-Fluoro-5-nitro-benzoyl chloride and 1-(2-fluorophenyl)-piperazine (52%, orange solid, MS (m/e): 348.1 (M+H, 100%)

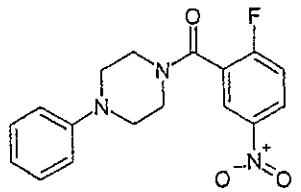
Example 190

[4-(2-Fluoro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

The title compound was prepared according to the procedure described for example 1 from (2-Fluoro-5-nitro-phenyl)-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone and morpholine (87%, yellow solid, MS (m/e): 415.2 (M+H, 100%)

Example BF

(2-Fluoro-5-nitro-phenyl)-(4-phenyl-piperazin-1-yl)-methanone



The title compound was prepared according to the procedure described for example 46 from 2-Fluoro-5-nitro-benzoyl chloride and 1-phenyl-piperazine (70%, orange solid, MS (m/e): 330.1 (M+H, 100%)

Example 191

(2-Morpholin-4-yl-5-nitro-phenyl)-(4-phenyl-piperazin-1-yl)-methanone

The title compound was prepared according to the procedure described for example 1 from (2-Fluoro-5-nitro-phenyl)-(4-phenyl-piperazin-1-yl)-methanone and morpholine (87%, yellow solid, MS (m/e): 397.3 (M+H, 100%)

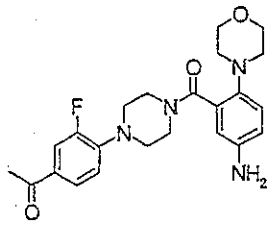
Example 192

[4-(4-Chloro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

The title compound was prepared according to the procedure described for example 46 from 2-morpholin-4-yl-5-nitro-benzoyl chloride and 4-chloro-phenyl-piperazine (orange solid), MS (m/e): 449.2 (M+H, 100%).

Example BG

1-{4-[4-(5-Amino-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone



The title compound was prepared according to the procedure described for example AT from 1-{4-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone (72%, yellow solid, MS (m/e): 427.2 (M+H, 100%)

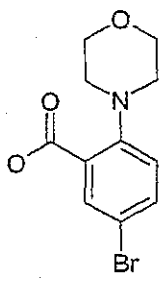
Example 193

N-{3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-phenyl}-methanesulfonamide

To a solution of 1-{4-[4-(5-Amino-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone (50 mg, 0.12 mmol) and triethylamine (33 ul, 0.234 mmol) in dioxane (1.5 ml) was added a solution of methanesulfonyl chloride (15 mg, 0.13 mmol) in dioxane (0.5 ml). The mixture was stirred at room temperature for 3 hours. The reaction mixture was stirred in water. The yellow solid was filtered, washed with water and dissolved in CH_2Cl_2. The solution was dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was chromatographed over silica gel eluent: Heptane/ethyl acetate 0%-100% (5 minutes) to provide the title compound (35 mg, 59%) as a yellow solid MS (m/e): 505.3 (M+H, 100%)

Example BH

5-Bromo-2-morpholin-4-yl-benzoic acid

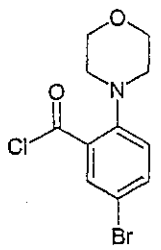


The title compound was prepared according to the procedure described for example B step1 from 5-Bromo-2-fluorobenzoic acid and morpholine except that the mixture was

heated at 130 °C for 48 hours (77%, white solid), 1-H-NMR (300 MHz, $CDCl_3$) δ= 8.45 (d), 7.74 (dxd, 7.33 (d)

Example BI

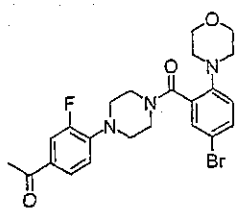
5-Bromo-2-morpholin-4-yl-benzoyl chloride



The title compound was prepared according to the procedure described for example B step2 from 5-Bromo-2-morpholin-4-yl-benzoic acid (100%, yellow oil, MS (m/e): 305.0 (M+H, 100%)

Example BJ

1-{4-[4-(5-Bromo-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone



The title compound was prepared according to the procedure described for example 46 from 5-Bromo-2-morpholin-4-yl-benzoyl chloride and 1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (94%, yellow foam, MS (m/e): 490.3 (M+, 100%)

Example 194

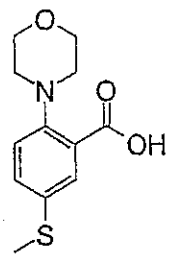
1-{4-[4-(5-Acetyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone

To a suspension of 1-{4-[4-(5-Bromo-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone (160 mg, 0.33 mmol) in toluene (2 ml) were added $PdCl_2(PPh_3)_2$ (5 mg, 0.0065 mmol) and tributyl(1-ethoxyvinyl)tin (125 ul, 0.36 mmol). The mixture was heated to 100°C for 6 hours. The mixture was cooled in an ice bath and

2N HCl (0.55 ml) was added. The mixture was stirred at room temperature overnight. The mixture was filtered. The organic layer was separated and 10% aqueous KF solution was added. The mixture was stirred at room temperature for 3 hours and filtered. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude gum was chromatographed on silica gel, eluent: heptane/ethylacetate 0%-50% (10 minutes) to provide the title compound (15 mg, 10%) as a white solid MS (m/e): 454.2 (M+H, 100%).

Example BK

5-Methylsulfanyl-2-morpholin-4-yl-benzoic acid



A mixture of 2-Chloro-5-(methylthio)-benzoic acid (1g, 4.7 mmol), morpholine (620ul, 7.1 mmol), potassium carbonate (1.05 g, 7.6 mmol) and Copper (24 mg, 0.38 mmol) in pentanol (6 ml) was stirred for 1h at room temperature. The mixture was heated to 100°C and stirred for 40 minutes. The solvent was evaporated. The residue was taken up in water and acidified to pH 2. The aqueous layer was extracted twice with ethylacetate. The organic layers were combined, dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude oil was chromatographed over silicagel: eluent: heptane/ethylacetate 0-20% over 15 minutes to provide the title compound as a brown solid (120 mg, 10%), MS (m/e): 252.1 (M-H, 100%)

Example 195

1-{3-Fluoro-4-[4-(5-methylsulfanyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone

The title compound was prepared according to the procedure described for example K step 2 from 5-Methylsulfanyl-2-morpholin-4-yl-benzoic acid and 1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (8%, white solid), MS (m/e): 458.2 (M+, 100%)

Example 196

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzonitrile

The title compound was prepared according to the procedure described for example 1 from 3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile (example L) and morpholine (71%, white solid), MS (m/e): 437.2 (M+H, 100%)

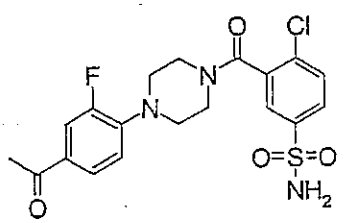
Example 197

1-{3-Fluoro-4-[4-(5-methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone

The title compound was prepared according to the procedure described for example 1 from 1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone (example K) and morpholine (57%, white solid), MS (m/e): 490.2 (M+H, 100%)

Example BL

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-chloro-benzenesulfonamide



The title compound was prepared according to the procedure described for example K/ step2 from 1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone and 2-Chloro-5-sulfamoyl-benzoic acid (CAS: 97-04-1; Basu; D.-G.; J.Indian Chem.Soc.; 16; 1939; 100, 106) (42%, white solid), MS (m/e): 438.1 (M-H, 100%)

Example 198

3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzenesulfonamide

The title compound was prepared according to the procedure described for example 1 from 3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-chloro-benzenesulfonamide and morpholine (39%, yellow solid), MS (m/e): 489.4 (M-H, 100%)

Example 199

1-{3-Fluoro-4-[4-(5-imidazol-1-yl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone

In a tube were added successively 1-{4-[4-(5-Bromo-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone (example BJ, 0.05 g, 0.1 mmol), imidazole (8.4 mg, 0.12 mmol), cesium carbonate (70 mg, 0.21 mmol), CuI (4 mg, 0.02 mmol), 1,10-phenanthroline (7.3 mg, 0.04 mmol) and dioxane (0.2 ml). The mixture was heated under argon at 120°C for 12 hours. The reaction mixture was cooled to room temperature and quenched with water/ethyl acetate. The aqueous layer was extracted twice with ethylacetate. The organic layers were combined, dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude oil was chromatographed over silicagel: eluent: CH_2Cl_2/methanol: 0-5% to provide the title compound as a brown solid (20 mg, 40%), MS (m/e): 478.4 (M+H, 100%)

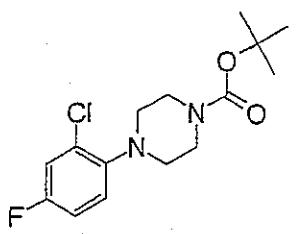
Example 200

[4-(2,4-Difluoro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

The title compound was prepared according to the procedure described for example 46 from 2-Morpholin-4-yl-5-nitro-benzoyl chloride and 1-(2,4-difluorophenyl)-piperazine (87%, yellow solid, MS (m/e): 433.4 (M+H, 100%)

Example BM

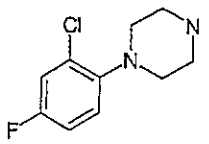
4-(2-Chloro-4-fluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester



The title compound was prepared according to the procedure described for example AX from 1-bromo-2-chloro-4-fluorobenzene and N-Boc-piperazine (10%, off white solid, MS (m/e): 315.1(M+H, 100%)

Example BN

1-(2-Chloro-4-fluoro-phenyl)-piperazine



The title compound was prepared according to the procedure described for example D step 2 from 4-(2-Chloro-4-fluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

(91%, light yellow oil, MS (m/e): 215.2(M+H, 100%)

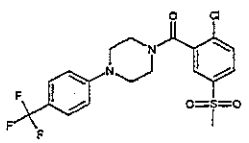
Example 201

[4-(2-Chloro-4-fluoro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

The title compound was prepared according to the procedure described for example 46 from 2-Morpholin-4-yl-5-nitro-benzoyl chloride and 1-(2-Chloro-4-fluoro-phenyl)-piperazine (70%, yellow solid, MS (m/e): 449.2 (M+H, 100%)

Example BO

(2-Chloro-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone



To a solution of 2-Chloro-5-methanesulfonyl-benzoic acid (102mg, 0.43 mmol) in dimethylformamide (20 ml) were successively added TBTU (153mg, 0.48 mmol), N-ethyldiisopropylamine (0.28 ml, 2.17 mmol) and 1-(4-trifluromethylphenyl)piperazine (ABCR F07741NB, [30459-17-7], 100 mg, 0.43 mmol). The reaction was then stirred at room temperature for two hours, then concentrated *in vacuo* and purified by column chromatography (SiO_2, 50g, heptane/ethylacetate = 0 to 100%), to give the title compound as a colorless gum (170 mg, 0.38 mmol). MS (m/e): 464.3 ($M+NH_4^+$, 100%)

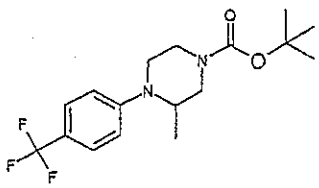
Example 202

5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

To a solution of (2-Chloro-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (0.28 mmol, 130 mg) was added morpholine (0.5 ml). The reaction mixture was then stirred at 100°C for 48 hours before being concentrated *in vacuo*. The residue was then purified by column chromatography (SiO_2, 20 g, Heptane/EtOAc 0-100%) to give the title compound as a white solid (118 mg, 85 %). MS (m/e): 497.5 ($M+H^+$, 100%).

Example BP

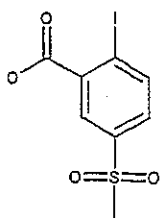
rac-3-Methyl-4-(4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester



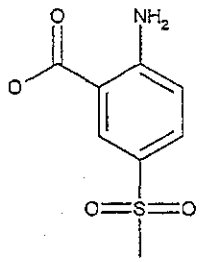
To a solution of 3-Methyl-piperazine-1-carboxylic acid tert-butyl ester (1.0 g, 5.3 mmol) and of 1-Bromo-4-trifluoromethyl-benzene (1.0 g, 4.4 mmol) in toluene (10 ml) were added sodium-tert butylate (0.6 g, 6.2 mmol), 2-(dicyclohexylphosphino)biphenyl (31 mg, 89 mmol), and tris(dibenzylideneacetone)dipalladium-chloroform complex (23 mg, 22 mmol). The reaction mixture was then stirred for 16 hours at 80 °C. After allowing to cool to room temperature the reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 70g, heptane/ethyl acetate 0-30%) to give the title compound as a light brown solid (0.47 g, 31 %). MS (m/e): 345.2 ($M+H^+$, 100%).

Example BQ

2-Iodo-5-methanesulfonyl-benzoic acid

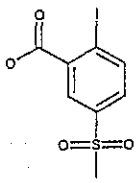


(a) 2-Amino-5-methanesulfonyl-benzoic acid



A mixture of 4.26 mmol 2-chloro-5-methanesulfonyl-benzoic acid (see example K, step1), 0.39 mmol Copper powder and 10 ml ammonium hydroxide 25% was heated at 125-130°C with stirring for 18 hours. Mixture was cooled to room temperature and filtered. The solid was washed with methanol. The filtrate was concentrated in vacuo. The residue was acidified with HCl 1N to pH=2. The obtained solid was washed with water and dried (HV, 50°C, 1 hour) to yield the title compound. MS (m/e): 214.1 (M-H, 100%)

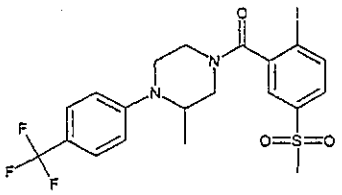
(b) 2-Iodo-5-methanesulfonyl-benzoic acid



To a suspension of 3.0 mmol 2-amino-5-methanesulfonyl-benzoic acid in a mixture of 1.7 ml sulfuric acid and 1.7 ml water was added dropwise a solution of 3.92 mmol sodium nitrite in 1.7 ml water at such rate that the temperature did not exceed 3°C. The mixture was stirred at 0°C for 1 hour. A solution of 3.0 mmol KI in 1.7 ml water was added dropwise at 0°C. The brown suspension was allowed to warm to rt and stirred for 30 minutes. Excess iodine was destroyed by addition of a few drops of a sodium hydrogenosulfite solution. The solid was filtered, washed with water and dried (HV, 50°C, 1 hour) to yield the title compound. MS (m/e): 325.0 (M-H, 100%)

Example BR

rac-(2-Iodo-5-methanesulfonyl-phenyl)-[3-methyl-4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone



To a solution of *rac*-3-Methyl-4-(4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (95 mg, 0.27 mmol) in dichloromethane (2 ml) was added trifluoroacetic acid (1 ml) and the reaction mixture was stirred at room temperature for 30 min. After such time the reaction mixture was concentrated *in vacuo*, and the residue was dissolved in dimethylformamide (3 ml). To the solution were added 2-Iodo-5-methanesulfonyl-benzoic acid (81 mg, 0.25 mmol), *N*-ethyldiisopropylamine (0.29 ml, 1.7 mmol), and TBTU (99 mg, 0.3 mmol). The reaction mixture was then allowed to stir at room temperature for 2 hours. The reaction mixture was then concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, 20g, Heptane/EtOAc 0-100%) to give the title compound as a light brown solid (135 mg, 90 %). MS (m/e): 553.1 ($M+H^+$).

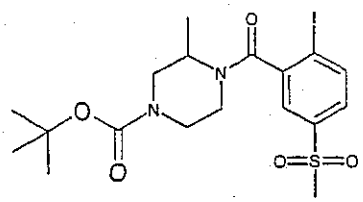
Example 203

rac-(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[3-methyl-4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

(2-Iodo-5-methanesulfonyl-phenyl)-[3-methyl-4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (50 mg, 0.09 mmol) was poured into morpholine (2.0 ml) and the reaction mixture was stirred for 24 h at 100°C before being concentrated *in vacuo*. The residue was then purified by column chromatography (SiO_2, 20g, Heptane/EtOAc 0-100%) to give the title compound as a light brown solid (43.5 mg, 94 %). MS (m/e): 512.3 ($M+H^+$).

Example BS

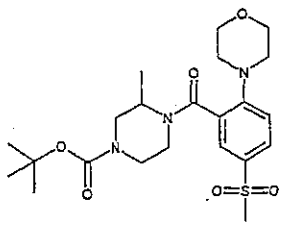
rac-4-(2-Iodo-5-methanesulfonyl-benzoyl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester



To a solution of *rac*-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester (350 mg, 1.75 mmol) in dimethylformamide (3 ml) were added 2-Iodo-5-methanesulfonyl-benzoic acid (540 mg, 1.67 mmol), *N*-ethyldiisopropylamine (1.8 ml, 10.5 mmol), and TBTU (630 mg, 1.92 mmol). The reaction mixture was then allowed to stir at room temperature for 16 hours. The reaction mixture was then concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, 20g, Heptane/EtOAc 0-100%) to give the title compound (400 mg, 45 %). MS (m/e): 526.2 ($M+NH_4^+$).

Example BT

rac-4-(5-Methanesulfonyl-2-morpholin-4-yl-benzoyl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester



rac-4-(2-Iodo-5-methanesulfonyl-benzoyl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (400 mg, 0.78 mmol) was poured into morpholine (5.0 ml) and the reaction mixture was stirred for 15 h at 100°C before being concentrated *in vacuo*. The residue was then purified by column chromatography (SiO_2, 20g, dichloromethane/methanol = 0-5%) to give the title compound as a colorless foam (322 mg, 88 %). MS (m/e): 468.3 ($M+H^+$).

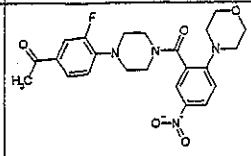
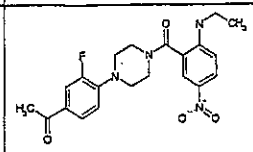
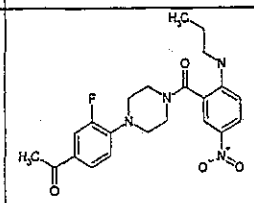
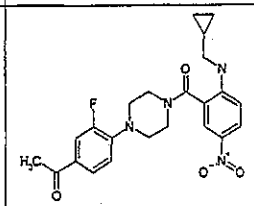
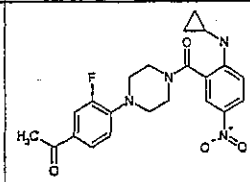
Example 204

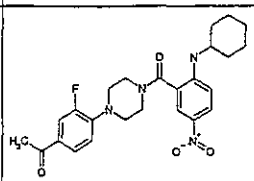
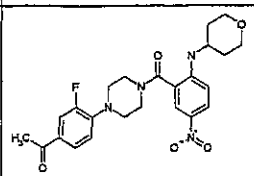
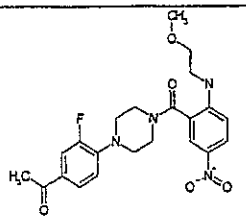
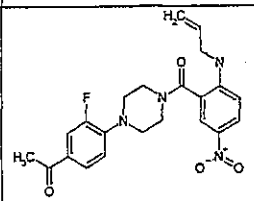
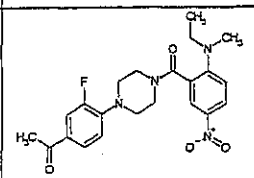
rac-(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[2-methyl-4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

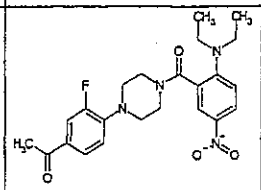
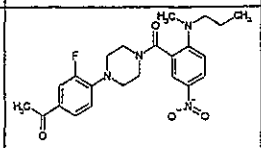
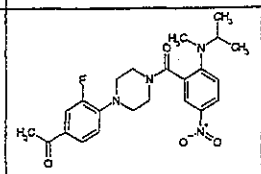
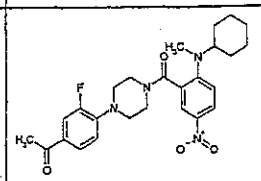
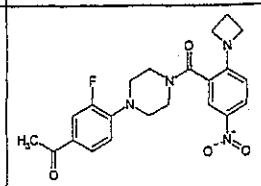
To a solution of *rac*-4-(5-Methanesulfonyl-2-morpholin-4-yl-benzoyl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (250 mg, 0.54 mmol) in dichloromethane (2 ml) was added trifluoroacetic acid (1 ml) and the reaction mixture was stirred at room temperature for 30 min. After such time the reaction mixture was concentrated *in vacuo*, and the residue was dissolved in toluene (5 ml). To the solution were added 1-Bromo-4-trifluoromethyl-benzene (0.15 ml, 1.1 mmol), sodium-tert butylate (128 mg, 1.4 mmol), 2-(dicyclohexylphosphino)biphenyl (3.8.mg, 0.011 mmol), and tris(dibenzylideneacetone)dipalladium-chloroform complex (5.5 mg, 0.005 mmol). The

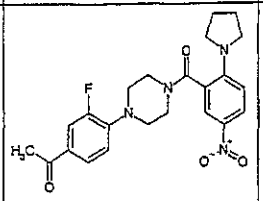
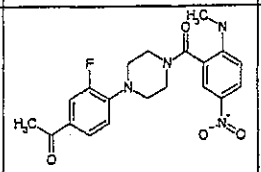
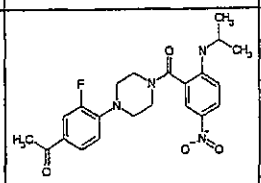
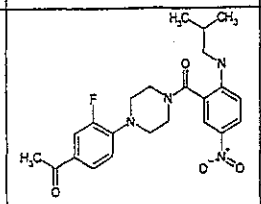
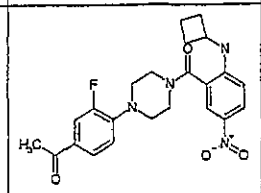
reaction mixture was then stirred for 16 hours at 80 °C. After allowing to cool to room temperature the reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 70g, dichloromethane/methanol 0-5%) to give the title compound (83 mg, 30 %). MS (m/e): 512.3 ($M+H^+$)

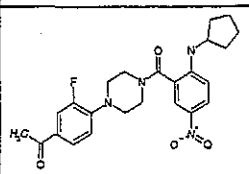
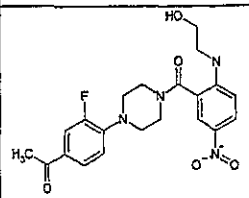
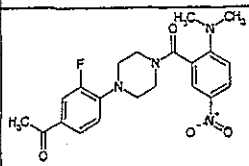
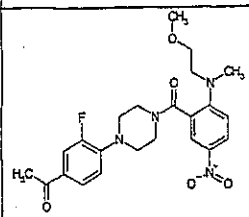
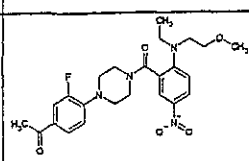
Table 1

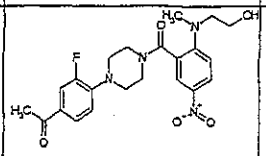
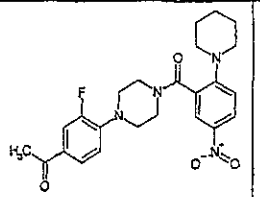
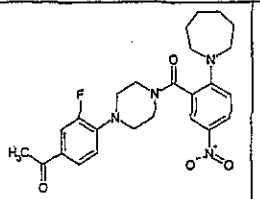
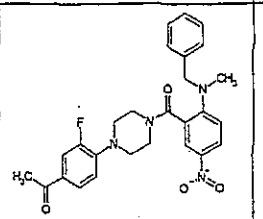
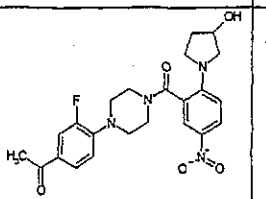
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
1		456.5	1-{4-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and morpholine	457.3
2		414.4	1-{4-[4-(2-Ethylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and ethylamine (commercially available)	415.2
3		428.5	1-{3-Fluoro-4-[4-(5-nitro-2-propylamino-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and propylamine (commercially available)	429.2
4		440.5	1-(4-{4-[2-(Cyclopropylmethyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and cyclopropylmethylamine (commercially available)	441.2
5		426.5	1-{4-[4-(2-Cyclopropylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and cyclopropylamine (commercially available)	427.2

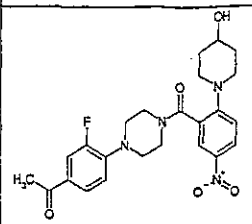
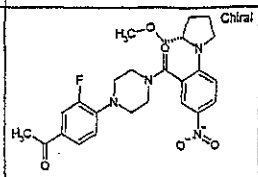
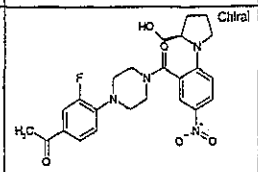
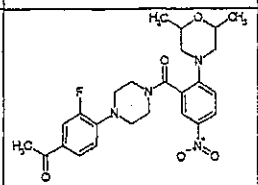
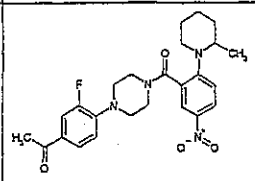
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
6		468.5	1-{4-[4-(2-Cyclohexylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and cyclohexylamine (commercially available)	469.2
7		470.5	1-(3-Fluoro-4-{4-[5-nitro-2-(tetrahydro-pyran-4-ylamino)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and tetrahydro-pyran-4-ylamine (commercially available)	471.2
8		444.5	1-(3-Fluoro-4-{4-[2-(2-methoxy-ethylamino)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 2-Methoxy-ethylamine (commercially available)	445.2
9		426.5	1-{4-[4-(2-Allylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and allylamine (commercially available)	427.1
10		428.5	1-(4-{4-[2-(Ethyl-methyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and methyl ethylamine (commercially available)	429.2

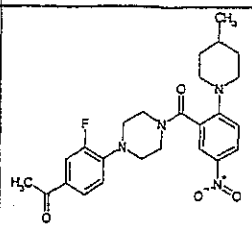
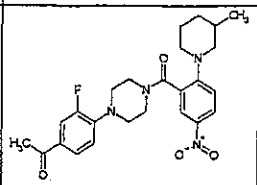
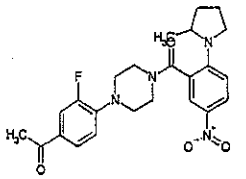
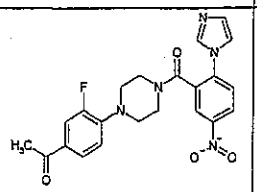
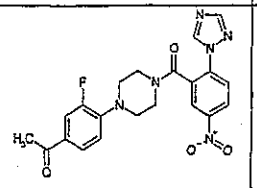
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
11		442.5	1-{4-[4-(2-Diethylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and diethylamine (commercially available)	443.2
12		442.5	1-(3-Fluoro-4-{4-[2-(methyl-propyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and methylpropylamine (commercially available)	443.2
13		442.5	1-(3-Fluoro-4-{4-[2-(isopropyl-methyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and isopropylmethylamine (commercially available)	443.2
14		482.6	1-(4-{4-[2-(Cyclohexyl-methyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and cyclohexylmethylamine (commercially available)	483.3
15		426.5	1-{4-[4-(2-Azetidin-1-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and azetidine (commercially available)	427.1

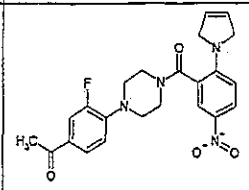
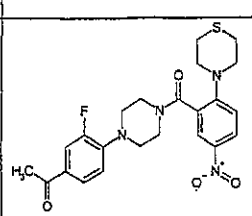
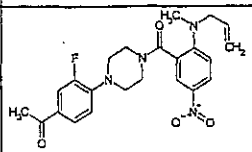
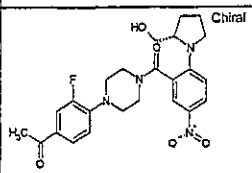
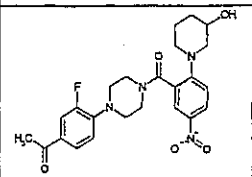
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
16		440.5	1-{3-Fluoro-4-[4-(5-nitro-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and pyrrolidine (commercially available)	441.2
17		400.4	1-{3-Fluoro-4-[4-(2-methylamino-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and methylamine (commercially available)	401.2
18		428.5	1-{3-Fluoro-4-[4-(2-isopropylamino-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and isopropylamine (commercially available)	429.2
19		442.5	1-{3-Fluoro-4-[4-(2-isobutylamino-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and isobutylamine (commercially available)	443.2
20		440.5	1-{4-[4-(2-Cyclobutylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and cyclobutylamine (commercially available)	441.2

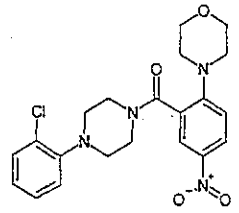
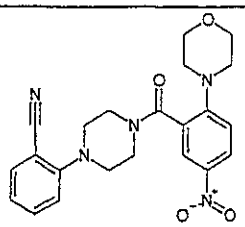
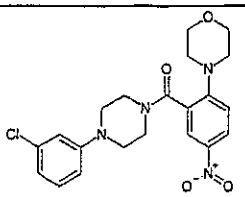
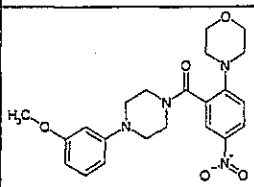
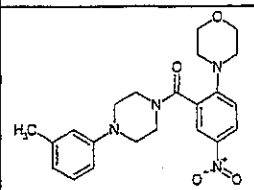
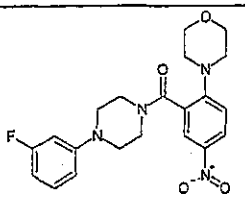
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
21		454.5	1-{4-[4-(2-Cyclopentylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and cyclopentylamine (commercially available)	455.2
22		430.4	1-(3-Fluoro-4-{4-[2-(2-hydroxy-ethylamino)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and hydroxyethylamine (commercially available)	431.2
23		414.4	1-{4-[4-(2-Dimethylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and dimethylamine (commercially available)	415.2
24		458.5	1-[3-Fluoro-4-(4-{2-[(2-methoxy-ethyl)-methyl-amino]-5-nitro-benzoyl}-piperazin-1-yl)-phenyl]-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and (2-Methoxy-ethyl)-methyl-amine (commercially available)	459.2
25		472.5	1-[4-(4-{2-[Ethyl-(2-methoxy-ethyl)-amino]-5-nitro-benzoyl}-piperazin-1-yl)-3-fluoro-phenyl]-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and (2-Methoxy-ethyl)-ethyl-amine (commercially available)	473.2

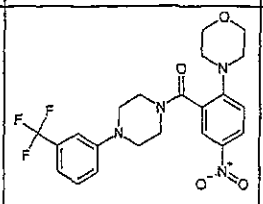
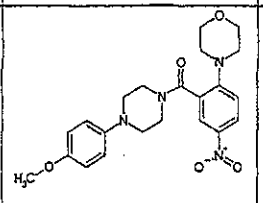
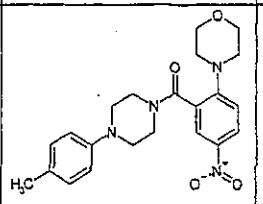
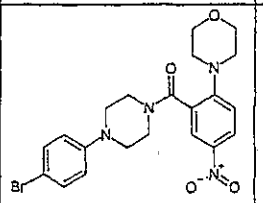
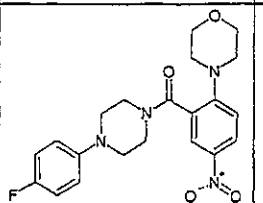
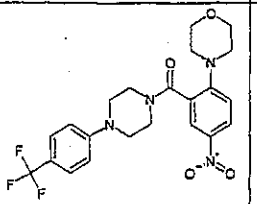
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
26		444.5	1-[3-Fluoro-4-(4-{2-[(2-hydroxy-ethyl)-methyl-amino]-5-nitro-benzoyl}-piperazin-1-yl)-phenyl]-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and (2-hydroxy-ethyl)-methyl-amine (commercially available)	445.2
27		454.5	1-{3-Fluoro-4-[4-(5-nitro-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and piperidine (commercially available)	455.2
28		468.5	1-{4-[4-(2-Azepan-1-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and azepan (commercially available)	469.2
29		490.5	1-(4-{4-[2-(Benzyl-methyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and benzylmethylamine (commercially available)	491.3
30		456.5	1-(3-Fluoro-4-{4-[2-(3-hydroxy-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 3-hydroxypyrrolidine (commercially available)	457.2

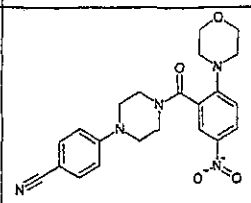
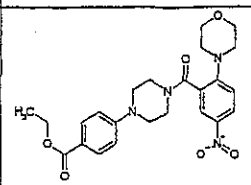
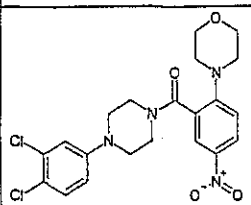
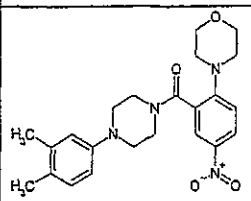
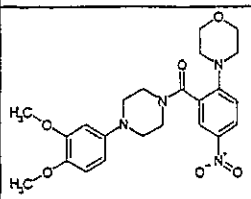
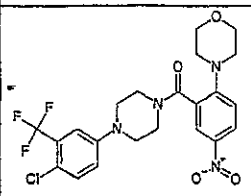
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
31		470.5	1-(3-Fluoro-4-{4-[2-(4-hydroxy-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 4-hydroxy-piperidine (commercially available)	471.2
32		484.5	1-(3-Fluoro-4-{4-[2-((S)-2-methoxymethyl-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 2-((S)-2-methoxymethyl-pyrrolidine (commercially available)	485.3
33		470.5	1-(3-Fluoro-4-{4-[2-((R)-2-hydroxymethyl-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 2-((R)-2-methoxymethyl-pyrrolidine (commercially available)	471.2
34		484.5	1-(4-{4-[2-(2,6-Dimethyl-morpholin-4-yl)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 2,6-Dimethylmorpholine (commercially available)	485.3
35		468.5	1-(3-Fluoro-4-{4-[2-(2-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 2-methyl-piperidine (commercially available)	469.2

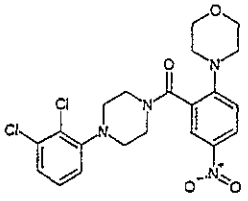
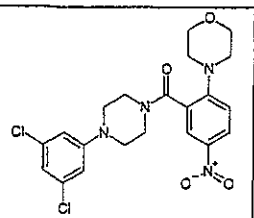
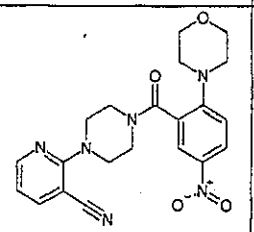
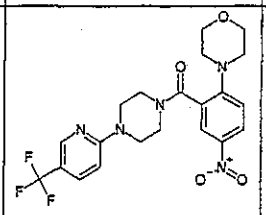
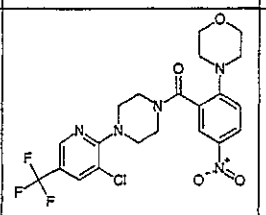
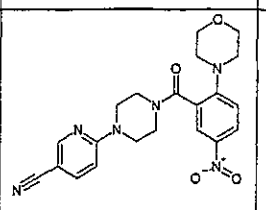
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
36		468.5	1-(3-Fluoro-4-{4-[2-(4-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 4-methyl-piperidine (commercially available)	469.2
37		468.5	1-(3-Fluoro-4-{4-[2-(3-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 3-methyl-piperidine (commercially available)	469.2
38		454.5	1-(3-Fluoro-4-{4-[2-(2-methyl-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 2-methyl-pyrrolidine (commercially available)	455.2
39		437.4	1-{3-Fluoro-4-[4-(2-imidazol-1-yl-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and imidazole (commercially available)	438.1
40		438.4	1-{3-Fluoro-4-[4-(5-nitro-2-[1,2,4]triazol-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and triazole (commercially available)	439.2

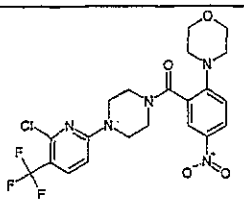
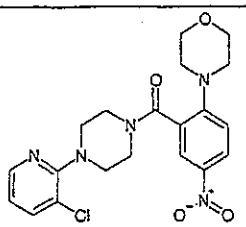
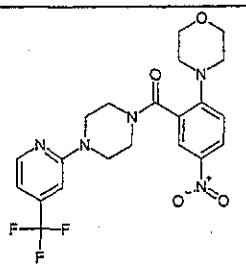
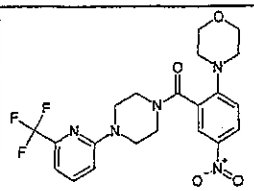
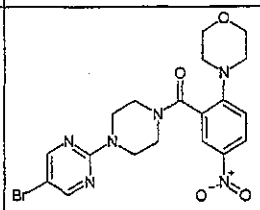
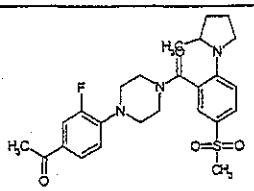
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
41		438.5	1-(4-{4-[2-(2,5-Dihydro-pyrrol-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 2,5-Dihydro-pyrrol (commercially available)	439.2
42		472.5	1-{3-Fluoro-4-[4-(5-nitro-2-thiomorpholin-4-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and thiomorpholine	473.1
43		440.5	1-(4-{4-[2-(Allyl-methyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and allylmethylamine (commercially available)	441.2
44		470.5	1-(3-Fluoro-4-{4-[2(S)-(2-hydroxymethyl-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 2(S)-(2-hydroxymethyl-pyrrolidin (commercially available)	471.2
45		470.5	1-(3-Fluoro-4-{4-[2-(3-hydroxy-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-Fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 3-hydroxy-piperidine (commercially available)	471.2

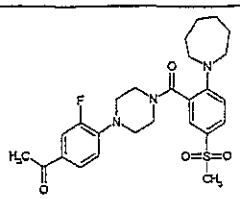
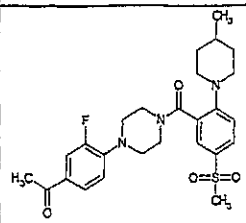
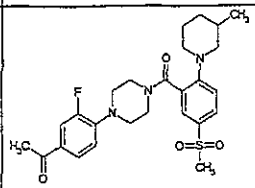
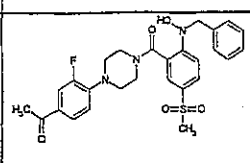
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
46		430.9	[4-(2-Chloro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(2-Chloro-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	431.2
47		421.5	2-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzonitrile	1-(2-Cyano-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	422.2
48		430.9	[4-(3-Chloro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(3-Chloro-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	431.2
49		426.5	[4-(3-Methoxy-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(3-Methoxy-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	427.2
50		410.5	(2-Morpholin-4-yl-5-nitro-phenyl)-(4-m-tolyl-piperazin-1-yl)-methanone	1-(3-Methyl-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	411.2
51		414.4	[4-(3-Fluoro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(3-Fluoro-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	415.2

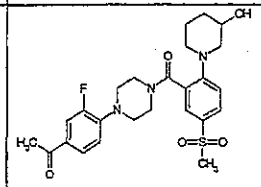
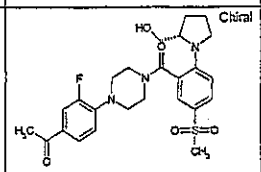
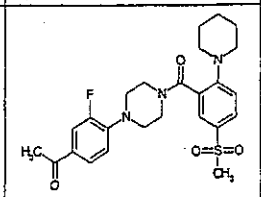
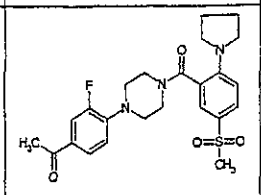
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
52		464.4	(2-Morpholin-4-yl-5-nitro-phenyl)-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(3-Trifluoromethyl-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	465.2
53		426.5	[4-(4-Methoxy-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone Known compound, *RN 433242-97-8*	1-(4-Methoxy-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	427.2
54		410.5	(2-Morpholin-4-yl-5-nitro-phenyl)-(4-p-tolyl-piperazin-1-yl)-methanone	1-(4-Methyl-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	411.2
55		475.3	[4-(4-Bromo-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(4-Bromo-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	477.0
56		414.4	[4-(4-Fluoro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(4-Fluoro-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	415.2
57		464.4	(2-Morpholin-4-yl-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	465.2

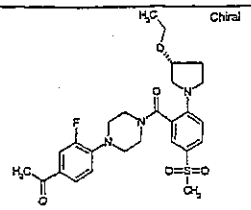
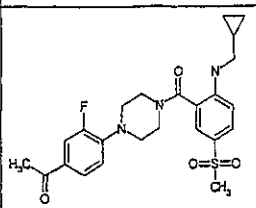
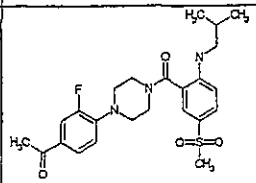
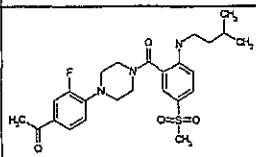
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
58		421.5	4-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzonitrile	1-(4-Cyano-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	422.2
59		468.5	4-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzoic acid ethyl ester	4-Piperazin-1-yl-benzoic acid ethyl ester (WO9938849) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	469.2
60		465.3	[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(3,4-Dichloro-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	466.2
61		424.5	[4-(3,4-Dimethyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(3,4-Dimethyl-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	425.2
62		456.5	[4-(3,4-Dimethoxy-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(3,4-Dimethoxy-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	457.2
63		498.9	[4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(4-Chloro-3-trifluoromethyl-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	499.3

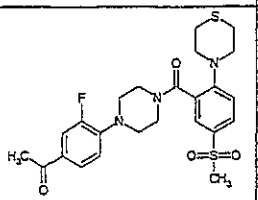
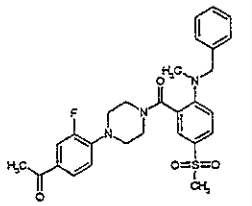
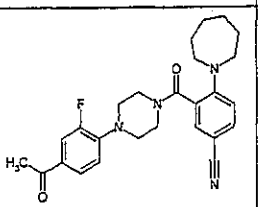
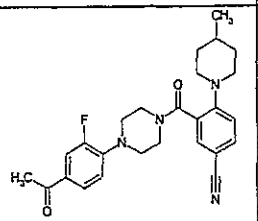
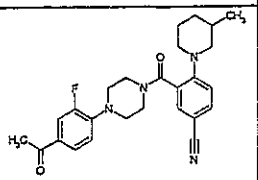
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
64		465.3	[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(2,3-Dichloro-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	465.1
65		465.3	[4-(3,5-Dichloro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(3,5-Dichloro-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	464.9
66		422.4	2-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-nicotinonitrile	2-Piperazin-1-yl-nicotinonitrile and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	423.2
67		465.4	(2-Morpholin-4-yl-5-nitro-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Trifluoromethyl-pyridin-2-yl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	466.2
68		499.9	[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	500.1
69		422.4	6-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-nicotinonitrile	6-Piperazin-1-yl-nicotinonitrile and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	423.2

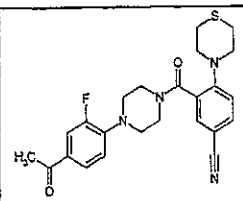
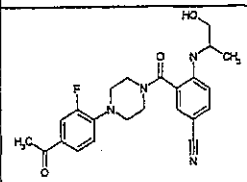
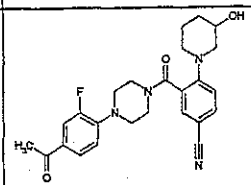
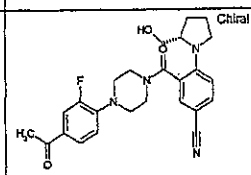
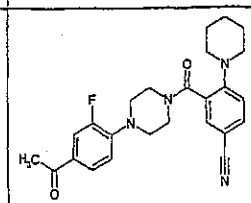
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
70		499.9	[4-(6-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(6-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	500.1
71		431.9	[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(3-Chloro-pyridin-2-yl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	432.2
72		465.4	(2-Morpholin-4-yl-5-nitro-phenyl)-[4-(4-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-pyridin-2-yl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	466.2
73		465.4	(2-Morpholin-4-yl-5-nitro-phenyl)-[4-(6-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(6-Trifluoromethyl-pyridin-2-yl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	466.2
74		477.3	[4-(5-Bromo-pyrimidin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	5-Bromo-2-piperazin-1-yl-pyrimidine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	477.0
75		487.6	1-(3-Fluoro-4-{4-[5-methanesulfonyl-2-(2-methyl-pyrrolidin-1-yl)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and 2-methyl-pyrrolidin (commercially available)	488.2

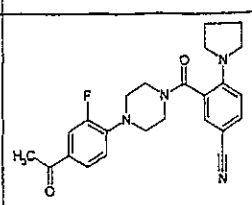
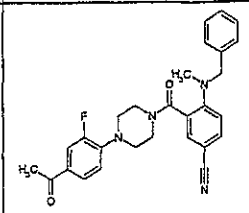
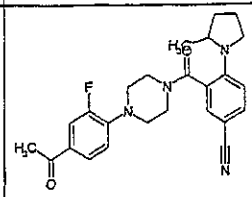
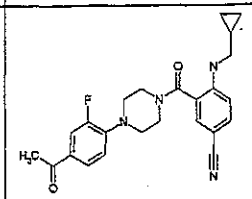
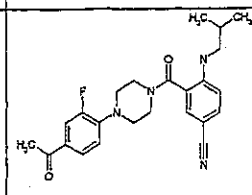
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
76		501.6	1-{4-[4-(2-Azepan-1-yl-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and azepane (commercially available)	502.2
77		501.6	1-(3-Fluoro-4-{4-[5-methanesulfonyl-2-(4-methyl-piperidin-1-yl)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and 4-methylpiperidine (commercially available)	502.2
78		501.6	1-(3-Fluoro-4-{4-[5-methanesulfonyl-2-(3-methyl-piperidin-1-yl)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and 3-methylpiperidine (commercially available)	502.2
79		525.6	1-(4-{4-[2-(Benzyl-hydroxy-amino)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and benzylhydroxylamine (commercially available)	527.1

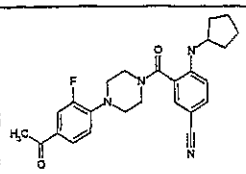
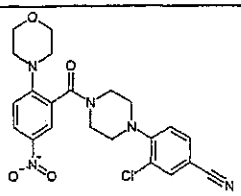
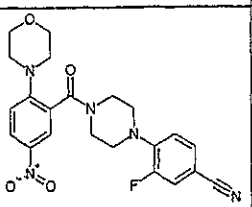
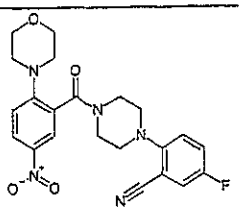
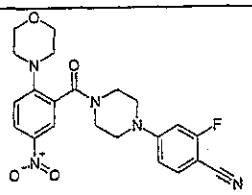
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
80		503.6	1-(3-Fluoro-4-{4-[2-(3-hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and 3-hydroxypiperidine (commercially available)	504.2
81		503.6	1-(3-Fluoro-4-{4-[2(S)-(2-hydroxymethyl-pyrrolidin-1-yl)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and 2(S)-(2-hydroxymethyl-pyrrolidine (commercially available)	504.2
82		487.6	1-{3-Fluoro-4-[4-(5-methanesulfonyl-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and piperidine (commercially available)	488.2
83		473.6	1-{3-Fluoro-4-[4-(5-methanesulfonyl-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and pyrrolidine (commercially available)	474.1

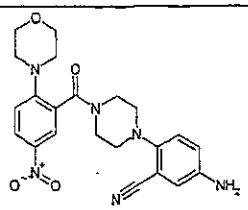
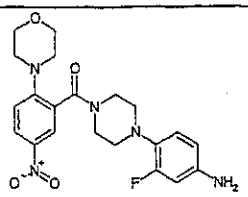
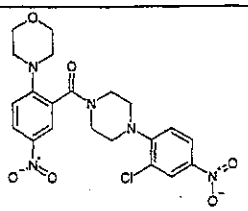
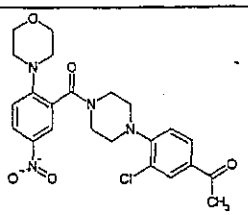
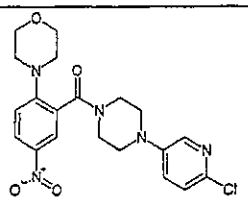
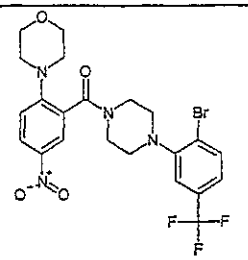
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
84		517.6	1-(4-{4-[2-(R)-(3-Ethoxy-pyrrolidin-1-yl)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and 2-(R)-3-Ethoxy-pyrrolidine (commercially available)	518.2
85		473.6	1-(4-{4-[2-(Cyclopropylmethyl-amino)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and cyclopropylmethylamine (commercially available)	474.2
86		475.6	1-{3-Fluoro-4-[4-(2-isobutylamino-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and isobutylamine (commercially available)	476.3
87		489.6	1-(3-Fluoro-4-{4-[5-methanesulfonyl-2-(3-methyl-butylamino)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and 3-methylbutylamine (commercially available)	490.4

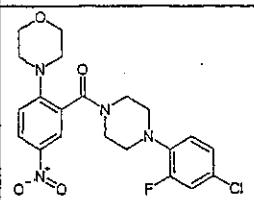
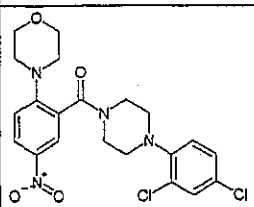
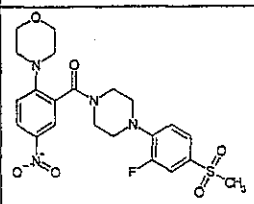
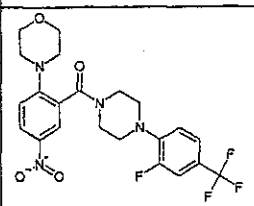
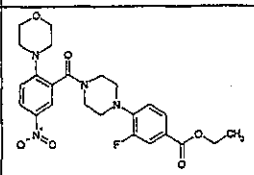
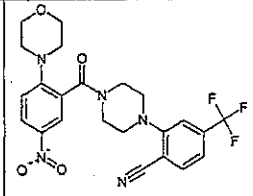
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
88		505.6	1-{3-Fluoro-4-[4-(5-methanesulfonyl-2-thiomorpholin-4-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and thiomorpholine (commercially available)	506.3
89		523.6	1-(4-{4-[2-(Benzyl-methyl-amino)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and benzylmethylamine (commercially available)	524.2
90		448.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-azepan-1-yl-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and azepane (commercially available)	449.2
91		448.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(4-methyl-piperidin-1-yl)-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and 4-methyl-piperidine (commercially available)	449.2
92		448.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(3-methyl-piperidin-1-yl)-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and 3-methyl-piperidine (commercially available)	449.2

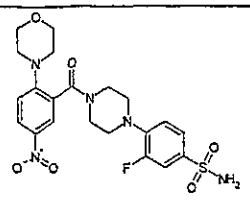
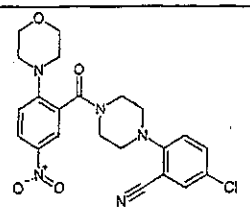
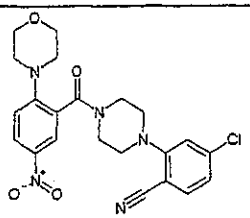
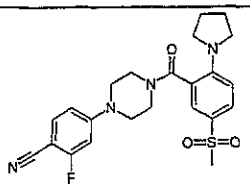
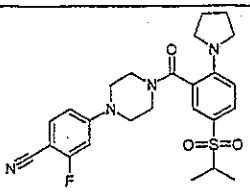
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
93		452.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-thiomorpholin-4-yl-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and thiomorpholine (commercially available)	453.1
94		424.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(2-hydroxy-1-methyl-ethylamino)-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and 2-hydroxy-1-methyl-ethylamine (commercially available)	425.1
95		450.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxy-piperidin-1-yl)-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and 3-hydroxy-piperidine (commercially available)	451.2
96		450.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(2-(S)-hydroxymethyl-pyrrolidin-1-yl)-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and 2-(S)-hydroxymethyl-pyrrolidine (commercially available)	451.2
97		434.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-piperidin-1-yl-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and piperidine (commercially available)	435.2

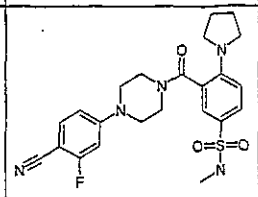
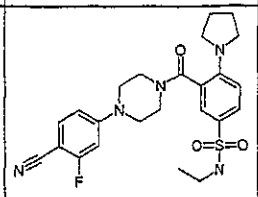
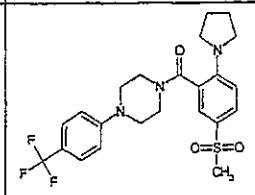
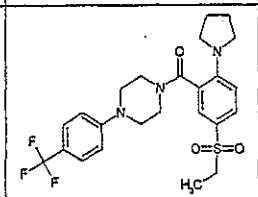
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
98		420.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-pyrrolidin-1-yl-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and pyrrolididne (commercially available)	421.1
99		470.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(benzyl-methyl-amino)-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and benzylmethylamine (commercially available)	471.2
100		434.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(2-methyl-pyrrolidin-1-yl)-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and 2-methylpyrrolidine (commercially available)	435.2
101		420.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(cyclopropylmethyl-amino)-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and cyclopropylmethylamine (commercially available)	421.2
102		422.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-isobutylamino-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and isobutylamine (commercially available)	423.2

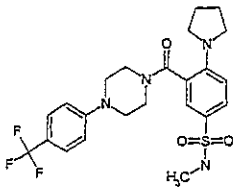
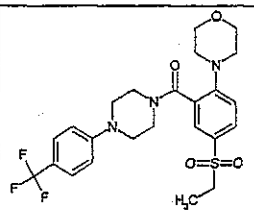
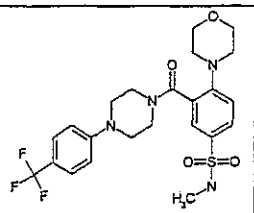
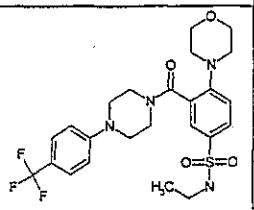
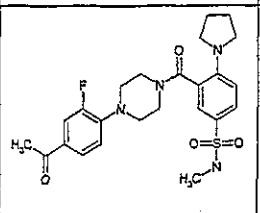
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
103		434.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopentylamino-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and cyclopentylamine (commercially available)	435.2
104		455.9	3-Chloro-4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzonitrile	3-Chloro-4-piperazin-1-yl-benzonitrile (WO9625414) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	456.2
105		439.5	3-Fluoro-4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	440.3
106		439.5	5-Fluoro-2-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzonitrile	5-Fluoro-2-piperazin-1-yl-benzonitrile (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	440.3
107		439.5	2-Fluoro-4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	440.3

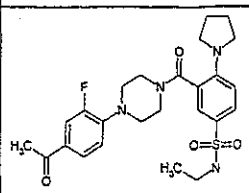
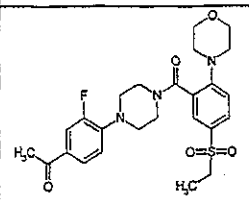
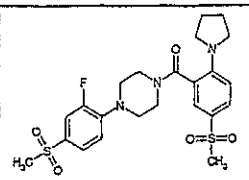
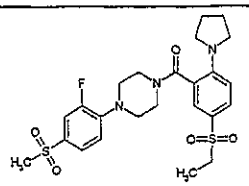
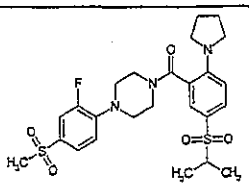
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
108		436.5	5-Amino-2-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzonitrile	5-Amino-2-piperazin-1-yl-benzonitrile (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	437.2
109		429.5	[4-(4-Amino-2-fluoro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	3-Fluoro-4-piperazin-1-yl-phenylamine (DE190798440) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	430.3
110		475.9	[4-(2-Chloro-4-nitro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(2-Chloro-4-nitro-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	476.1
111		472.9	1-{3-Chloro-4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-(3-Chloro-4-piperazin-1-yl-phenyl)-ethanone and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	473.1
112		431.9	[4-(6-Chloro-pyridin-3-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(6-Chloro-pyridin-3-yl)-piperazine (WO0230405) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	432.2
113		543.3	[4-(2-Bromo-5-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(2-Bromo-5-trifluoromethyl-phenyl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	545.0

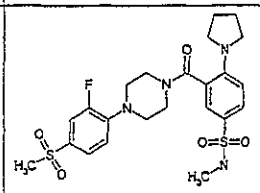
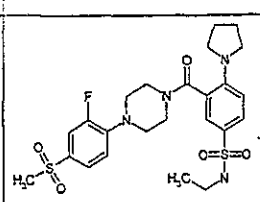
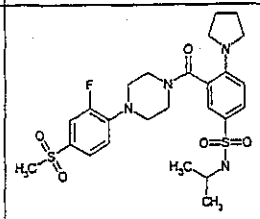
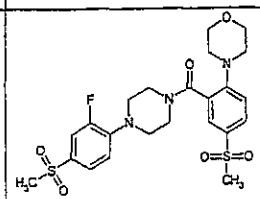
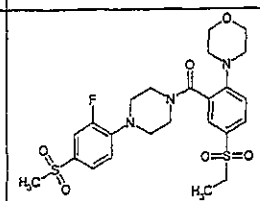
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
114		448.9	[4-(4-Chloro-2-fluoro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(4-Chloro-2-fluoro-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	449.2
115		465.3	[4-(2,4-Dichloro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(2,4-Dichloro-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	465.1
116		492.5	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	492.5
117		482.4	[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	482.4
118		486.5	3-Fluoro-4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzoic acid ethyl ester	3-Fluoro-4-piperazin-1-yl-benzoic acid ethyl ester and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	487.3
119		489.5	2-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-4-trifluoromethyl-benzonitrile	2-Piperazin-1-yl-4-trifluoromethyl-benzonitrile (WO0259108) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	490.3

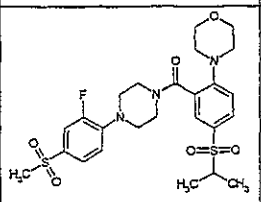
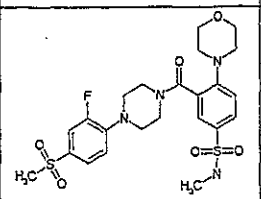
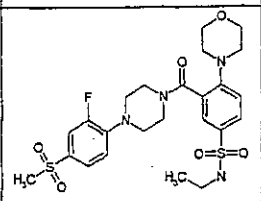
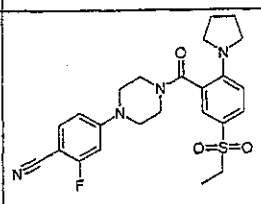
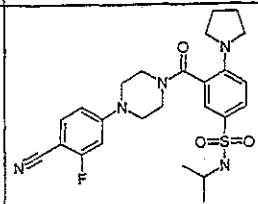
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
120		493.5	3-Fluoro-4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzenesulfonamide and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	494.4
121		455.9	5-Chloro-2-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzonitrile	5-Chloro-2-piperazin-1-yl-benzonitrile (WO9625414) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	455.8
122		455.9	4-Chloro-2-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzonitrile	4-Chloro-2-piperazin-1-yl-benzonitrile (WO0105765) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	455.8
123		456.5	2-Fluoro-4-[4-(5-methanesulfonyl-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid	457.2
124		484.6	2-Fluoro-4-{4-[5-(propane-2-sulfony l)-2-pyrrolidin-1-yl-benzoyl]-piper azin-1-yl}-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 5-(Propane-2-sulfonyl)-2-pyrrolidin-1-yl-benzoic acid	485.3

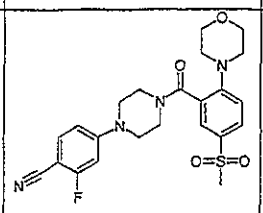
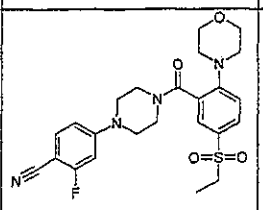
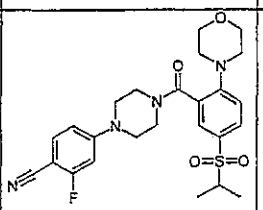
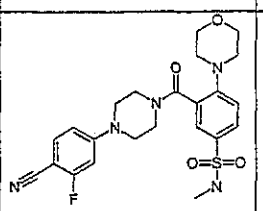
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
125		471.6	3-[4-(4-Cyano-3-fluoro-phenyl)-pipe razine-1-carbonyl]-N-methyl-4-pyrro lidin-1-yl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 5-Methylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	472.2
126		485.6	3-[4-(4-Cyano-3-fluoro-phenyl)-pipe razine-1-carbonyl]-N-ethyl-4-pyrrol idin-1-yl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 5-Ethylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	486.3
127		481.5	(5-Methanesulfonyl-2-pyrrolidin-1-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid	482.2
128		495.6	(5-Ethanesulfonyl-2-pyrrolidin-1-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and 5-Ethanesulfonyl-2-pyrrolidin-1-yl-benzoic acid	496.2

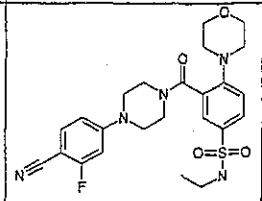
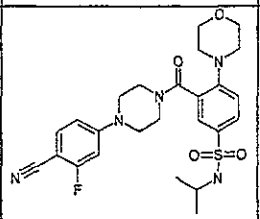
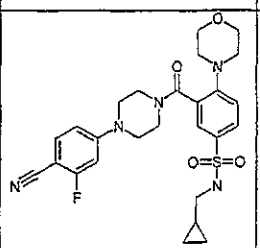
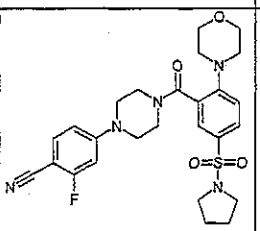
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
129		496.6	N-Methyl-4-pyrrolidin-1-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and 5-Methylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	497.2
130		511.6	(5-Ethanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and 5-Ethanesulfonyl-2-morpholin-1-yl-benzoic acid	512.3
131		512.6	N-Methyl-4-morpholin-4-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and 5-Methylsulfamoyl-2-morpholin-1-yl-benzoic acid	513.3
132		526.6	N-Ethyl-4-morpholin-4-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and 5-Ethylsulfamoyl-2-morpholin-1-yl-benzoic acid	527.2
133		488.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-Methylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	489.2

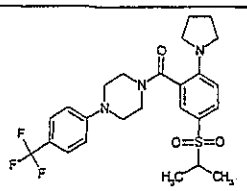
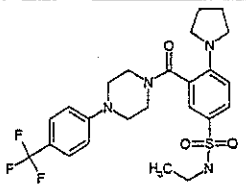
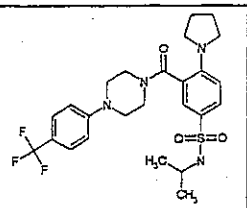
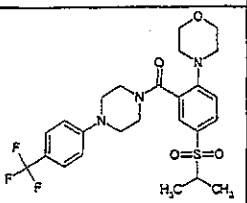
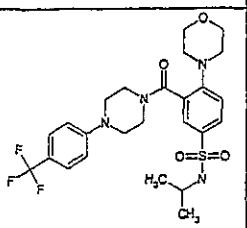
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
134		502.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-ethyl-4-pyrrolidin-1-yl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-Ethylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	503.1
135		503.6	1-{4-[4-(5-Ethanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-Ethanesulfonyl-2-morpholin-4-yl-benzoic acid	504.2
136		509.6	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-pyrrolidin-1-yl-phenyl)-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid	510.2
137		523.7	(5-Ethanesulfonyl-2-pyrrolidin-1-yl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 5-Ethanesulfonyl-2-pyrrolidin-1-yl-benzoic acid	524.3
138		537.7	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-(propane-2-sulfonyl)-2-pyrrolidin-1-yl-phenyl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 5-(Propane-2-sulfonyl)-2-pyrrolidin-1-yl-benzoic acid	538.3

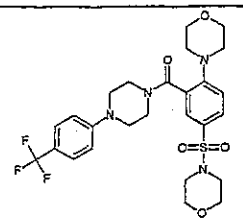
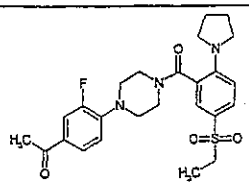
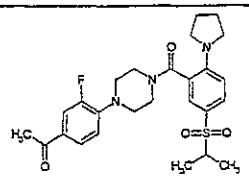
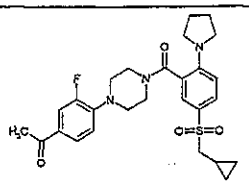
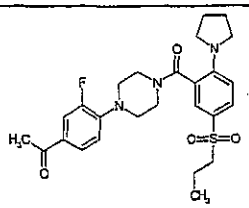
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
139		524.6	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 5-Methylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	525.2
140		538.7	N-Ethyl-3-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-pyrrolidin-1-yl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 5-Ethylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	539.3
141		552.7	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-isopropyl-4-pyrrolidin-1-yl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 5-Isopropylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	553.3
142		525.6	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid	526.2
143		539.6	(5-Ethanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 5-Ethanesulfonyl-2-morpholin-4-yl-benzoic acid	540.3

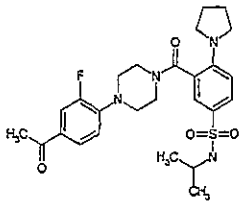
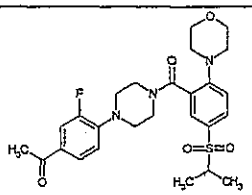
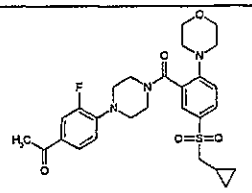
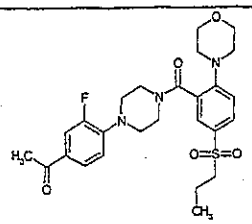
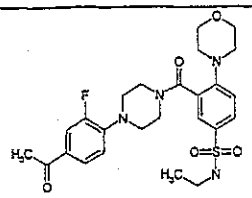
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
144		553.7	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[2-morpholin-4-yl-5-(propane-2-sulfonyl)-phenyl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 2-Morpholin-4-yl-5-(propane-2-sulfonyl)-benzoic acid	554.2
145		540.6	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 5-Methylsulfamoyl-2-morpholin-4-yl-benzoic acid	541.2
146		554.7	N-Ethyl-3-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzenesulfonamide	1 -(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine and 5-Ethylsulfamoyl-2-morpholin-4-yl-benzoic acid	555.2
147		470.6	4-[4-(5-Ethanesulfonyl-2-pyrrolidin -1-yl-benzoyl)-piperazin-1-yl]-2-fl uoro-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 5-Ethanesulfonyl-2-pyrrolidin-1-yl-benzoic acid	471.2
148		499.6	3-[4-(4-Cyano-3-fluoro-phenyl)-pipe razine-1-carbonyl]-N-isopropyl-4-py rrolidin-1-yl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and Isopropylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	500.2

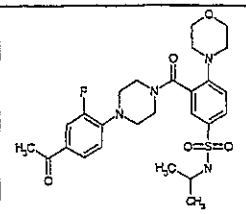
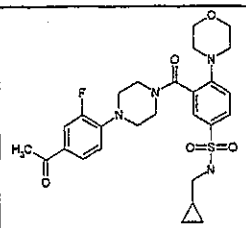
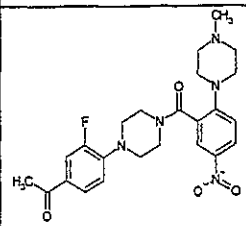
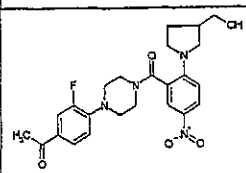
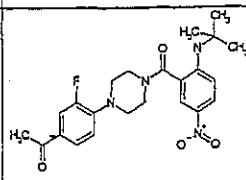
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
149		472.5	2-Fluoro-4-[4-(5-methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid	473.1
150		486.6	4-[4-(5-Ethanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 5-Ethanesulfonyl-2-morpholin-4-yl-benzoic acid	487.3
151		500.6	2-Fluoro-4-{4-[2-morpholin-4-yl-5-(propane-2-sulfonyl)-benzoyl]-piperazin-1-yl}-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 2-Morpholin-4-yl-5-(propane-2-sulfonyl)-benzoic acid	501.2
152		487.6	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 5-Methylsulfamoyl-2-morpholin-4-yl-benzoic acid	488.2

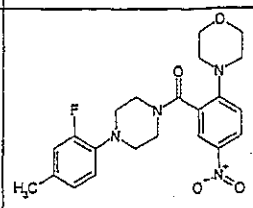
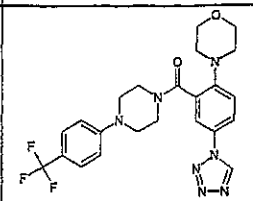
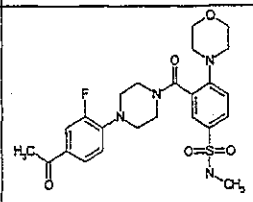
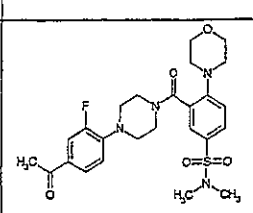
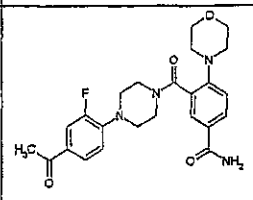
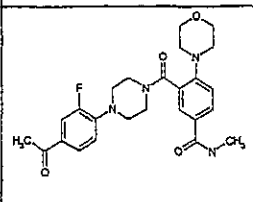
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
153		501.6	3-[4-(4-Cyano-3-fluoro-phenyl)-pipe razine-1-carbonyl]-N-ethyl-4-morpho lin-4-yl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 5-Ethylsulfamoyl-2-morpholin-4-yl-benzoic acid	502.2
154		515.6	3-[4-(4-Cyano-3-fluoro-phenyl)-pipe razine-1-carbonyl]-N-isopropyl-4-mo rpholin-4-yl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and Isopropylsulfamoyl-2-morpholin-1-yl-benzoic acid	516.2
155		527.6	3-[4-(4-Cyano-3-fluoro-phenyl)-pipe razine-1-carbonyl]-N-cyclopropylmet hyl-4-morpholin-4-yl-benzenesulfona mide	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 5-(Cyclopropylmethyl-sulfamoyl)-2-morpholin-4-yl-benzoic acid	528.2
156		527.6	2-Fluoro-4-{4-[2-morpholin-4-yl-5-(pyrrolidine-1-sulfonyl)-benzoyl]-pi perazin-1-yl}-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (Org. Proc. Res. Dev. 1999, 460) and 2-Morpholin-4-yl-5-(pyrrolidine-1-sulfonyl)-benzoic acid	528.2

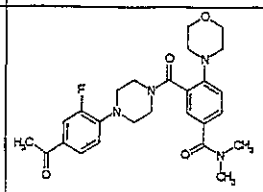
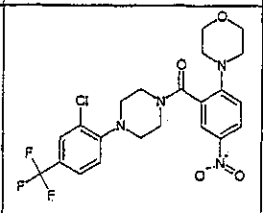
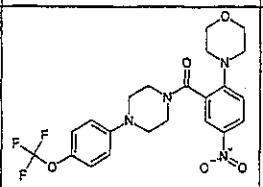
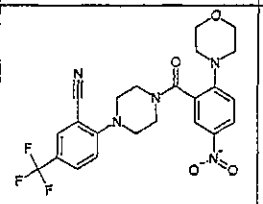
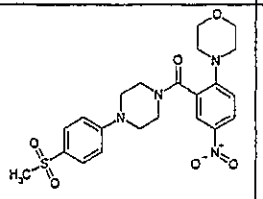
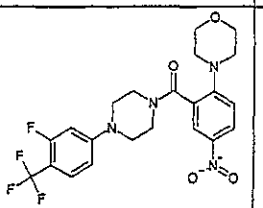
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
157		509.6	[5-(Propane-2-sulfonyl)-2-pyrrolidin-1-yl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and 5-(Propane-2-sulfonyl)-2-pyrrolidin-1-yl-benzoic acid	510.2
158		510.6	N-Ethyl-4-pyrrolidin-1-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and 5-Ethylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	511.3
159		524.6	N-Isopropyl-4-pyrrolidin-1-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and Isopropylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	525.3
160		525.6	[2-Morpholin-4-yl-5-(propane-2-sulfonyl)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and 2-Morpholin-4-yl-5-(propane-2-sulfonyl)-benzoic acid	526.2
161		540.6	N-Isopropyl-4-morpholin-4-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and Isopropylsulfamoyl-2-morpholin-1-yl-benzoic acid	541.3

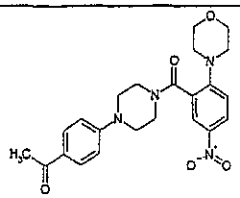
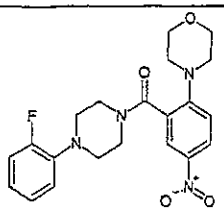
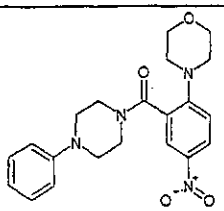
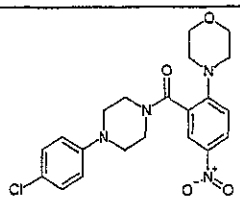
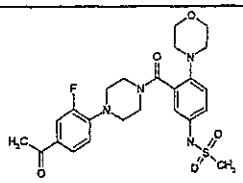
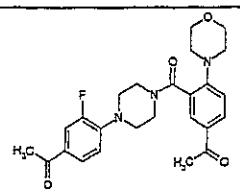
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
162		568.6	[5-(Morpholine-4-sulfonyl)-2-morpholin-4-yl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercially available) and 5-(Morpholine-4-sulfonyl)-2-morpholin-4-yl-benzoic acid	569.3
163		487.6	1-{4-[4-(5-Ethanesulfonyl-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-Ethylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	488.2
164		501.6	1-(3-Fluoro-4-{4-[5-(propane-2-sulfonyl)-2-pyrrolidin-1-yl-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-(Propane-2-sulfonyl)-2-pyrrolidin-1-yl-benzoic acid	502.2
165		513.6	1-{4-[4-(5-Cyclopropylmethanesulfonyl-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-Cyclopropylmethanesulfonyl-2-pyrrolidin-4-yl-benzoic acid	514.3
166		501.6	1-(3-Fluoro-4-{4-[5-(propane-1-sulfonyl)-2-pyrrolidin-1-yl-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-(Propane-1-sulfonyl)-2-pyrrolidin-1-yl-benzoic acid	502.2

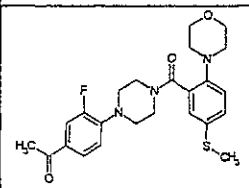
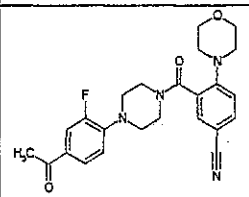
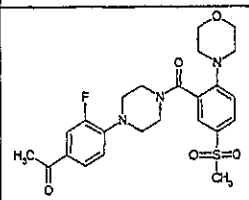
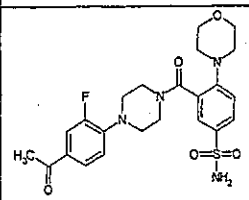
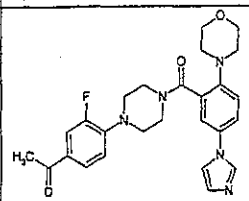
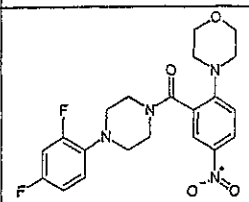
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
167		516.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-isopropyl-4-pyrrolidin-1-yl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and Isopropylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid	517.3
168		517.6	1-(3-Fluoro-4-{4-[2-morpholin-4-yl-5-(propane-2-sulfonyl)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-(Propane-2-sulfonyl)-2-morpholin-1-yl-benzoic acid	518.3
169		529.6	1-{4-[4-(5-Cyclopropylmethanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-Cyclopropylmethanesulfonyl-2-morpholin-4-yl-benzoic acid	530.1
170		517.6	1-(3-Fluoro-4-{4-[2-morpholin-4-yl-5-(propane-1-sulfonyl)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-(Propane-1-sulfonyl)-2-morpholin-1-yl-benzoic acid	518.3
171		518.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-ethyl-4-morpholin-4-yl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-Ethylsulfamoyl-2-morpholin-4-yl-benzoic acid	519.2

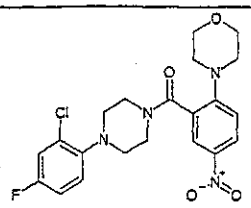
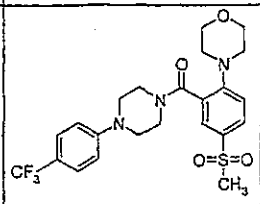
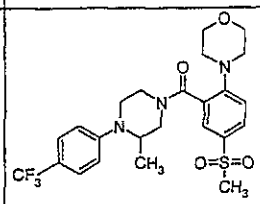
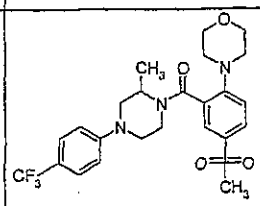
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
172		532.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-isopropyl-4-morpholin-4-yl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and Isopropylsulfamoyl-2-morpholin-1-yl-benzoic acid	533.2
173		544.7	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-cyclopropylmethyl-4-morpholin-4-yl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (comercially available) and 5-(Cyclopropylmethyl-sulfamoyl)-2-morpholin-4-yl-benzoic acid	545.2
174		469.5	1-(4-{4-[2-(4-Methyl-piperazin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and 1-methylpiperazine	471.2
175		470.5	1-(3-Fluoro-4-{4-[2-(3-hydroxymethyl-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-{3-fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and rac-pyrrolidin-3-yl-methanol	472.1
176		442.5	1-{3-Fluoro-4-[4-(2-tert.-butylamino-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{3-fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and tert.-butylamine	443.1

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
177		428.5	[4-(2-Fluoro-4-methyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(2-Fluoro-4-methyl-phenyl)-piperazine and 2-morpholin-4-yl-5-nitro-benzoyl chloride	429.2
178		487.5	(2-Morpholin-4-yl-5-tetrazol-1-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(5-Amino-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	488.2
179		504.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-chloro-N-methyl-benzenesulfonamide and morpholine	503.1
180		518.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N,N-dimethyl-4-morpholin-4-yl-benzenesulfonamide	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-chloro-N,N-dimethyl-benzenesulfonamide and morpholine	519.2
181		454.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzamide	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzoic acid and ammonia	455.2
182		468.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzamide	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzoic acid and methylamine	469.3

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
183		482.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N,N-dimethyl-4-morpholin-4-yl-benzamide	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzoic acid and dimethylamine	483.2
184		498.9	[4-(2-Chloro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(2-Chloro-4-trifluoromethyl-phenyl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	499.2
185		480.4	(2-Morpholin-4-yl-5-nitro-phenyl)-[4-(4-trifluoromethoxy-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethoxy-phenyl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	481.2
186		489.5	2-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile	2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	490.2
187		474.5	[4-(4-Methanesulfonyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(4-Methanesulfonyl-phenyl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	475.1
188		482.4	[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine and 2-Morpholin-4-yl-5-nitro-benzoyl chloride	483.2

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
189		438.5	1-{4-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{4-[4-(2-Fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone and morpholine	439.3
190		414.4	[4-(2-Fluoro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	(2-Fluoro-5-nitro-phenyl)-[4-(2-fluoro-phenyl)-piperazin-1-yl]-methanone and morpholine	415.2
191		396.4	(2-Morpholin-4-yl-5-nitro-phenyl)-(4-phenyl-piperazin-1-yl)-methanone	(2-Fluoro-5-nitro-phenyl)-(4-phenyl-piperazin-1-yl)-methanone and morpholine	397.3
192		430.9	[4-(4-Chloro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	2-morpholin-4-yl-5-nitro-benzoyl chloride and 4-chloro-phenyl-piperazine	449.2
193		504.6	N-{3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-phenyl}-methanesulfonamide	1-{4-[4-(5-Amino-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and methanesulfonyl chloride	505.3
194		453.5	1-{4-[4-(5-Acetyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-{4-[4-(5-Bromo-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and tributyl(1-ethoxyvinyl)tin	454.2

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
195		457.6	1-{3-Fluoro-4-[4-(5-methylsulfanyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	5-Methylsulfanyl-2-morpholin-4-yl-benzoic acid and 1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone	458.2
196		436.5	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzonitrile	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-bromo-benzonitrile and morpholine	437.2
197		489.6	1-{3-Fluoro-4-[4-(5-methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{4-[4-(2-Chloro-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and morpholine	490.2
198		490.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzenesulfonamide	3 -[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-chloro-benzenesulfonamide and morpholine	489.4
199		477.5	1-{3-Fluoro-4-[4-(5-imidazol-1-yl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-{4-[4-(5-Bromo-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and imidazole	478.4
200		432.4	[4-(2,4-Difluoro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	2-Morpholin-4-yl-5-nitro-benzoyl chloride and 1-(2,4-difluorophenyl)-piperazine	433.4

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
201		448.9	[4-(2-Chloro-4-fluoro-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone	2-Morpholin-4-yl-5-nitro-benzoyl chloride and 1-(2-Chloro-4-fluoro-phenyl)-piperazine	449.2
202			5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)piperazin-1-yl]-methanone	Morpholine and (2-Chloro-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]methanone	497.5
203			*rac*-(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[3-methyl-4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	Morpholine and (2-iodo-5- methanesulfonyl-phenyl)-[3-methyl-4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]methanone	512.3
204			*rac*-(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[2-methyl-4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	*rac*-4-(5-Methanesulfonyl-2-morpholin-4-yl-benzoyl)-3-methyl-piperazine-1-carboxylic acid tert-butylester and trifluoroacetic acid then 1-Bromo-4-trifluoromethyl-benzene	512.3

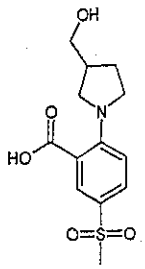
Example 205

4-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-benzoic acid butyl ester

The title compound was prepared according to the procedure described for example 46 from 4-Piperazin-1-yl-benzoic acid butyl ester (CAS: 86620-18-0) and 2-Morpholin-4-yl-5-nitro-benzoyl chloride (example B) (yield :16 %, MS (m/e): 497.3 (M+H, 100%)

Example BU

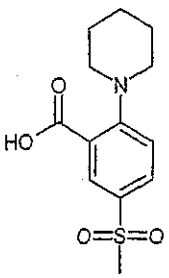
rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl)-5-methanesulfonyl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example Y) from 2-Chloro-5-methanesulfonyl-benzoic acid and rac-pyrrolidin-3-yl-methanol and obtained in 39 % yield. MS (m/e): 298.1 (M-H, 100%).

Example BV

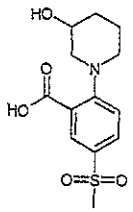
5-Methanesulfonyl-2-piperidin-1-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example Y) from 2-Chloro-5-methanesulfonyl-benzoic acid and piperidine and obtained in 78 % yield. MS (m/e): 282.0 ($M-H^+$ 100%)

Example BW

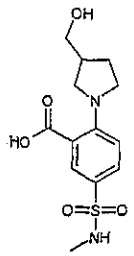
rac-2-(3-Hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoic acid



The title compound was synthesised according to the procedure described for the *synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example Y) from* 2-Chloro-5-methanesulfonyl-benzoic acid and rac-3-hydroxy-piperidine and obtained in 9 % yield. MS (m/e): 298.1 (M-H 100%).

Example BX

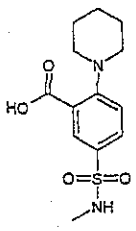
rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl)-5-methylsulfamoyl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example S) from 2-Chloro-5-methylsulfamoyl-benzoic acid and rac-pyrrolidin-3-yl-methanol and obtained in 25 % yield. MS (m/e): 313.0 MH- (100%).

Example BY

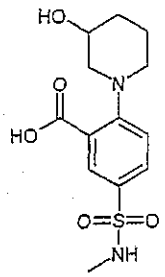
5-Methylsulfamoyl-2-piperidin-1-yl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example S) from 2-Chloro-5-methylsulfamoyl-benzoic acid and piperidine and obtained in 48 % yield. MS (m/e): 297.4 MH- (100%).

Example BZ

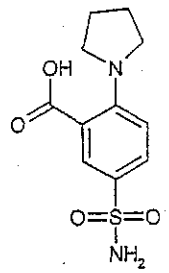
rac-2-(3-Hydroxy-piperidin-1-yl)-5-methylsulfamoyl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example S) from 2-Chloro-5-methylsulfamoyl-benzoic acid and rac-3-hydroxy-piperidine and obtained in 15 % yield. MS (m/e): 312.9 (MH^- 100%).

Example CA

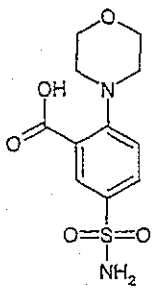
2-Pyrrolidin-1-yl-5-sulfamoyl-benzoic acid



The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example S) from 2-Chloro-5-sulfamoyl-benzoic acid (CAS: 97-04-1; Basu; D.-G.; J.Indian Chem.Soc.; 16; 1939; 100, 106) and pyrrolidine and obtained in 19% yield. MS (m/e): 269.4 (MH^- 100%).

Example CB

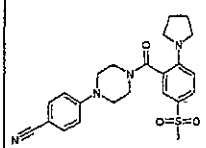
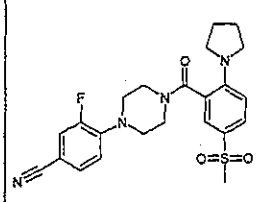
2-Morpholin-4-yl-5-sulfamoyl-benzoic acid

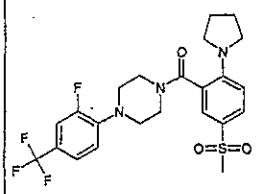
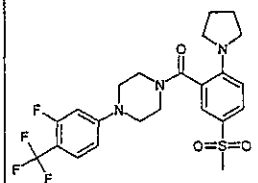
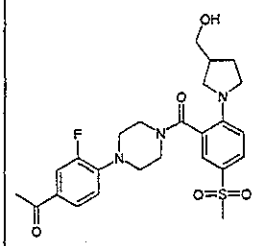
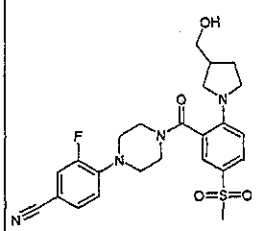


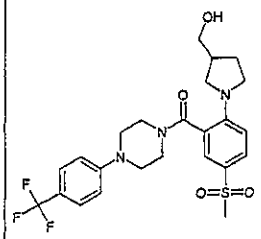
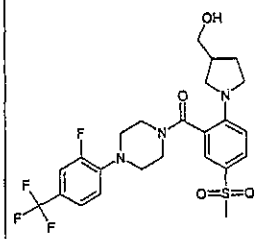
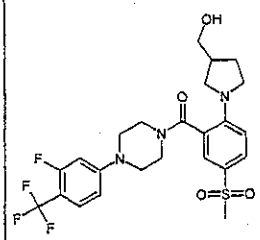
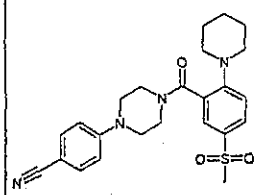
The title compound was synthesised according to the procedure described for the synthesis of 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example S) from 2-Chloro-5-sulfamoyl-benzoic acid (CAS: 97-04-1; Basu; D.-G.; J.Indian Chem.Soc.; 16; 1939; 100, 106) and morpholine and obtained in 85% yield. MS (m/e): 285.1 (MH^- 100%).

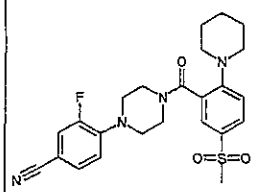
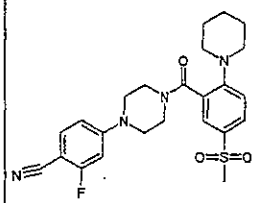
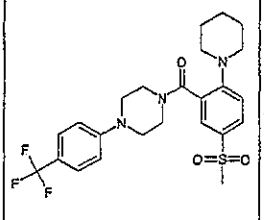
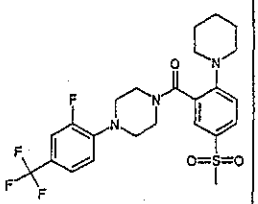
According to the procedure described for the synthesis of Example 123 further derivatives have been synthesised from acid derivatives and piperazine derivatives and comprise Examples 206-279 in Table 2.

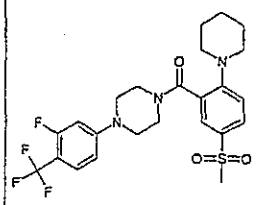
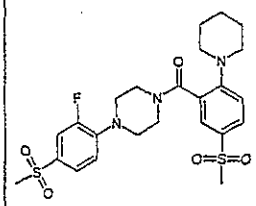
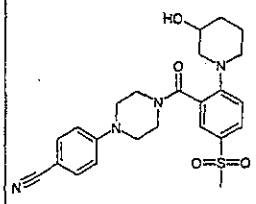
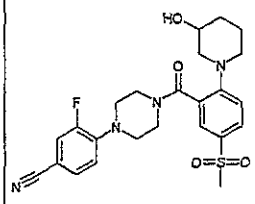
Table 2

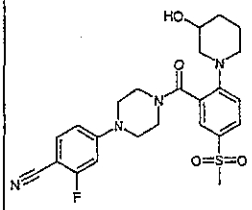
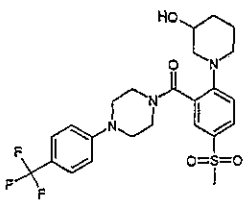
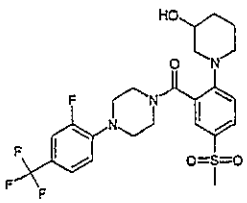
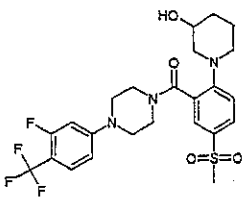
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
206		438.5	4-[4-(5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example Y)	439.3
207		456.5	3-Fluoro-4-[4-(5-methanesulfonyl-2-pyrrolidin-1yl-benzoyl)-piperazin-1-yl]-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example Y)	457.3

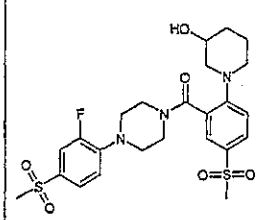
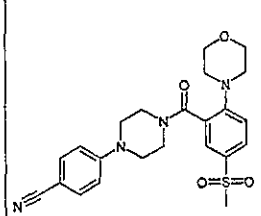
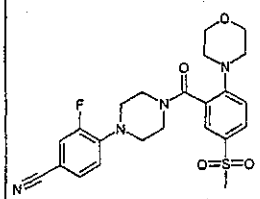
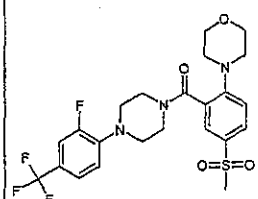
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
208		499.5	[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-pyrrolidin-1-yl-phenyl)-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example Y)	500.2
209		499.5	[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-pyrrolidin-1-yl-phenyl)-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC) and 5-Methanesulfonyl-2-pyrrolidin-1-yl-benzoic acid (Example Y)	500.2
210		503.6	rac-1-(3-Fluoro-4-{4-[2-(3-hydroxymethyl-pyrrolidin-1-yl)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl) -5-methanesulfonyl-benzoic acid (example BU)	504.2
211		486.6	rac-3-Fluoro-4-{4-[2-(3-hydroxymethyl-pyrrolidin-1-yl)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl) -5-methanesulfonyl-benzoic acid (example BU)	487.3

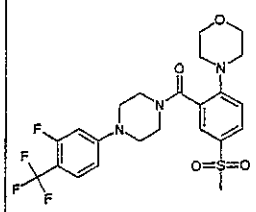
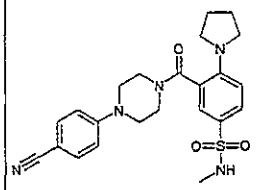
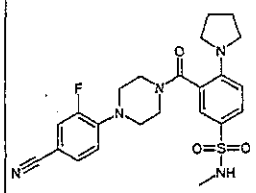
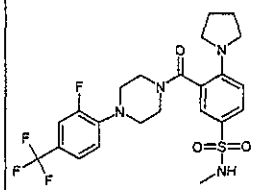
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
212		511.6	rac-[2-(3-Hydroxymethyl-pyrrolidin-1-yl)-5-methanesulfonyl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl) -5-methanesulfonyl-benzoic acid (example BU)	512.4
213		529.6	rac-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[2-(3-hydroxymethyl-pyrrolidin-1-yl)-5-methanesulfonyl-phenyl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl) -5-methanesulfonyl-benzoic acid (example BU)	530.1
214		529.6	rac-[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[2-(3-hydroxymethyl-pyrrolidin-1-yl)-5-methanesulfonyl-phenyl]-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl) -5-methanesulfonyl-benzoic acid (example BU)	530.1
215		452.6	4-[4-(5-Methanesulfonyl-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methanesulfonyl-2-piperidin-1-yl-benzoic acid (example BV)	453.2

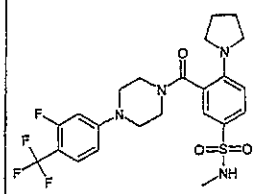
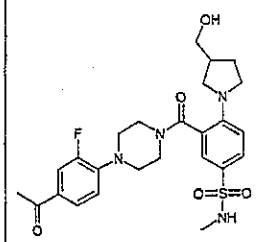
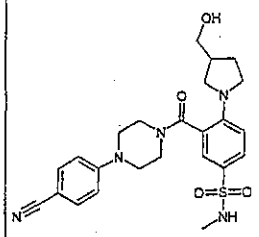
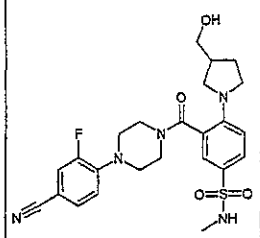
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
216		470.6	3-Fluoro-4-[4-(5-methanesulfonyl-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methanesulfonyl-2-piperidin-1-yl-benzoic acid (example BV)	471.3
217		470.6	2-Fluoro-4-[4-(5-methanesulfonyl-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methanesulfonyl-2-piperidin-1-yl-benzoic acid (example BV)	471.3
218		495.6	(5-Methanesulfonyl-2-piperidin-1-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-piperidin-1-yl-benzoic acid (example BV)	496.3
219		513.6	[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-piperidin-1-yl-phenyl)-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and 5-Methanesulfonyl-2-piperidin-1-yl-benzoic acid (example BV)	514.3

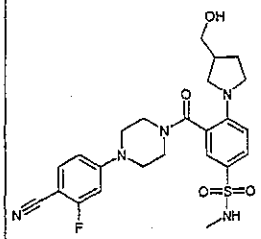
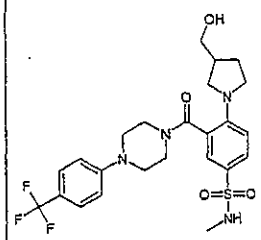
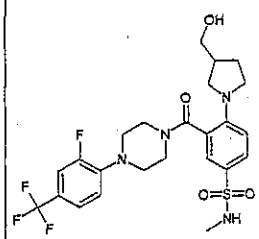
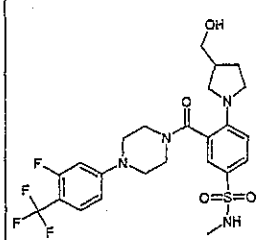
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
220		513.6	[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-piperidin-1-yl-phenyl)-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC) and 5-Methanesulfonyl-2-piperidin-1-yl-benzoic acid (example BV)	514.3
221		523.6	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-piperidin-1-yl-phenyl)-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-piperidin-1-yl-benzoic acid (example BV)	524.3
222		468.6	rac-4-{4-[2-(3-Hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoic acid (example BW)	469.2
223		486.6	rac-3-Fluoro-4-{4-[2-(3-hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoic acid (example BW)	487.3

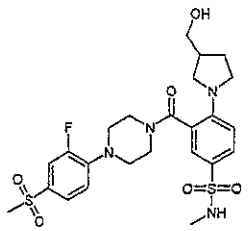
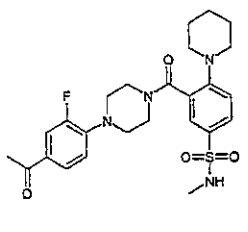
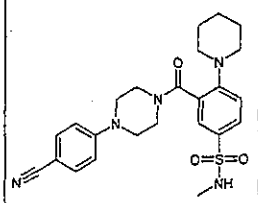
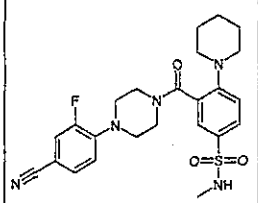
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
224		486.6	rac-2-Fluoro-4-{4-[2-(3-hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoyl] -piperazin-1-yl}-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoic acid (example BW)	487.3
225		511.6	rac-[2-(3-Hydroxy-piperidin-1-yl)-5-methanesulfonyl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoic acid (example BW)	512.4
226		529.6	rac-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[2-(3-hydroxy-piperidin-1-yl)-5-methanesulfonyl-phenyl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoic acid (example BW)	530.1
227		529.6	rac-[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[2-(3-hydroxy-piperidin-1-yl)-5-methanesulfonyl-phenyl]-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoic acid (example BW)	530.1

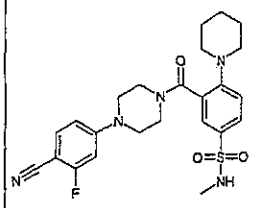
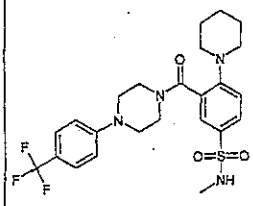
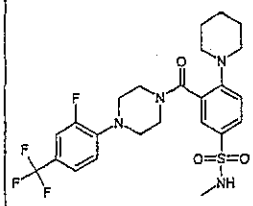
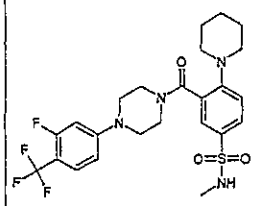
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
228		539.6	rac-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[2-(3-hydroxy-piperidin-1-yl)-5-methanesulfonyl-phenyl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methanesulfonyl-benzoic acid (example BW)	540.3
229		454.5	4-[4-(5-Methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	455.2
230		472.5	3-Fluoro-4-[4-(5-methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	473.2
231		515.5	[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	516.2

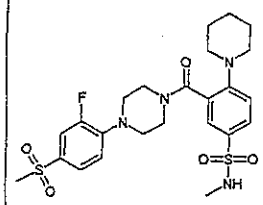
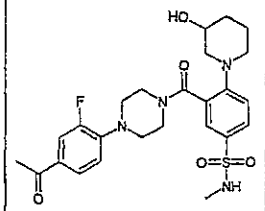
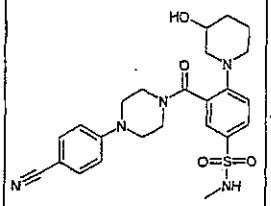
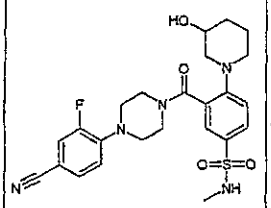
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
232		515.5	[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	516.2
233		453.6	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methylsulfamoyl-2-pyrrolidin-1-yl -benzoic acid (example AC)	454.3
234		471.6	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methylsulfamoyl-2-pyrrolidin-1-yl -benzoic acid (example AC)	472.3
235		514.5	3-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and 5-Methylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid (example AC)	515.3

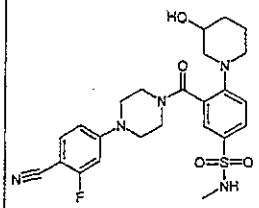
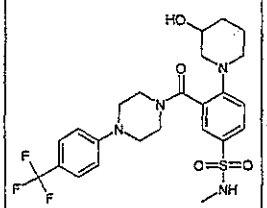
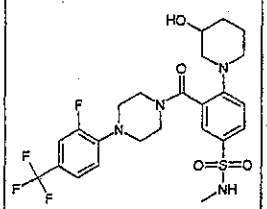
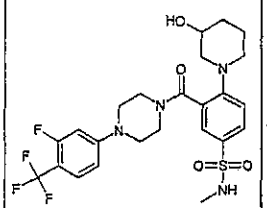
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
236		514.5	3-[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC) and 5-Methylsulfamoyl-2-pyrrolidin-1-yl-benzoic acid (example AC)	515.3
237		518.6	rac-3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxymethyl-pyrrolidin-1-yl)-N-methyl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BX)	519.3
238		483.6	rac-3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxymethyl-pyrrolidin-1-yl)-N-methyl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BX)	484.3
239		501.6	rac-3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxymethyl-pyrrolidin-1-yl)-N-methyl-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl) -5-methylsulfamoyl-benzoic acid (example BX)	502.3

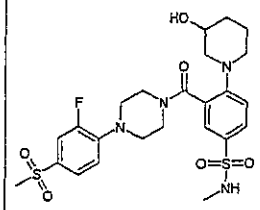
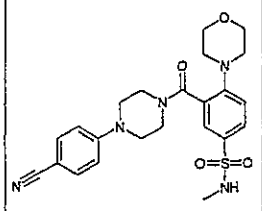
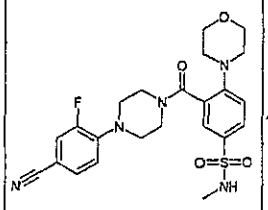
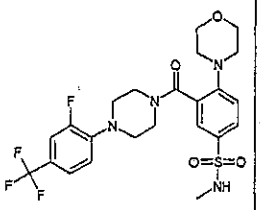
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
240		501.579	rac-3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxymethyl-pyrrolidin-1-yl)-N-methyl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl) -5-methylsulfamoyl-benzoic acid (example BX)	502.3
241		526.6	rac-4-(3-Hydroxymethyl-pyrrolidin-1-yl) -N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BX)	527.3
242		544.6	rac-3-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxymethyl-pyrrolidin-1-yl)-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl) -5-methylsulfamoyl-benzoic acid (example BX)	545.3
243		544.6	rac-3-[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxymethyl-pyrrolidin-1-yl)-N-methyl-benzenesulfonamide	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BX)	545.3

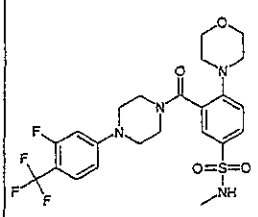
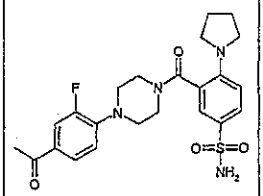
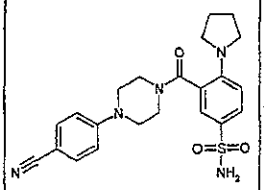
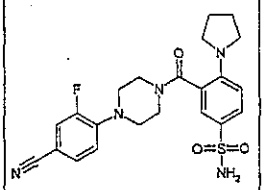
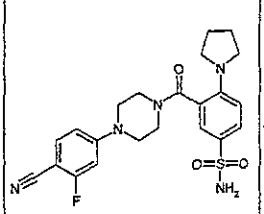
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
244		554.7	rac-3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxymethyl-pyrrolidin-1-yl)-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and rac-2-(3-Hydroxymethyl-pyrrolidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BX)	555.2
245		502.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 5-Methylsulfamoyl-2-piperidin-1-yl-benzoic acid (example BY)	503.2
246		467.6	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methylsulfamoyl-2-piperidin-1-yl-benzoic acid (example BY)	468.2
247		485.6	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methylsulfamoyl-2-piperidin-1-yl-benzoic acid (example BY)	486.3

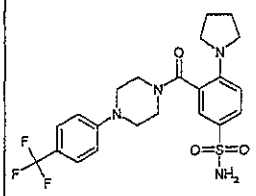
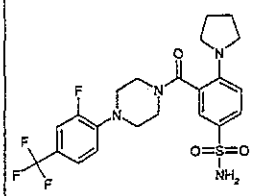
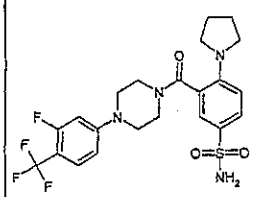
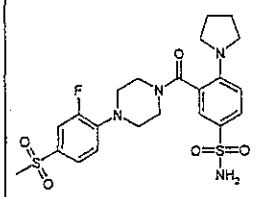
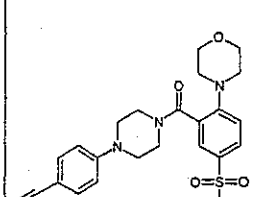
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
248		485.58	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methylsulfamoyl-2-piperidin-1-yl-benzoic acid (example BY)	486.3
249		510.6	N-Methyl-4-piperidin-1-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 5-Methylsulfamoyl-2-piperidin-1-yl-benzoic acid (example BY)	511.4
250		528.6	3-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and 5-Methylsulfamoyl-2-piperidin-1-yl-benzoic acid (example BY)	529.2
251		528.6	3-[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC)and 5-Methylsulfamoyl-2-piperidin-1-yl-benzoic acid (example BY)	529.2

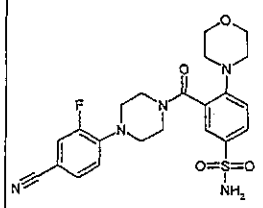
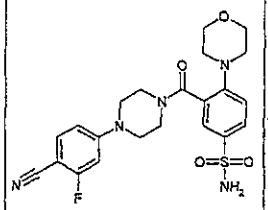
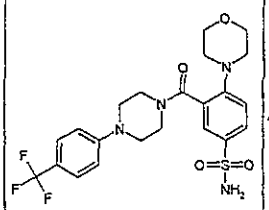
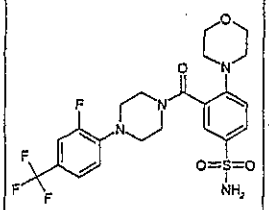
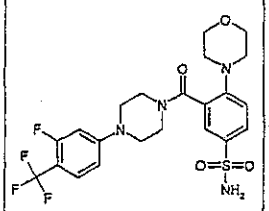
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
252		538.7	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methylsulfamoyl-2-piperidin-1-yl-benzoic acid (example BY)	539.3
253		518.6	rac-3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxy-piperidin-1-yl)-N-methyl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BZ)	519.3
254		483.6	rac-3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxy-piperidin-1-yl)-N-methyl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BZ)	484.3
255		501.6	rac-3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxy-piperidin-1-yl)-N-methyl-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BZ)	502.3

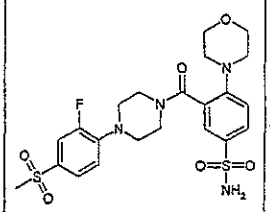
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
256		501.6	rac-3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxy-piperidin-1-yl)-N-methyl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BZ)	502.2
257		526.6	rac-4-(3-Hydroxy-piperidin-1-yl)-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BZ)	527.3
258		544.6	rac-3-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxy-piperidin-1-yl)-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BZ)	545.3
259		544.6	rac-3-[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxy-piperidin-1-yl)-N-methyl-benzenesulfonamide	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BZ)	545.3

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
260		554.7	rac-3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-(3-hydroxy-piperidin-1-yl)-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and rac-2-(3-Hydroxy-piperidin-1-yl)-5-methylsulfamoyl-benzoic acid (example BZ)	555.2
261		469.6	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methylsulfamoyl-2-morpholin-4-yl-benzoic acid (example AL)	470.2
262		487.6	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methylsulfamoyl-2-morpholin-4-yl-benzoic acid (example AL)	488.2
263		530.5	3-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and 5-Methylsulfamoyl-2-morpholin-4-yl-benzoic acid (example AL)	531.2

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
264		530.5	3-[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC) and 5-Methylsulfamoyl-2-morpholin-4-yl-benzoic acid (example AL)	531.2
265		474.6	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-pyrrolidin-1-yl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 2-Pyrrolidin-1-yl-5-sulfamoyl-benzoic acid (example CA)	475.2
266		439.5	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-pyrrolidin-1-yl-benzene sulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 2-Pyrrolidin-1-yl-5-sulfamoyl-benzoic acid (example CA)	440.3
267		457.5	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-pyrrolidin-1-yl-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 2-Pyrrolidin-1-yl-5-sulfamoyl-benzoic acid (example CA)	458.3
268		457.6	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-pyrrolidin-1-yl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-Pyrrolidin-1-yl-5-sulfamoyl-benzoic acid (example CA)	458.3

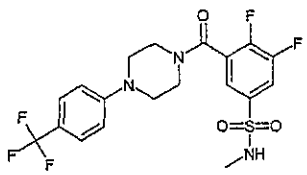
No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
269		482.5	4-Pyrrolidin-1-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-Pyrrolidin-1-yl-5-sulfamoyl-benzoic acid (example CA)	483.2
270		500.5	3-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-pyrrolidin-1-yl-enzenesulfonamide	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and 2-Pyrrolidin-1-yl-5-sulfamoyl-benzoic acid (example CA)	501.2
271		500.5	3-[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-pyrrolidin-1-yl-enzenesulfonamide	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC) and 2-Pyrrolidin-1-yl-5-sulfamoyl-benzoic acid (example CA)	501.2
272		510.6	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-pyrrolidin-1-yl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Pyrrolidin-1-yl-5-sulfamoyl-benzoic acid (example CA)	511.3
273		455.5	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 2-Morpholin-4-yl-5-sulfamoyl-benzoic acid (example CB)	456.2

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
274		473.5	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 2-Morpholin-4-yl-5-sulfamoyl-benzoic acid (example CB)	474.1
275		473.5	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-Morpholin-4-yl-5-sulfamoyl-benzoic acid (example CB)	474.2
276		498.5	4-Morpholin-4-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-Morpholin-4-yl-5-sulfamoyl-benzoic acid (example CB)	499.3
277		516.5	3-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzenesulfonamide	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H) and 2-Morpholin-4-yl-5-sulfamoyl-benzoic acid (example CB)	517.2
278		516.5	3-[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzenesulfonamide	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example BC) and 2-Morpholin-4-yl-5-sulfamoyl-benzoic acid (example CB)	517.2

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
279		526.6	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-morpholin-4-yl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Morpholin-4-yl-5-sulfamoyl-benzoic acid (example CB)	527.2

Example CC

3,4-Difluoro-N-methyl-5-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide



(a) 5-Chlorosulfonyl-2,3-difluoro-benzoic acid

To 2,3-difluoro-benzoic acid (3g) was added to a solution of chlorosulfonic acid and the reaction mixture was stirred for 2 hours at room temperature. After such time, the reaction mixture was poured onto ice. The resulting solid precipitate was then filtered off and dried *in vacuo* to yield the title compound as a light grey solid (4.8 g, mp = 109-114°C, MS (EI): 256.0 (M^+) and was used directly in the next step without any further purification.

(b)-2,3-Difluoro-5-methylsulfamoyl-benzoic acid

To a solution of 5-chlorosulfonyl-2,3-difluoro-benzoic acid (400 mg) in dichloromethane (5 mL) at -10°C was added a solution of methylamine in ethanol (8M). The reaction mixture was then stirred at -10°C for 5 minutes and poured over 1N NaOH solution. The aqueous phase was extracted with diethyl ether twice and then acidified with a concentrated solution of HCl. The aqueous phase was then extracted 3 times with a mixture of dichoromethane:ethanol (9:1) and the combined organic layer were dried

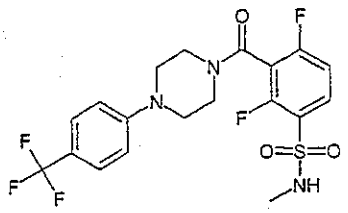
over sodium sulfate and concentrated *in vacuo* to yield the title compound as a light brown solid (390 mg, mp=191-194°C, MS (m/e): 250.1 (M-H, 100%).

(c) 3,4-Difluoro-N-methyl-5-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide

The title compound was prepared in analogy to Example BO by reaction of 2,3-Difluoro-5-methylsulfamoyl-benzoic acid and 1-(4-trifluromethylphenyl)piperazine (ABCR F07741NB, [30459-17-7]) to yield the title compound as a light yellow amorpous solid. (m/e): 462.1 (M-H, 100%).

Example CD

2,4-Difluoro-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide



The title compound was prepared in analogy to Example CC using 3-chlorosulfonyl-2,6-difluoro-benzoic acid [142576-91-8] to yield the title compound as a light brown solid (m/e): 462.3 (M-H, 100%).

Example 280

(5-Methanesulfonyl-2-thiomorpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

The title compound was prepared according to the procedure described for example 202 from (2-Chloro-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (example BO) and thiomorpholine to yield the title compound as a pale yellow solid. MS (m/e): 514.5 (M+H, 100%).

Example 281

3-Fluoro-N-methyl-4-morpholin-4-yl-5-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide

The title compound was prepared according to the procedure described for example 202 from 3,4-Difluoro-N-methyl-5-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide (example CC) and morpholine to yield the title compound as a colourless foam, MS (m/e): 531.1 (M+H, 100%).

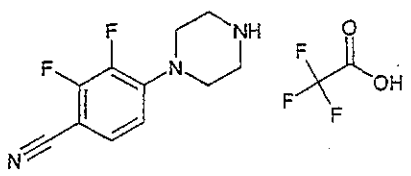
Example 282

2-Fluoro-N-methyl-4-morpholin-4-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide

The title compound was prepared according to the procedure described for example 202 from 2,4-Difluoro-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide (example CD) and morpholine to yield the title compound as a colourless foam, MS (m/e): 529.3 (M+H, 100%).

Example CE

2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid



(a) 4-(4-Cyano-2,3-difluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

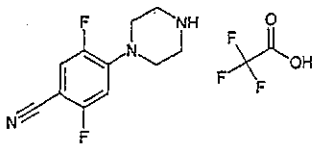
To a solution of *N*-Boc-Piperazine (0.65 g) in DMA (20 mL) was slowly added a solution of 2,3,4-trifluorobenzonitrile (0.49 g) in DMA (10 mL). The reaction mixture was stirred for 2 hours at 80°C. After such time the solvent was removed *in vacuo* and purified by column chromatography (SiO_2) to yield the title compound as white solid (0.76 g).

(b) 2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid

To a solution of 4-(4-Cyano-2,3-difluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (0.72 g) in dichloromethane (5 mL) was added trifluoroacetic acid and the reaction mixture was stirred at room temperature for 30 minutes. After such time the reaction mixture was concentrated *in vacuo* to yield the title compound (0.63 g). MS (m/e): 224.3 ($M+H^+$, 100%).

Example CF

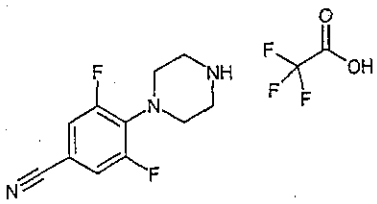
2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid



Example CF was prepared in analogy to Example CE using 2,4,5-trifluorobenzonitrile. MS (m/e): 224.3 ($M+H^+$, 100%).

Example CG

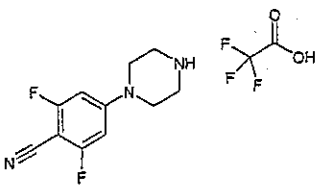
3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid



Compound CG was prepared in analogy to compound CE using 3,4,5-trifluorobenzonitrile. MS (m/e): 224.1 ($M+H^+$, 100%).

Example CH

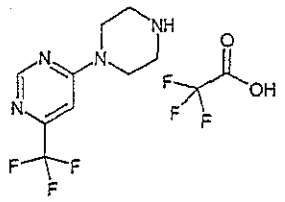
2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid



Compound CH was prepared in analogy to compound CE using 2,4,6-trifluorobenzonitrile. MS (m/e): 224.1 ($M+H^+$, 100%).

Example CI

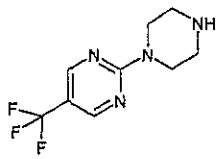
4-Piperazin-1-yl-6-trifluoromethyl-pyrimidine trifluoro-acetic acid



Compound CI was prepared in analogy to compound CE using 4-chloro-6-trifluoromethyl-pyrimidine [37552-81-1]. MS (m/e): 233.1 ($M+H^+$).

Example *CJ*

2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine



(a) 2-(4-Benzyl-piperazin-1-yl)-5-trifluoromethyl-pyrimidine

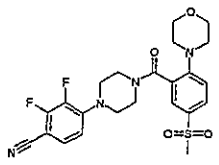
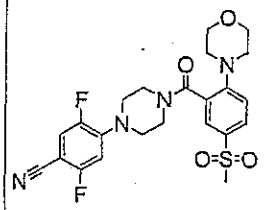
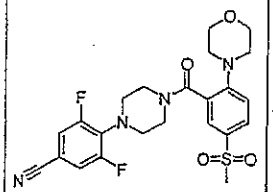
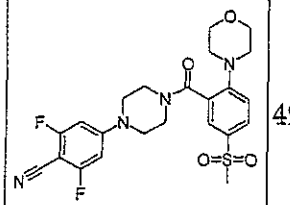
To a solution of (3-Dimethylamino-2-trifluoromethyl-allylidene)-dimethyl-ammonium chloride ([176214-18-9], 0.60 g) in acetonitrile (10 mL) was added 4-Benzyl-piperazine-1-carboxamidine hydrochloride ([7773-69-5], 0.66 g) and triethylamine (0.87 mL) and the reaction mixture was stirred for 3 hours at room temperature. After such time the reaction mixture was concentrated *in vacuo* and purified by column chromatography to yield the title compound as a light yellow solid (0.79 g). MS (m/e): 323.4 ($M+H^+$).

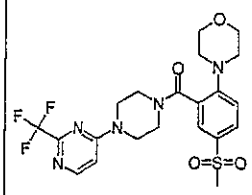
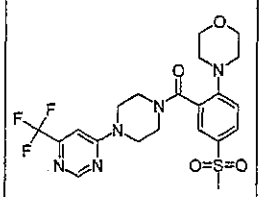
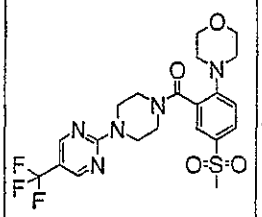
(b) 2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine

To a solution of 2-(4-Benzyl-piperazin-1-yl)-5-trifluoromethyl-pyrimidine (0.63 g) in methanol was added Palladium-C (Degussa E101N; 5%) and the reaction mixture was heated at 60°C under hydrogen atmosphere. The reaction mixture was then allowed to cool down to room temperature, the catalyst was filtered of and solvent was removed *in vacuo* to yield the title compound as a colorless solid (0.41 g). MS (m/e): 233.1 ($M+H^+$).

According to the procedure described for the synthesis of Example 123 further derivatives have been synthesised from acid derivatives and piperazine derivatives and comprise Examples 283-289 in Table 3.

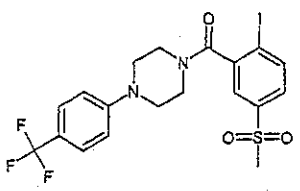
Table 3

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
283		490.528	2,3-Difluoro-4-[4-(5-methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid (compound CE) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	491.1
284		490.528	2,5-Difluoro-4-[4-(5-methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound CF) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	491.1
285		490.528	3,5-Difluoro-4-[4-(5-methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound CG) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	491.1
286		490.528	2,6-Difluoro-4-[4-(5-methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound CH) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	508.4 ($M+NH_4^+$)

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
287		499.51	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(2-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone	4-Piperazin-1-yl-2-trifluoromethyl-pyrimidine trifluoro-acetic acid (WO030249) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	500.4
288		499.51	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone	4-Piperazin-1-yl-6-trifluoromethyl-pyrimidine trifluoro-acetic acid (compound CI) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	500.3
289		499.511	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine (compound CJ) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	500.3

Example CK

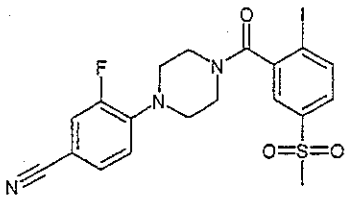
(2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone



Example CK was prepared in analogy to Example 123 from 2-Iodo-5-methanesulfonyl-benzoic acid (example BQ) and 1-(4-Trifluoromethyl-phenyl)-piperazine (commercial). MS (m/e): 539.1 ($M+H^+$, 100%).

Example CL

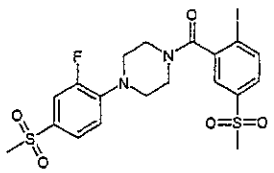
3-Fluoro-4-[4-(2-iodo-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile



Example CL was prepared in analogy to Example 123 from 2-Iodo-5-methanesulfonyl-benzoic acid (example BQ) and 3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414). MS (m/e): 514.0 ($M+H^+$, 100%).

Example CM

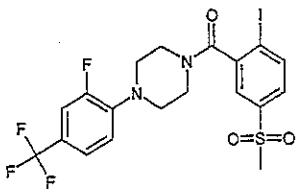
[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-iodo-5-methanesulfonyl-phenyl)-methanone



Example CM was prepared in analogy to Example 123 from 2-Iodo-5-methanesulfonyl-benzoic acid (example BQ) and 1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial). MS (m/e): 567.0 ($M+H^+$, 100%).

Example CN

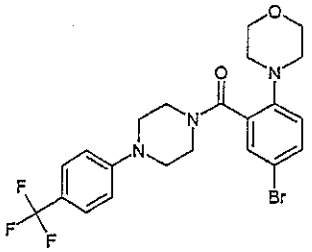
[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-iodo-5-methanesulfonyl-phenyl)-methanone.



Example CN was prepared in analogy to Example 123 from 2-Iodo-5-methanesulfonyl-benzoic acid (example BQ) and 1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (example H). MS (m/e): 574.2 ($M+NH_4^+$, 100%).

Example CR

(5-Bromo-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone



Example CR was prepared in analogy to Example 46 from 5-Bromo-2-morpholin-4-yl-benzoyl chloride (example BI) and 1-(4-Trifluoromethyl-phenyl)-piperazine (commercial). MS (m/e): 500.1 ($M+H^+$, 100%).

Example 290

(2-Imidazol-1-yl-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

The title compound was prepared according to the procedure described for example 199 from (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound CK) and imidazole (20%, light grey solid , MS (m/e): 479.2 (M+H, 100%)

Example 291

5-Methanesulfonyl-2-(2-methyl-imidazol-1-yl)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

The title compound was prepared according to the procedure described for example 199 from (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound CK) and 2-methyl-imidazole (10% yield, yellow solid , MS (m/e): 493.1 (M+H, 100%)

Example 292

[5-Methanesulfonyl-2-(4-methyl-imidazol-1-yl)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

The title compound was prepared according to the procedure described for example 199 from (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound CK) and 4-Methyl-1H-imidazole (32% yield, white solid , MS (m/e): 493.4 (M+H, 100%)

Example 293

[[5-(2-Cyclopropyl-imidazol-1-yl)-2-morpholin-4-yl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

The title compound was prepared according to the procedure described for example 199 from (5-Bromo-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound CR) and 2-Cyclopropyl-1H-imidazole (CAS: 89532-38-7) (16% yield, white solid , MS (m/e): 526.3(M+H, 100%)

Example 294

(5-Methanesulfonyl-2-pyrazol-1-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

In a tube were added successively (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound CK, 0.1 g, 0.19 mmol), pyrazole (15 mg, 0.223 mmol), potassium carbonate (51 mg, 0.37 mmol), CuI (7 mg, 0.037 mmol), Trans-1,2-diaminocyclohexane (9 ul, 0.07 mmol) and dioxane (0.4 ml). The mixture was heated under argon at 120°C for 24 hours. The reaction mixture was cooled to room temperature and quenched with water/dichloromethane. The aqueous layer was extracted twice with dichloromethane. The organic layers were combined, dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude oil was chromatographed over silicagel: eluent: heptane/ethylacetate: 0-5% to provide the title compound as a light grey powder (19 mg, 21%), MS (m/e): 479.1 (M+H, 100%)

Example 295

[5-Methanesulfonyl-2-(3-methyl-pyrazol-1-yl)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

The title compound was prepared according to the procedure described for example 294 from (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-

yl]-methanone (compound CK) and 3-Methyl-1H-pyrazole (15%yield, white solid , MS (m/e): 493.5 (M+H, 100%)

Example 296

[5-Methanesulfonyl-2-(4-methyl-pyrazol-1-yl)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

The title compound was prepared according to the procedure described for example 294 from (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound CK) and 4-Methyl-1H-pyrazole (43 %yield, white solid , MS (m/e): 493.1 (M+H, 100%)

Example 297

3-Fluoro-4-{4-[5-methanesulfonyl-2-(4-methyl-pyrazol-1-yl)-benzoyl]-piperazin-1-yl}-benzonitrile

The title compound was prepared according to the procedure described for example 294 . from 3-Fluoro-4-[4-(2-iodo-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile (compound CL) and 4-Methyl-1H-pyrazole (20% yield, white foam , MS (m/e): 468.3 (M+H, 100%)

Example 298

[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(4-methyl-pyrazol-1-yl)-phenyl]-methanone

The title compound was prepared according to the procedure described for example 294 from [4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-iodo-5-methanesulfonyl-phenyl)-methanone (compound CM) and 4-Methyl-1H-pyrazole (29% yield, yellow foam, MS (m/e): 521.3(M+H, 100%)

Example 299

[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(4-methyl-pyrazol-1-yl)-phenyl]-methanone

The title compound was prepared according to the procedure described for example 294 from [4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-iodo-5-methanesulfonyl-phenyl)-methanone (compound CN) and 4-Methyl-1H-pyrazole (30% yield, light brown solid, MS (m/e): 511.2(M+H, 100%)

Example 300

(5-Methanesulfonyl-2-[1,2,4]triazol-1-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

In a tube were added successively (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound CK, 0.1 g, 0.19 mmol), 1,2,4-triazole (11 mg, 0.155 mmol), potassium phosphate (71 mg, 0.326 mmol), CuI (7 mg, 0.037 mmol), (1R,2R)-diaminomethylcyclohexane (2.3 mg, 0.015 mmol) and DMF (1 ml). The mixture was heated under argon at 120°C for 24 hours. The reaction mixture was cooled to room temperature and quenched with water/dichloromethane. The aqueous layer was extracted twice with dichloromethane. The organic layers were combined, dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude oil was chromatographed over silicagel: eluent: heptane/ethylacetate: 0-100% to provide the title compound as a light grey solid (5 mg, 6%), MS (m/e): 480.4 (M+H, 100%)

Example 301

(2-Cyclobutylamino-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

A solution of (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound CK, 0.05 g, 0.09 mmol) and of cyclobutylamine (0.1 ml) in dimethylacetamide was heated in a microwave oven (180 deg) for 10 min before being concentrated *in vacuo*. The residue was disolve in ethyl acetate, washed with water dried over sodiumsulfate, filtered and concentrated. The residue was purified by column chromatography (SiO_2, 5 g, Heptane/EtOAc 0-50%) to give the title compound as a white foam (24 mg, 54%). MS (m/e): 482.5 ($M+H^+$, 100%).

Example 302

[2-(Cyclopropylmethyl-amino)-5-methanesulfonyl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

The title compound was prepared according to the procedure described for example 301 from (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound CK) and Cyclopropanemethylamine (40% yield, white foam, MS (m/e): 482.5 (M+H, 100%)

Example 303

(2-Isobutylamino-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

The title compound was prepared according to the procedure described for example 301 from (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound CK) and and Isobutylamine (49% yield, off white foam, MS (m/e): 484.5 (M+H, 100%)

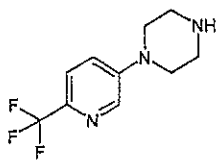
Example 304

rac-{5-Methanesulfonyl-2-[(tetrahydro-furan-2-ylmethyl)-amino]-phenyl}-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

The title compound was prepared according to the procedure described for example 301 from (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound CK) and tetrahydrofurfurylamine (28% yield, MS (m/e): 512.4 (M+H, 100%)

Example CO

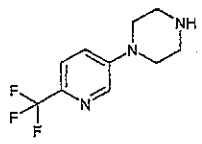
1-(6-Trifluoromethyl-pyridin-3-yl)-piperazine



The compound was prepared in analogy to example H from 5-Bromo-2-trifluoromethyl-pyridine [436799-32-5]. MS (m/e): 232.1 ($M+H^+$, 100%)

Example CP

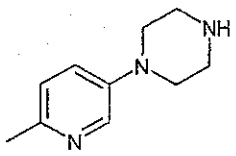
1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine



The compound was prepared in analogy to example CE from 2,3-Difluoro-5-trifluoromethyl-pyridine (EP0104715). MS (m/e): 250.2 (MH^+, 100%)

Example CQ

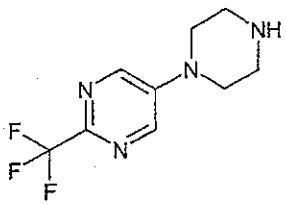
1-(6-Methyl-pyridin-3-yl)-piperazine



The compound was prepared in analogy to example H from 5-Bromo-2-methyl-pyridine (commercial). MS (m/e): 178.1 ($M+H^+$, 100%)

Example CS

5-Piperazin-1-yl-2-trifluoromethyl-pyrimidine



(a) 5-Chloro-2-trifluoromethyl-pyrimidine

To a solution of 38 mmol trifluoroacetamidine in 70 ml acetonitrile was added 37.92 mmol ((Z)-2-Chloro-3-dimethylamino-allylidene)-dimethyl-ammonium hexafluoro phosphate (CAS: 291756-76-8) followed by 45.5 mmol triethylamine. The yellow solution was stirred at room temperature for 5 hours, then poured onto water and extracted 3 times with ether. The combined extracts were dried over sodium sulfate, filtered and distilled at 760 mm Hg to provide the title compound. MS (m/e): 182.2 (M^+, 100%)

(b) 4-(2-Trifluoromethyl-pyrimidin-5-yl)-piperazine-1-carboxylic acid tert-butyl ester

0.26 mmol 5-Chloro-2-trifluoromethyl-pyrimidine was added to 0.26 mmol piperazine-1-carboxylic acid tert-butyl ester in 1.5 ml dimethylacetamide and the reaction mixture

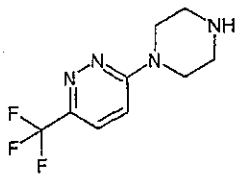
was stirred at 150°C for 10 min. in a microwave oven. After such time the reaction mixture was concentrated and the residue was then purified by column chromatography (SiO_2, Heptane/EtOAc) to yield the title compound. MS (m/e): 333.2 ($M+H^+$, 100%)

(c) 5-Piperazin-1-yl-2-trifluoromethyl-pyrimidine

The title compound was prepared in analogy to Example H from 4-(2-trifluoromethyl-pyrimidin-5-yl)-piperazine-1-carboxylic acid tert-butyl ester MS (m/e): 233.0 ($M+H^+$, 100%)

Example CT

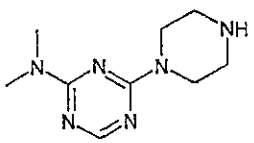
3-Piperazin-1-yl-6-trifluoromethyl-pyridazine



The title compound was prepared in analogy to Example CS (b-c) from 3-Chloro-6-trifluoromethyl-pyridazine (CAS: 258506-68-2). MS (m/e): 233.0 ($M+H^+$, 100%)

Example CU

Dimethyl-(4-piperazin-1-yl-[1,3,5]triazin-2-yl)-amine



(a) 4-(4-Chloro-[1,3,5]triazin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

A solution of 11 mmol of 2,4-dichlorotriazine (WO 02/083654) in 20ml of acetonitrile was chilled and treated with 11 mmol of triethylamine and 11 mmol of N-BOC-piperazine. The reaction mixture was stirred for 2 hours at 0° C then for 2 hours at room temperature. Addition of 100ml brine and extraction with ethyl acetate yielded the crude product which was purified through trituration in ethyl acetate. MS (m/e): 300.3 (MH^+, 100%)

(b) 4-(4-Dimethylamino-[1,3,5]triazin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

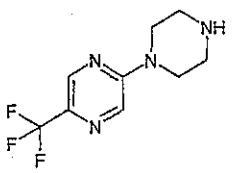
A solution of 2 mmol of 4-(4-Chloro-[1,3,5]triazin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 15 ml of 2M dimethylamine in methanol was stirred at room temperature for 1 hour. Concentration and purification by chromatography (SiO_2; ethyl acetate / cyclohexane 1:1) yielded the title compound as a colorless solid. MS (m/e): 309.1 (MH^+, 100%)

(c) Dimethyl-(4-piperazin-1-yl-[1,3,5]triazin-2-yl)-amine

A solution of 1 mmol of 4-(4-Dimethylamino-[1,3,5]triazin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 10 ml dichloromethane was chilled and treated with 14 mmol of trifluoroacetic acid. The reaction mixture was heated to 40° C for 30 min. After cooling, 50ml of 2M aqueous sodium hydroxide is added. The organic layer was separated, dried and concentrated to yield the title compound as a yellowish oil. MS (m/e): 267.0 ($M+CH_3COO^+$, 100%)

Example CV

5'-Trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl



(a) 2-Bromo-5-trifluoromethyl-pyrazine

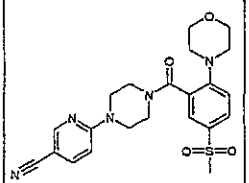
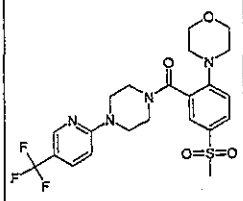
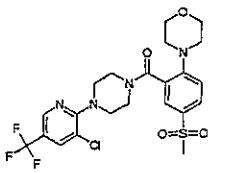
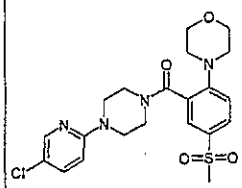
To a suspension of 0.423 mmol copper (II) bromide in THF (1 ml) was added dropwise 0.51 mmol tert-butylnitrite at 0°C within 2 minutes. 0.37 mmol 5-Trifluoromethyl-pyrazin-2-ylamine (CAS: 69816-38-2; WO9518097) in solution in THF (0.5 ml) was added dropwise within 5 minutes at 0°C. The mixture was stirred at 0°C for 1 hour, at room temperature for 21 hours and quenched with water. The aqueous phase was extracted with ether. The combined extracts were dried over sodium sulfate and filtered and concentrated at atmospheric pressure. The residue was then purified by column chromatography (SiO_2, ether) to yield the title compound.

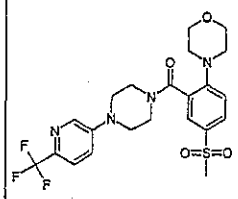
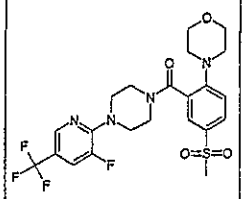
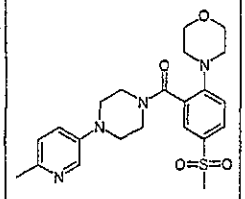
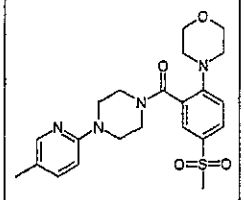
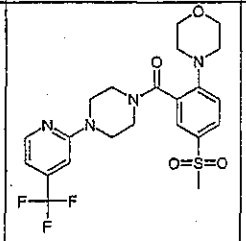
(b) 5'-Trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl

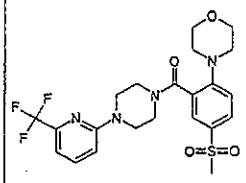
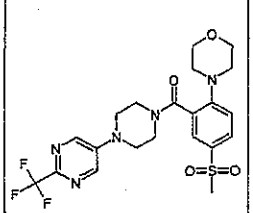
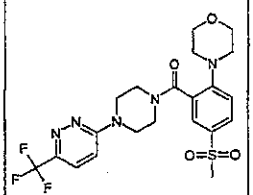
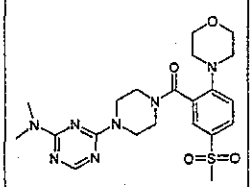
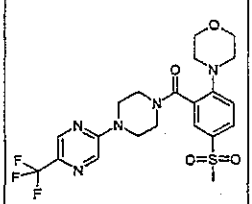
The title compound was prepared in analogy to Example CS (b-c) from 2-Bromo-5-trifluoromethyl-pyrazine MS (m/e): 233.0 ($M+H^+$, 100%)

According to the procedure described for the synthesis of Example 123 further derivatives have been synthesised from acid derivatives and piperazine derivatives and comprise Examples 305-318 in Table 4.

Table 4

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
305		455.536	6-[4-(5-Methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-nicotinonitrile	6-Piperazin-1-yl-nicotinonitrile (commercial) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	456.5
306		498.523	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	499.3
307		532.968	[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone	1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	533.4
308		464.971	[4-(5-Chloro-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone	1-(5-Chloro-pyridin-2-yl)-piperazine (WO01062751) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	465.4

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
309		498.523	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Trifluoromethyl-pyridin-3-yl)-piperazine (compound CO) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	499.4
310		516.513	[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone	1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (compound CP) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	516.9
311		444.553	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-methyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Methyl-pyridin-3-yl)-piperazine (compound CQ) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	445.4
312		444.553	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-methyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Methyl-pyridin-2-yl)-piperazine (WO03032996) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	445.1
313		498.523	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-pyridin-2-yl)-piperazine (WO02002529) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	499.1

No.	Structure	MW	Systematic Name	Starting materials	MW found (MH^+)
314		498.523	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(6-Trifluoromethyl-pyridin-2-yl)-piperazine (EP 462638) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	499.1
315		499.511	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(2-trifluoromethyl-pyrimidin-5-yl)-piperazin-1-yl]-methanone	5-Piperazin-1-yl-2-trifluoromethyl-pyrimidine (compound CS) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	500.0
316		499.511	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyridazin-3-yl)-piperazin-1-yl]-methanone	3-Piperazin-1-yl-6-trifluoromethyl-pyridazine (compound CT) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	500.4
317		475.571	[4-(4-Dimethylamino-[1,3,5]triazin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone	Dimethyl-(4-piperazin-1-yl-[1,3,5]triazin-2-yl)-amine (compound CU) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	476.1
318		499.511	(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-(5'-trifluoromethyl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone	5'-Trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl (compound CV) and 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (example AG)	500.4

Tablet Formulation (Wet Granulation)

Item	Ingredients	mg/tablet			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

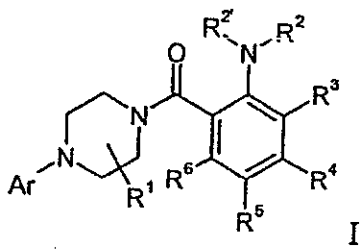
Item	Ingredients	mg/capsule			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Claims

1. A compound of formula



I

wherein

Ar is unsubstituted or substituted aryl or 6-membered heteroaryl with the exception of unsubstituted phenyl, containing one, two or three nitrogen atoms, and wherein the aryl and the heteroaryl groups are substituted by one or more substituents selected from the group consisting of hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

R^1 is hydrogen or (C_1-C_6)-alkyl;

R^2 and $R^{2'}$ are independently from each other hydrogen, $(CR_2)_n$-hydroxy for R being hydrogen or $C_1-C_6)$-alkyl, or are (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_1-C_6)-alkyl substituted by halogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl, $(CH_2)_n$-heterocycloalkyl, $(CH_2)_n$-O-(C_1-C_6)-alkyl or $(CH_2)_n$-aryl or

R^2 and $R^{2'}$ form together with the N atom to which they are attach a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O, which rings are unsubstituted or substituted by $(CH_2)_n$-hydroxy, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $(CH_2)_n$-O-(C_1-C_6)-alkyl, or form together with the N atom a 5-membered heteroaryl group, optionnally containing in addition to the N atom one, two or three further nitrogen atoms and wherein the heteroaryl group is optionally substituted by (C_1-C_6)-alkyl;

R^3, R^4 and R^6 are independently from each other hydrogen, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy;

R^5 is NO_2, CN, $C(O)R^9$, S-$(C_1$-$C_6)$-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other hydrogen, $(CH_2)_n$-$(C_3$-$C_6)$-cycloalkyl or $(C_1$-$C_6)$-alkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, $(C_1$-$C_6)$-alkoxy or NR^7R^8;

R^{10} is $(C_1$-$C_6)$-alkyl, $(CH_2)_n$-$(C_3$-$C_6)$-cycloalkyl or NR^7R^8;

R^{11} and R^{12} are independently from each other hydrogen, $C(O)$-$(C_1$-$C_6)$-alkyl, SO_2-$(C_1$-$C_6)$-alkyl, or form together with the N-atom a 5-membered heteroaryl group optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, $(C_1$-$C_6)$-alkyl or $(CH_2)_n(C_3$-$C_6)$-cycloalkyl;

n is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof,

with the proviso that

1-(4-methoxyphenyl)-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine

1-(4-methoxyphenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,

1-[2-(4-morpholinyl)-5-nitrobenzoyl]-4-[2-nitro-4-(trifluoromethyl)phenyl]-piperazine,

1-(4-methoxyphenyl)-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,

1-[2-[4-(2-hydroxyethyl)-1-piperazinyl]-5-nitrobenzoyl]-4-(4-methoxyphenyl)-piperazine,

1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-piperidinyl)benzoyl]-piperazine,

1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,

1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperidinyl)-5-nitrobenzoyl]-piperazine,

1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine,

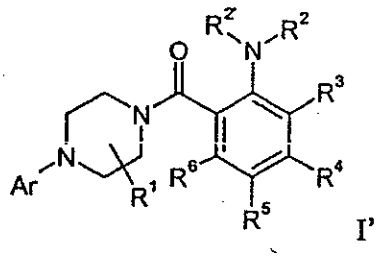
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,

1-[5-[[methyl(phenylmethyl)amino]sulfonyl]-2-(4-morpholinyl)benzoyl]-4-(4-nitrophenyl)-piperazine and

1-(4-acetyl-2-fluorophenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]- piperazine,

are excluded.

2. A compound of formula



I'

wherein

Ar is unsubstituted or substituted aryl or 6-membered heteroaryl with the exception of unsubstituted phenyl, containing one, two or three nitrogen atoms, and wherein the aryl and the heteroaryl groups are substituted by one or more substituents selected from the group consisting of hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

R^1 is hydrogen or (C_1-C_6)-alkyl;

R^2 and $R^{2'}$ are independently from each other hydrogen, hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-alkenyl, (C_2-C_6)-alkyl substituted by halogen, (C_3-C_6)-cycloalkyl, heterocycloalkyl, (C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl-heterocycloalkyl, (C_1-C_6)-alkyl-$C(O)-R^9$, (C_1-C_6)-alkyl-CN, (C_2-C_6)-alkyl-$O-R^{13}$, (C_2-C_6)-alkyl-NR^7R^8, aryl or 6-membered heteroaryl containing one, two or three nitrogen atoms, (C_1-C_6)-alkyl-aryl or (C_1-C_6)-alkyl-5 or-6-membered heteroaryl containing one, two or three heteroatoms, selected from the group consisting of oxygen, sulphur or nitrogen, wherein aryl, heterocycloalkyl and heteroaryl are unsubstituted or substituted by one or more substituents selected from the group consisting of hydroxy, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy; or R^2 and $R^{2'}$ form together with the N atom to which they are attach a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O, which rings are unsubstituted or substituted by hydroxy, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkyl-$O-R^{13}$, or form together with the N atom a 5-membered heteroaryl group, optionnally containing in addition to the N atom one, two or three further nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen or (C_3-C_6)-cycloalkyl;

R^3, R^4 and R^6 are independently from each other hydrogen, hydroxy, halogen, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy or NR^7R^8;

R^5 is NO_2, CN, $C(O)R^9$, S-(C_1-C_6)-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other hydrogen, (C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl, or (C_3-C_6)-cycloalkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy or NR^7R^8;

R^{10} is (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl-(C_3-C_6)-cycloalkyl or NR^7R^8;

R^{11} and R^{12} are independently from each other hydrogen, $C(O)$-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, or form together with the N-atom a 5-membered heteroaryl group optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen or (C_3-C_6)-cycloalkyl;

R^{13} is hydrogen, (C_1-C_6)-alkyl or (C_3-C_6)-cycloalkyl;

and pharmaceutically acceptable acid addition salts thereof,

with the proviso that

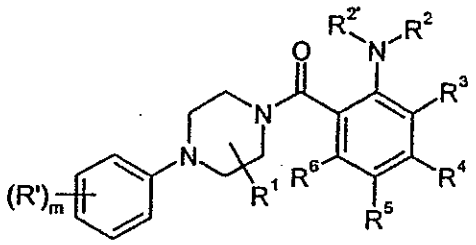
1-[2-[[2-(diethylamino)ethyl]amino]-5-nitrobenzoyl]-4-(methoxyphenyl)-piperazine,
1-(4-methoxyphenyl)-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine,
1-(4-methoxyphenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[2-(4-morpholinyl)-5-nitrobenzoyl]-4-[2-nitro-4-(trifluoromethyl)phenyl]-piperazine,
1-(4-methoxyphenyl)-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-[4-(2-hydroxyethyl)-1-piperazinyl]-5-nitrobenzoyl]-4-(4-methoxyphenyl)-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-piperidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperidinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,

1-[5-[[methyl(phenylmethyl)amino]sulfonyl]-2-(4-morpholinyl)benzoyl]-4-(4-nitrophenyl)-piperazine and

1-(4-acetyl-2-fluorophenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]- piperazine,

are excluded.

3. A compound of formula I-1 according to claim 1



I-1

wherein

R' is hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

m is 1, 2 or 3;

R^1 is hydrogen or (C_1-C_6)-alkyl;

R^2 and $R^{2'}$ are independently from each other hydrogen, $(CR_2)_n$-hydroxy for R being hydrogen or $C_1-C_6)$-alkyl, or are (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_1-C_6)-alkyl substituted by halogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl, $(CH_2)_n$-heterocycloalkyl, $(CH_2)_n$-O-(C_1-C_6)-alkyl or $(CH_2)_n$-aryl;

R^3, R^4 and R^6 are independently from each other hydrogen, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy;

R^5 is NO_2, CN, $C(O)R^9$, S-(C_1-C_6)-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other hydrogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or (C_1-C_6)-alkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, $(C_1\text{-}C_6)$-alkoxy or NR^7R^8;

R^{10} is $(C_1\text{-}C_6)$-alkyl, $(CH_2)_n\text{-}(C_3\text{-}C_6)$-cycloalkyl or NR^7R^8;

R^{11} and R^{12} are independently from each other hydrogen, $C(O)\text{-}(C_1\text{-}C_6)$-alkyl, $SO_2\text{-}(C_1\text{-}C_6)$-alkyl, or form together with the N-atom a 5-membered heteroaryl group optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, $(C_1\text{-}C_6)$-alkyl or $(CH_2)_n(C_3\text{-}C_6)$-cycloalkyl;

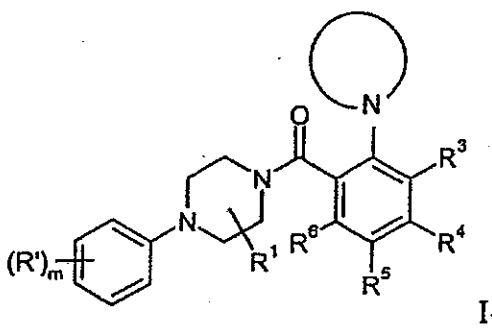
n is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

4. A compound of formula I-1 according to claim 3, which compounds are

1-(4-{4-[2-(cyclopropylmethyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro- phenyl)-ethanone,
1-{4-[4-(2-cyclohexylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
1-{4-[4-(2-diethylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
1-{3-fluoro-4-[4-(2-isobutylamino-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
1-{4-[4-(2-cyclobutylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
1-{4-[4-(2-cyclobutylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
1-{4-[4-(2-cyclopentylamino-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone or
1-(4-{4-[2-(allyl-methyl-amino)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone.

5. A compound of formula I-2 according to claim 1



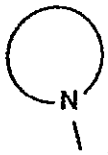
I-2

wherein

R' is hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

m is 1, 2 or 3;

R^1 is hydrogen or (C_1-C_6)-alkyl;



is a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O, which rings are unsubstituted or substituted by $(CH_2)_n$-hydroxy, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $(CH_2)_n$-O-(C_1-C_6)-alkyl, or form together with the N atom a 5-membered heteroaryl group, optionnally containing in addition to the N atom one, two or three further nitrogen atoms and wherein the heteroaryl group is optionally substituted by (C_1-C_6)-alkyl;

R^3, R^4 and R^6 are independently from each other hydrogen, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy;

R^5 is NO_2, CN, $C(O)R^9$, S-(C_1-C_6)-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other are hydrogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or (C_1-C_6)-alkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy or NR^7R^8;

R^{10} is (C_1-C_6)-alkyl, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or NR^7R^8;

R^{11} and R^{12} are independently from each other hydrogen, C(O)-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, or form together with the N-atom a 5-membered heteroaryl group optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, (C_1-C_6)-alkyl or $(CH_2)_n(C_3-C_6)$-cycloalkyl;

n is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

6. A compound of formula I-2 according to claim 5, which compounds are

1-{4 [4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
1-{3-fluoro-4-[4-(5-nitro-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
1-{3-fluoro-4-[4-(5-nitro-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
1-{4-[4-(2-azepan-1-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
1-(3-fluoro-4-{4-[2-(2-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
1-(3-fluoro-4-{4-[2-(4-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
1-(3-fluoro-4-{4-[2-(3-methyl-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
1-(3-fluoro-4-{4-[2-(2-methyl-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
1-(4-{4-[2-(2,5-dihydro-pyrrol-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone,
1-{3-fluoro-4-[4-(5-nitro-2-thiomorpholin-4-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
1-(3-fluoro-4-{4-[2-(3-hydroxy-piperidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
1-{4-[4-(2-azepan-1-yl-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
1-{3-fluoro-4-[4-(5-methanesulfonyl-2-pyrrolidin-1-yl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
N-methyl-4-pyrrolidin-1-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
N-methyl-4-morpholin-4-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide,
1-(3-fluoro-4-{4-[2-(3-hydroxymethyl-pyrrolidin-1-yl)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
2-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile,
3-fluoro-4-[4-(5-methanesulfonyl-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-benzonitrile,
2-fluoro-4-[4-(5-methanesulfonyl-2-piperidin-1-yl-benzoyl)-piperazin-1-yl]-benzonitrile,

[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-piperidin-1-yl-phenyl)-methanone,

[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-piperidin-1-yl-phenyl)-methanone,

3-[4-(4-cyano-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide,

3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide,

3-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide,

3-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-pyrrolidin-1-yl-benzenesulfonamide,

3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

3-[4-(4-cyano-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

N-methyl-4-piperidin-1-yl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,

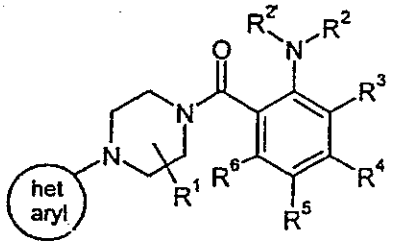
3-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

3-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-piperidin-1-yl-benzenesulfonamide,

3-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide or

3-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide.

7. A compound of formula I-3 according to claim 1



I-3

wherein

hetaryl is a 6-membered heteroaryl, containing one, two or three nitrogen atoms, optionally substituted by one or more substituents selected from the group consisting of hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

R^1 is hydrogen or (C_1-C_6)-alkyl;

R^2 and $R^{2'}$ are independently from each other hydrogen, $(CR_2)_n$-hydroxy for R being hydrogen or $C_1-C_6)$-alkyl, or are (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_1-C_6)-alkyl substituted by halogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl, $(CH_2)_n$-heterocycloalkyl, $(CH_2)_n$-O-(C_1-C_6)-alkyl or $(CH_2)_n$-aryl or

R^3, R^4 and R^6 are independently from each other hydrogen, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy;

R^5 is NO_2, CN, $C(O)R^9$, S-(C_1-C_6)-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other are hydrogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or (C_1-C_6)-alkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy or NR^7R^8;

R^{10} is (C_1-C_6)-alkyl, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or NR^7R^8;

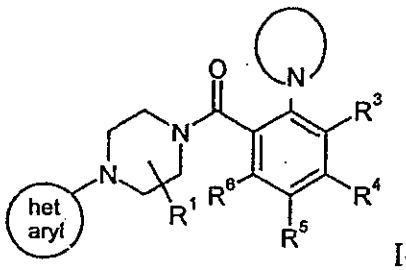
R^{11} and R^{12} are independently from each other hydrogen, $C(O)$-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, or form together with the N-atom a 5-membered heteroaryl group

optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, (C_1-C_6)-alkyl or $(CH_2)_n(C_3-C_6)$-cycloalkyl;

n is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

8. A compound of formula I-4 according to claim 1



I-4

wherein

hetaryl is a 6-membered heteroaryl, containing one, two or three nitrogen atoms, optionally substituted by one or more substituents selected from the group consisting of hydroxy, halogen, NO_2, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy substituted by halogen, NR^7R^8, $C(O)R^9$ or SO_2R^{10};

R^1 is hydrogen or (C_1-C_6)-alkyl;



is a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O, which rings are unsubstituted or substituted by $(CH_2)_n$-hydroxy, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $(CH_2)_n$-O-(C_1-C_6)-alkyl, or form together with the N atom a 5-membered heteroaryl group, optionnally containing in addition to the N atom one, two or three further nitrogen atoms and wherein the heteroaryl group is optionally substituted by (C_1-C_6)-alkyl;

R^3, R^4 and R^6 are independently from each other hydrogen, halogen, (C_1-C_6)-alkyl or (C_1-C_6)-alkoxy;

R^5 is NO_2, CN, $C(O)R^9$, S-(C_1-C_6)-alkyl, SO_2R^{10} or is $NR^{11}R^{12}$;

R^7 and R^8 are independently from each other hydrogen, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or (C_1-C_6)-alkyl, or form together with the N atom to which they are attached a heterocycloalkyl ring, optionally containing in addition to the N atom a further heteroatom, selected from the group consisting of N, S or O;

R^9 is hydroxy, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy or NR^7R^8;

R^{10} is (C_1-C_6)-alkyl, $(CH_2)_n$-(C_3-C_6)-cycloalkyl or NR^7R^8;

R^{11} and R^{12} are independently from each other hydrogen, C(O)-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, or form together with the N-atom a 5-membered heteroaryl group optionally containing in addition to the N atom one, two or three nitrogen atoms and wherein the heteroaryl group is optionally substituted by halogen, (C_1-C_6)-alkyl or $(CH_2)_n$(C_3-C_6)-cycloalkyl;

n is 0, 1 or 2;
and to pharmaceutically acceptable acid addition salts thereof.

9. A compound of formula I-4 according to claim 8, which compounds are

3-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-morpholin-4-yl-benzenesulfonamide

(2-morpholin-4-yl-5-nitro-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

[4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

6-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-nicotinonitrile

[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

(2-morpholin-4-yl-5-nitro-phenyl)-[4-(4-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

(2-morpholin-4-yl-5-nitro-phenyl)-[4-(6-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

[4-(5-bromo-pyrimidin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

[4-(6-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(2-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone

6-[4-(5-methanesulfonyl-2-morpholin-4-yl-benzoyl)-piperazin-1-yl]-nicotinonitrile

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

[4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone

[4-(5-chloro-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-methanone

[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-methyl-pyridin-3-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-methyl-pyridin-2-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(2-trifluoromethyl-pyrimidin-5-yl)-piperazin-1-yl]-methanone

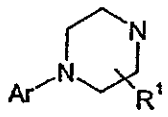
(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(6-trifluoromethyl-pyridazin-3-yl)-piperazin-1-yl]-methanone

[4-(4-dimethylamino-[1,3,5]triazin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone or

(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-(5'-trifluoromethyl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone.

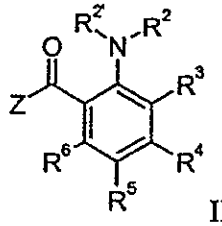
10. Processes for preparation of compounds of formula I and their pharmaceutically acceptable salts, which process comprises

a) reacting a compound of formula



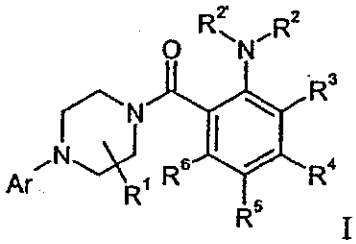
II

with a compound of formula



III

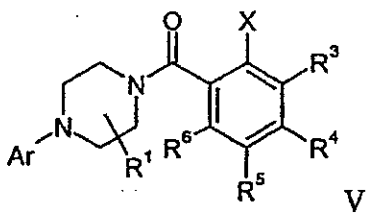
to a compound of formula



I

wherein Z is OH or halogen and the other substuents are as defined in claim 1, or

b) reacting a compound of formula

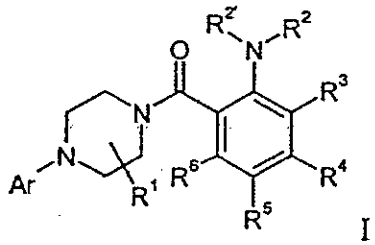


V

with a compound of formula

$R^2R^{2'}NH$

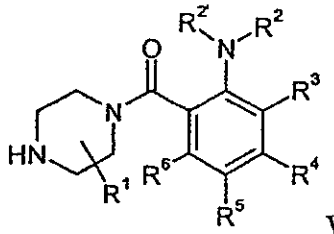
to a compound of formula



I

wherein X is halogen and the other substituents are as defined in claim 1,

c) reacting a compound of formula

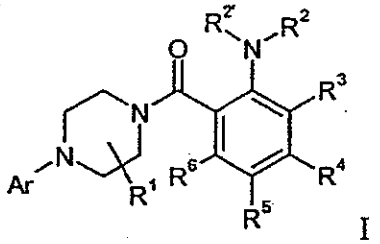


VII

with a compound of formula

ArX

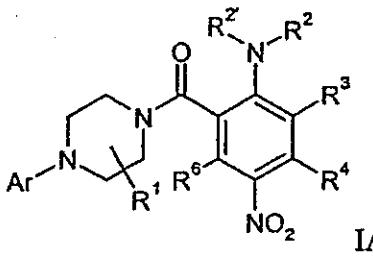
to a compound of formula



I

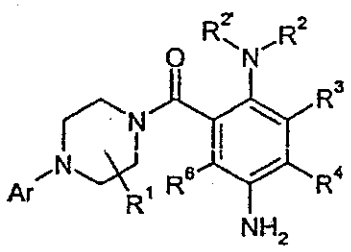
wherein X is halogen and the other substituents are as defined in claim 1,

d) reacting a compound of formula



IA

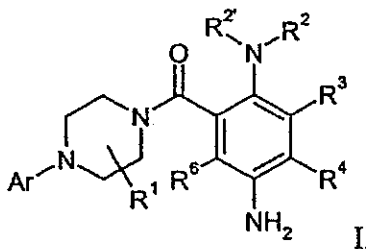
with hydrogen on Pd/C
to a compound of formula



IB

wherein the substituents are as defined in claim 1,

e) reacting a compound of formula

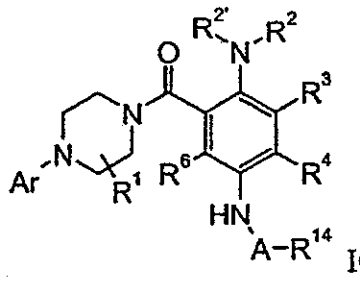


IB

with a compound of formula

$R^{14}AX$

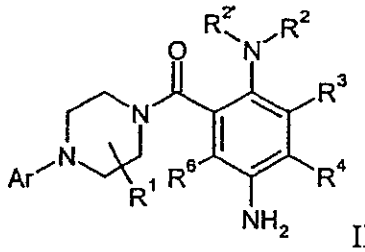
to a compound of formula



IC

wherein X is halogen, A is –C(O)- or $-SO_2-$, R^{14} is (C_1-C_6)-alkyl and the other substituents are as defined in claim 1,

f) reacting a compound of formula

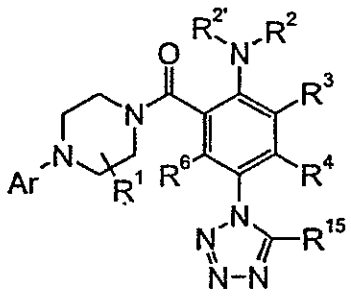


IB

with a compound of formula

$$R^{15}C(OEt)_3$$

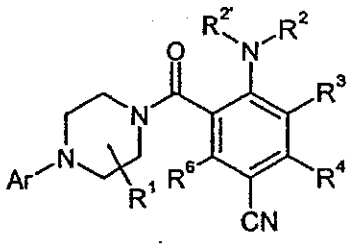
to a compound of formula



ID

wherein R^{15} is hydrogen, halogen, $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl substituted by halogen or $(C_3\text{-}C_6)$-cycloalkyl and the other substituents are as defined in claim 1,

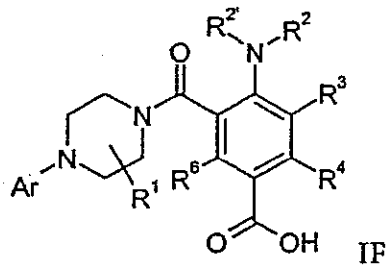
g) reacting a compound of formula



IE

with a base

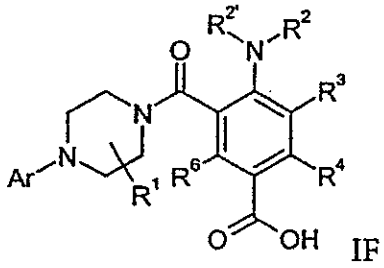
to a compound of formula



IF

wherein the substituents are as defined in claim 1,

h) reacting a compound of formula

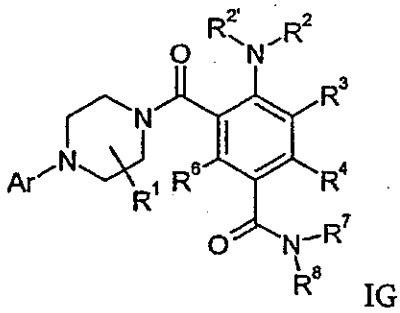


IF

with a compound of formula

R^7R^8NH

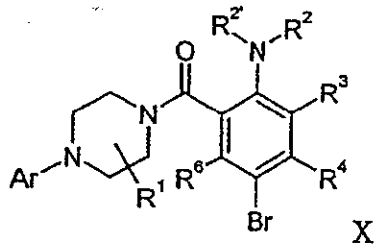
to a compound of formula



IG

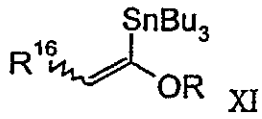
wherein the substituents are as defined in claim1,

i) reacting a compound of formula



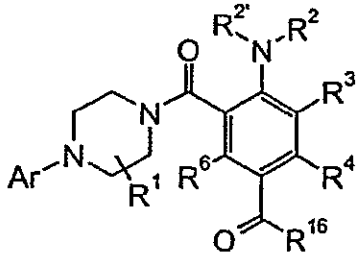
X

with a compound of formula



XI

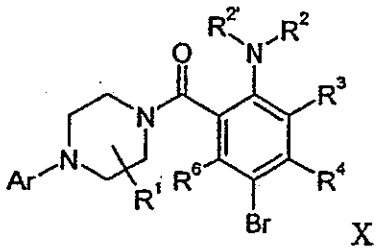
to a compound of formula



IH

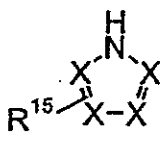
wherein R is $(C_1$-$C_6)$-alkyl, R^{16} is $(C_1$-$C_6)$-alkyl or $(C_3$-$C_6)$-cycloalkyl and the other substituents are as defined in claim 1,

j) reacting a compound of formula



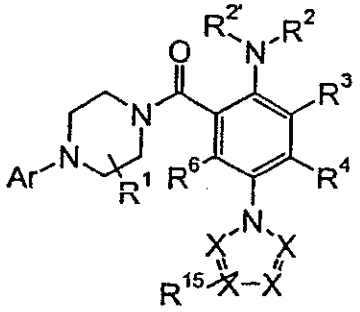
X

with a compound of formula



XII

to a compound of formula



II

wherein X is CH or N and the heteroaryl ring is selected from the group consisting of imidazole, pyrazole or triazole, R^{15} is hydrogen, halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted by halogen or (C_3-C_6)-cycloalkyl and the other substituents are as defined in claim 1,

and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

11. A compound according to claim 1, whenever prepared by a process as claimed in claim 10 or by an equivalent method.

12. A medicament containing one or more compounds as claimed in claim 1 or containing
1-(4-methoxyphenyl)-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine
1-(4-methoxyphenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[2-(4-morpholinyl)-5-nitrobenzoyl]-4-[2-nitro-4-(trifluoromethyl)phenyl]-piperazine,
1-(4-methoxyphenyl)-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-[4-(2-hydroxyethyl)-1-piperazinyl]-5-nitrobenzoyl]-4-(4-methoxyphenyl)-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-piperidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperidinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[5-[[methyl(phenylmethyl)amino]sulfonyl]-2-(4-morpholinyl)benzoyl]-4-(4-nitrophenyl)-piperazine,
1-(4-acetyl-2-fluorophenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]- piperazine,
1-{4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and
[4-(4-methoxy-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone.

and pharmaceutically acceptable excipients.

13. A medicament according to claim 12 for the treatment of illnesses based on the glycine uptake inhibitor.

14. A medicament according to claims 12 and 13, wherein the illnesses are psychoses, pain, disfunction in memory and learning, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

15. The use of a compound as claimed in claim 1 and of
1-(4-methoxyphenyl)-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine
1-(4-methoxyphenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[2-(4-morpholinyl)-5-nitrobenzoyl]-4-[2-nitro-4-(trifluoromethyl)phenyl]-piperazine,
1-(4-methoxyphenyl)-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-[4-(2-hydroxyethyl)-1-piperazinyl]-5-nitrobenzoyl]-4-(4-methoxyphenyl)-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-piperidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[5-nitro-2-(1-pyrrolidinyl)benzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperidinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-methyl-1-piperazinyl)-5-nitrobenzoyl]-piperazine,
1-[2-fluoro-4-(1-oxopropyl)phenyl]-4-[2-(4-morpholinyl)-5-nitrobenzoyl]-piperazine,
1-[5-[[methyl(phenylmethyl)amino]sulfonyl]-2-(4-morpholinyl)benzoyl]-4-(4-nitrophenyl)-piperazine,
1-(4-acetyl-2-fluorophenyl)-4-[2-(4-morpholinyl)-5-nitrobenzoyl]- piperazine,
1-{4-[4-(2-morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone and
[4-(4-methoxy-phenyl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

for the manufacture of medicaments for the treatment of psychoses, pain, neurodegenerative disfunction in memory and learning, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.