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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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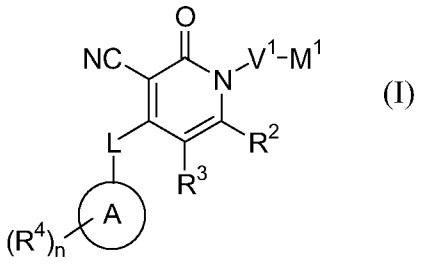
(54) Title: 1,4-DISUBSTITUTED 3-CYANO-PYRIDONE DERIVATIVES AND THEIR USE AS POSITIVE ALLOSTERIC MODULATORS OF MGLUR2-RECEPTORS



(I)

(57) Abstract: The present invention relates to novel compounds, in particular novel pyridinone de- rivat ives according to Formula (I) wherein all radicals are defined in the application and claims. The compounds according to the invention are positive allosteric modulators of metabotropic receptors - sub- type 2 ("mGluR2") which are useful for the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction and diseases in which the mGluR2 subtype of metabotropic receptors is involved. In particular, such diseases are central nervous system disorders selected from the group of anxiety, schizophrenia, migraine, depression, and epilepsy. The invention is also directed to pharmaceutical composit ions and processes to prepare such compounds and compositions, as well as to the use of such compounds for the prevention and treatment of such diseases in which mGluR2 is involved.

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1,4-DISUBSTITUTED 3-CYANO-PYRIDONE DERIVATIVES AND THEIR USE AS POSITIVE ALLOSTERIC MODULATORS OF MGLUR2-RECEPTORS

Field of the Invention

The present invention relates to novel compounds, in particular novel 1,4-disubstituted 3-cyano-pyridone-derivatives that are positive allosteric modulators of metabotropic receptors-subtype 2 ("mGluR2") which are useful for the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction and diseases in which the mGluR2 subtype of metabotropic receptors is involved. The invention is also directed to the pharmaceutical compositions, the processes to prepare such compounds and compositions and the use of such compounds for the prevention and treatment of such diseases in which mGluR2 is involved.

Background of the Invention

Glutamate is the major amino-acid transmitter in the mammalian central nervous system (CNS). Glutamate plays a major role in numerous physiological functions, such as learning and memory but also sensory perception, development of synaptic plasticity, motor control, respiration, and regulation of cardiovascular function. Furthermore, glutamate is at the centre of several different neurological and psychiatric diseases, where there is an imbalance in glutamatergic neurotransmission.

Glutamate mediates synaptic neurotransmission through the activation of ionotropic glutamate receptors channels (iGluRs), the NMDA, AMPA and kainate receptors which are responsible for fast excitatory transmission (Nakanishi et al., (1998) Brain Res Brain Res Rev., 26:230-235).

In addition, glutamate activates metabotropic glutamate receptors (mGluRs) which have a more modulatory role that contributes to the fine-tuning of synaptic efficacy.

The mGluRs are seven-transmembrane G protein-coupled receptors (GPCRs) belonging to family 3 of GPCRs along with the calcium-sensing, GABAb, and pheromone receptors.

Glutamate activates the mGluRs through binding to the large extracellular amino-terminal domain of the receptor, herein called the orthosteric binding site. This binding induces a conformational change in the receptor which results in the activation of the G-protein and intracellular signalling pathways.

The mGluR family is composed of eight members. They are classified into three groups (group I comprising mGluR1 and mGluR5; group II comprising mGluR2 and mGluR3; group III comprising mGluR4, mGluR6, mGluR7, and mGluR8) according to sequence homology, pharmacological profile, and nature of intracellular signalling cascades activated (Schoepp et al. (1999) Neuropharmacology, 38:1431-76).

Among mGluR members, the mGluR2 subtype is negatively coupled to adenylate cyclase via activation of Gαi-protein, and its activation leads to inhibition of glutamate release in the synapse (Cartmell & Schoepp (2000) J Neurochem 75:889-907). In the CNS, mGluR2 receptors are abundant mainly throughout cortex, thalamic regions, accessory olfactory bulb, hippocampus, amygdala, caudate-putamen and nucleus accumbens (Ohishi et al. (1998) Neurosci Res 30:65-82).

Activating mGluR2 was shown in clinical trials to be efficacious to treat anxiety disorders (Levine et al. (2002) Neuropharmacology 43: 294 ; Holden (2003) Science 300:1866-68; Grillon et al. (2003) Psychopharmacology 168:446–54 ; Kellner et al. (2005) Psychopharmacology 179: 310–15). In addition, activating mGluR2 in various animal models was shown to be efficacious, thus representing a potential novel therapeutic approach for the treatment of schizophrenia (reviewed in Schoepp & Marek (2002) Curr Drug Targets. 1:215-25), epilepsy (reviewed in Moldrich et al. (2003) Eur J Pharmacol. 476:3– 16), migraine (Johnson et al. (2002) Neuropharmacology 43:291), addiction/drug dependence (Helton et al. (1997) J Pharmacol Exp Ther 284: 651-660), Parkinson's disease (Bradley et al (2000) J Neurosci. 20(9):3085-94), pain (Simmons et al. (2002) Pharmacol Biochem Behav 73:419–27), sleep disorders (Feinberg et al. (2002) Pharmacol Biochem Behav 73:467–74) and Huntington's disease (Schiefer et al. (2004) Brain Res 1019:246-54).

To date, most of the available pharmacological tools targeting mGluRs are orthosteric ligands which activate several members of the family as they are structural analogs of glutamate (Schoepp et al. (1999) Neuropharmacology, 38:1431-76).

A new avenue for developing selective compounds acting at mGluRs is to identify molecules that act through allosteric mechanisms, modulating the receptor by binding to a site different from the highly conserved orthosteric binding site.

Positive allosteric modulators of mGluRs have emerged recently as novel pharmacological entities offering this attractive alternative. This type of molecule has been discovered for several mGluRs (reviewed in Mutel (2002) Expert Opin. Ther. Patents 12:1-8). In particular molecules have been described as mGluR2 positive allosteric modulators (Johnson MP et al. (2003) J Med Chem. 46:3189-92; Pinkerton et al. (2004) J Med Chem. 47:4595-9).

WO2004/092135 (NPS & Astra Zeneca), WO2004/018386, WO2006/014918 and WO2006/015158 (Merck) and WO2001/56990 (Eli Lilly) describe respectively phenyl sulfonamide, acetophenone, indanone and pyridylmethyl sulfonamide derivatives as mGluR2 positive allosteric modulators. However, none of the specifically disclosed compounds are structurally related to the compounds of the invention.

It was demonstrated that such molecules do not activate the receptor by themselves (Johnson MP et al. (2003) J Med Chem. 46:3189-92; Schaffhauser et al. (2003) Mol Pharmacol. 64:798-810). Rather, they enable the receptor to produce a maximal response to a concentration of glutamate which by itself induces a minimal response. Mutational analysis have demonstrated unequivocally that the binding of mGluR2 positive allosteric modulators does not occur at the orthosteric site, but instead at an allosteric site situated within the seven transmembrane region of the receptor (Schaffhauser et al. (2003) Mol Pharmacol. 64:798-810).

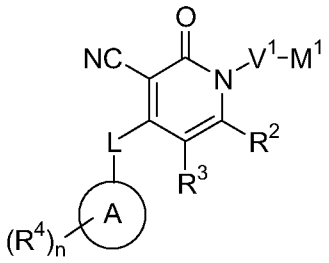
Animal data are suggesting that positive allosteric modulators of mGluR2 have the same effects in anxiety and psychosis models as those obtained with orthosteric agonists. Allosteric modulators of mGluR2 were shown to be active in fear-potentiated startle (Johnson et al. (2003) J Med Chem. 46:3189-92; Johnson et al. (2005) Psychopharmacology 179:271-83), and in stress-induced hyperthermia (Johnson et al. (2005) Psychopharmacology 179:271-83) models of anxiety. Furthermore, such com-

pounds were shown to be active in reversal of ketamine- (Govek et al. (2005) Bioorg Med Chem Lett 15(18):4068-72) or amphetamine- (Galici et al. (2005) J Pharm Exp Ther 315(3), 1181-1187) induced hyperlocomotion, and in reversal of amphetamine-induced disruption of prepulse inhibition of the acoustic startle effect (Galici et al. (2005) J Pharm Exp Ther 315(3), 1181-1187) models of schizophrenia.

Positive allosteric modulators enable potentiation of the glutamate response, but they have also been shown to potentiate the response to orthosteric mGluR2 agonists such as LY379268 (Johnson et al. (2004) Biochem Soc Trans 32:881-87) or DCG-IV (Poisik et al. (2005) Neuropharmacology 49:57-69). These data provide evidence for yet another novel therapeutic approach to treat above mentioned neurological diseases involving mGluR2, which would use a combination of a positive allosteric modulator of mGluR2 together with an orthosteric agonist of mGluR2.

Description of the Invention

The invention relates to compounds having metabotropic glutamate receptor 2 modulator activity. In its most general compound aspect, the present invention provides a compound according to general Formula (I),



(I)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein

V^1 is selected from the group of a covalent bond and a bivalent saturated or unsaturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms ;

M^1 is selected from the group of hydrogen ; cycloC_{3-7}alkyl ; aryl ; alkylcarbonyl ; alkyloxy ; aryloxy ; arylalkyloxy ; arylcarbonyl ; hexahydrothiopyranyl ; and Het^1 ;

L is selected from the group of a covalent bond ; -O- ; -OCH_2- ; -OCH_2CH_2- ; -OCH_2CH_2O- ; -$OCH_2CH_2OCH_2$- ; -S- ; -NR^7- ; -NR^7CH_2- ; -NR^7 cycloC_{3-7} ; -$NR^7CH_2CH_2$- ; -$OCH_2CH_2N(R^7)CH_2$- ; -CH_2- ; -CH_2CH_2-; -$CH_2CH_2CH_2$; -C≡C- ; -C=O- ; and -$C(R^8)=C(R^9)$- ; wherein each of R^7, independently of each other, is selected from the group of hydrogen and C_{1-3}alkyl ; and wherein R^8 and R^9, independently of each other, are selected from the group of hydrogen, halo and C_{1-3}alkyl ;

R^2 and R^3 are each independently of each other hydrogen, halo or alkyl ;

A is Het^2 or phenyl, wherein each radical is optionally substituted with n radicals R^4, wherein n is an integer equal to zero, 1, 2 or 3 ;

R^4 is selected from the group of halo ; cyano ; hydroxy ; oxo ; formyl ; ethanoyl ; carboxyl ; nitro ; thio ; alkyl ; alkyloxy ; alkyloxyalkyl ; alkyloxycarbonyl ; alkyloxycarbonylalkyl ; alkylcarbonyl ; alkylcarbonyloxy ; alkylcarbonylalkyloxy ; polyhaloC_{1-3}alkyl ; polyhaloC_{1-3}alkyloxy ; polyhaloC_{1-3}alkylthio ; alkylthio ; alkylsulfonyl ; Het^3 ; Het^3-alkyl ; Het^3-oxy ; Het^3-oxyalkyl ; Het^3-alkyloxy ; Het^3-oxyalkyloxy ; Het^3-carbonyl ; Het^3-carbonylalkyl ; Het^3-thio ; Het^3-thioalkyl ; Het^3-sulfonyl ; aryl ; arylalkyl ; aryloxy ; aryloxyalkyl ; arylalkyloxy ; arylalkenyl ; arylcarbonylalkyl ; arylthioalkyl ; arylsulfonyl ; -NR^aR^b ; alkyl-NR^aR^b ; O-alkyl-NR^aR^b ; -C(=O)-NR^aR^b ; -C(=O)-alkyl-NR^aR^b ; and O-alkyl-C(=O)-NR^aR^b ; wherein R^a and R^b are selected from the group of hydrogen, alkyl, alkylcarbonyl, arylalkyl, alkyloxyalkyl, Het^3, Het^3alkyl, alkylsulfonyl, alkyl-NR^cR^d and C(=O)alkyl-NR^cR^d, wherein R^c and R^d are selected from the group of hydrogen, alkyl and alkylcarbonyl ;

or two radicals R^4 may be combined to form a bivalent radical -X^1-C_{1-6}-X^2- wherein C_{1-6} is a saturated or unsaturated, straight or branched hydrocarbon radical having 1 to 6 carbon atoms and X^1 and X^2 are each independently C, O or NH ; wherein the bivalent radical is optionally substituted with one or more radi-

cals selected from the group of halo, polyhaloC_{1-3}alkyl, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl and ethanoyl ;

Het^1 is selected from the group of tetrahydropyranyl and pyridinyl ; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, C_{1-3}alkyl, polyhaloC_{1-3}alkyl, polyhaloC_{1-3}alkyloxy, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl, ethanoyl, and C_{1-3}alkyloxy ;

Het^2 is selected from the group of piperazinyl ; piperidinyl ; thienyl ; furanyl ; 1*H*-indazolyl ; 1*H*-benzimidazolyl ; 1,2,3,4-tetrahydro-isoquinolinyl ; 2,5-diaza-bicyclo[2.2.1]heptyl ; pyrrolidinyl ; azetidinyl ; 2,7-diaza-spiro[3.5]-nonyl ; pyridinyl ; pyrazolyl ; indolinyl ; 1*H*-indolyl ;1*H*-indazolyl ; benzomorpholinyl ; thiazolyl ; 1,2,3,4-tetrahydroquinolinyl ; 3,9-diazaspiro[5.5]undecyl ; 1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolinyl ; 1,2,3,4,4a,10a-hexahydro-benzo[5,6][1,4]dioxino[2,3-c]pyridinyl ; 2,3,4,9-tetrahydro-1*H*-indeno[2,1-c]-pyridinyl ; 2,3,4,9-tetrahydro-1*H*-β-carbolinyl; 1,2,3,4-tetrahydro-benzo[4,5]-furo[2,3-c]pyridinyl ; 1,2,3,4-tetrahydrobenzo[4,5]thieno[2,3-c]pyridinyl ; [1,4]diazepyl ; isoxazolyl ; indanyl ; and indolyl ;

Het^3 is selected from the group of pyridinyl ; pyrimidinyl ; pyridazilyl ; pyrazinyl ; piperidinyl ; pyrrolyl ; pyrrolidinyl ; piperazinyl ; triazolyl ; tetrazolyl ; indolyl ; thienyl ; furanyl ; tetrahydropyranyl ; tetrahydro-thiopyran-1,1-dioxide ; thiazolyl ; thiadiazolyl ; isothiazolyl ; oxazolyl ; morpholinyl ; oxadiazolyl ; isoxazolyl ; imidazolyl ; pyrazolyl ; benzoimidazolyl ; benzoxazolyl; benzothienyl ; benzothiazolyl ; benzofuranyl ; benzomorpholinyl ; 1,2,3,4-tetrahydro-isoquinolinyl ; thionaphtyl ; indolyl ; indolinyl ; quinolyl ; isoquinolyl ; quinoxalyl ; phthalazyl ; benzo[1,3]dioxyl ; and quinazolyl ; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, C_{1-6}alkyl, polyhaloC_{1-3}alkyl, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl, ethanoyl, phenyl, pyrrolidinyl, piperidinyl, pyridinyl, morpholinyl, mono- and di(alkyl)amino, and C_{1-3}alkyloxy ;

aryl is naphthyl, phenyl, or biphenyl ; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other selected from the

group of halo, C_{1-3}alkyl, polyhaloC_{1-3}alkyl, polyhaloC_{1-3}alkyloxy, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl, ethanoyl, ethyloxycarbonyl, and C_{1-3}alkyloxy ;

alkyl is a saturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms ; or is a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms ; or is saturated hydrocarbon radical from 4 to 12 carbonatoms, comprising at least one saturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and at least one saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms ; wherein each carbon atom may optionally be substituted with one or more radicals selected from the group of halo, polyhaloC_{1-3}alkyl, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl, ethanoyl, carbamoyl, phenyl, and a bivalent radical $-OCH_2CH_2O-$; and

alkenyl is alkyl, additionally containing one or more double bonds.

The invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a therapeutically effective amount of a compound according to the invention, in particular a compound according to Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof.

The invention also relates to the use of a compound according to the invention as a medicament and for the preparation of a medicament for the prevention and/or treatment of a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 positive allosteric modulators.

In particular, the invention relates to the use of a compound according to the invention for the preparation of a medicament for treating, or preventing, ameliorating, controlling or reducing the risk of various neurological and psychiatric disorders associated with glutamate dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 positive allosteric modulators.

Detailed Description of the Invention

In one embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein V^1 is selected from the group of a covalent bond, $-CH_2-$; $-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-$; $-CH_2-CH=CH-$; $-CH_2-CH_2-CH_2-CH_2-$; $-CH_2-CH(CH_3)-CH_2-$; $-CH(CH_3)-CH_2-CH_2-CH_2-$; $-CH_2-CH(CH_3-)CH_2-CH_2-$; and $-CH_2-CH_2-CH(CH_3)-CH_2-$.

In one embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein M^1 is selected from the group of hydrogen ; cycloC_{3-7}alkyl ; phenyl ; biphenyl ; phenyloxy ; benzyloxy ; furanyl ; and pyridinyl ; wherein M^1 is optionally substituted with one or more radicals selected from the group of halo ; C_{1-3}alkyl ; polyhaloC_{1-3}alkyl ; polyhaloC_{1-3}alkyloxy ; cyano ; hydroxy ; amino ; oxo ; carboxyl ; nitro ; thio ; formyl ; ethanoyl ; and C_{1-3}alkyloxy.

In one embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein M^1 is selected from the group of hydrogen ; cycloC_{3-7}alkyl ; phenyl ; biphenyl ; phenyloxy ; benzyloxy ; furanyl, and pyridinyl ; wherein any one of said radicals is optionally substituted with one or more radicals selected from the group of halo ; C_{1-3}alkyl ; polyhaloC_{1-3}alkyl ; polyhaloC_{1-3}alkyloxy ; and C_{1-3}alkyloxy.

In one embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein V^1-M^1 is selected from the group of $-CH_2-CH_2-CH_2-CH_3$; $-CH_2-CH(CH_3)-CH_3$; $-CH(CH_3)-CH_2-CH_2-CH_3$; $-CH_2-CH(CH_3-)CH_2-CH_3$; $-CH_2-CH_2-CH(CH_3)-CH_3$; or V^1 is selected from the group of covalent bond ; $-CH_2-$; $-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-$; and $-CH_2-CH=CH-$; and M^1 is selected from the group of cyclopropyl ; cyclopentyl ; cyclohexyl ; phenyl ; biphenyl ; phenyloxy ; benzyloxy ;

furanyl ; and pyridinyl ; wherein each radical M^1 is optionally substituted with one or more radicals selected from the group of halo ; C_{1-3}alkyl ; polyhaloC_{1-3}alkyl ; polyhaloC_{1-3}alkyloxy ; and C_{1-3}alkyloxy. In a particular embodiment, V^1-M^1 is $-CH_2-CH_2-CH_2-CH_3$.

In one embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein R^2 and R^3 are each independently hydrogen, chloro, fluoro or methyl. In one particular embodiment, R^2 and R^3 are each independently hydrogen or methyl. In another particular embodiment, R^2 and R^3 are each hydrogen. In another particular embodiment, R^2 is methyl and R^3 is hydrogen.

In one embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein L is selected from the group of a covalent bond ; -O- ; $-OCH_2-$; $-OCH_2CH_2-$; $-OCH_2CH_2O-$; $-OCH_2CH_2OCH_2-$; $-NR^7-$; $-NR^7CH_2-$; $-NR^7$cycloC_{3-7} ; $-OCH_2CH_2N(R^7)CH_2-$; $-CH_2CH_2-$; -C≡C- ; -C=O- ; and -CH=CH- ; wherein each of R^7, independently of each other, is selected from the group of hydrogen and C_{1-3}alkyl.

In another embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein A is selected from the group of phenyl, piperazinyl, and piperidinyl ; wherein each of said radicals is optionally substituted with n radicals R^4, wherein n is an integer equal to zero, 1, 2 or 3. In one particular embodiment, n is equal to zero or 1. In another particular embodiment, n is equal to 1.

In one embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein R^4 is selected from the group of halo ; cyano ; hydroxy ; ethanoyl ; alkyl ; alkyloxy ; alkyloxyalkyl ; alkyloxycarbonyl ; alkyloxycarbonylalkyl ; alkylcarbonyl ; alkylcarbonyloxy ; alkylcarbonylalkyloxy ; polyhaloC_{1-3}alkyl ; polyhaloC_{1-3}-

alkyloxy ; polyhaloC_{1-3}alkylthio ; alkylthio ; alkylsulfonyl ; Het^3 ; Het^3-alkyl ; Het^3-oxy ; Het^3-oxyalkyl ; Het^3-alkyloxy ; Het^3-oxyalkyloxy ; Het^3-carbonyl ; Het^3-thioalkyl ; aryl ; arylalkyl ; aryloxy ; aryloxyalkyl ; arylalkyloxy ; arylalkenyl ; arylcarbonylalkyl ; arylsulfonyl ; -NR^aR^b ; alkyl-NR^aR^b ; O-alkyl-NR^aR^b ; -C(=O)-NR^aR^b ; -C(=O)-alkyl-NR^aR^b ; and O-alkyl-C(=O)-NR^aR^b ; wherein R^a and R^b are selected from the group of hydrogen, alkyl, alkylcarbonyl, arylalkyl, alkyloxyalkyl, Het^3, Het^3alkyl, alkylsulfonyl, alkyl-NR^cR^d and C(=O)alkyl-NR^cR^d, wherein R^c and R^d are selected from the group of hydrogen, alkyl and alkylcarbonyl ; or two radicals R^4 may be combined to form a bivalent radical -X^1-C_{1-6}-X^2- wherein C_{1-6} is a saturated or unsaturated, straight or branched hydrocarbon radical having 1 to 6 carbon atoms and X^1 and X^2 are each independently C or O.

In another embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein two radicals R^4 may be combined to form a bivalent radical selected from the group of -CH_2CH_2-O- ; -O-CH_2-O- ; and -O-CH_2CH_2-O-.

In one embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein Het^1 is selected from the group of tetrahydropyranyl and pyridinyl ; wherein each radical Het^1 is optionally substituted with 1, 2 or 3 polyhaloC_{1-3}alkyl substituents.

In one embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein Het^3 is selected from the group of pyridinyl ; pyrimidinyl ; pyridazilyl ; pyrazinyl ; piperidinyl ; pyrrolidinyl ; piperazinyl ; triazolyl ; tetrahydropyranyl ; tetrahydro-thiopyran-1,1-dioxide ; thiazolyl ; oxazolyl ; morpholinyl ; oxadiazolyl ; imidazolyl ; benzoxazolyl; benzothienyl ; benzofuranyl ; 1,2,3,4-tetrahydroisoquinolinyl ; indolyl ; indolinyl ; phthalazyl ; and benzo[1,3]dioxyl. In one embodiment, each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, C_{1-6}alkyl, polyhaloC_{1-3}alkyl,

cyano, hydroxy, oxo, ethanoyl, phenyl, pyrrolidinyl, piperidinyl, pyridinyl, morpholinyl, mono- and di(alkyl)amino, and C_{1-3}alkyloxy.

In one further embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein

V^1 is selected from the group of a covalent bond, $-CH_2-$; $-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-$; $-CH_2-CH=CH-$; $-CH_2-CH_2-CH_2-CH_2-$; $-CH_2-CH(CH_3)-CH_2-$; $-CH(CH_3)-CH_2-CH_2-CH_2-$; $-CH_2-CH(CH_3-)CH_2-CH_2-$; and $-CH_2-CH_2-CH(CH_3)-CH_2-$;

M^1 is selected from the group of hydrogen; cycloC_{3-7}alkyl; phenyl; biphenyl; phenyloxy; benzyloxy; furanyl; and pyridinyl; wherein M^1 is optionally substituted with one or more radicals selected from the group of halo; C_{1-3}alkyl; polyhaloC_{1-3}alkyl; polyhaloC_{1-3}alkyloxy; and C_{1-3}alkyloxy;

L is selected from the group of covalent bond; -O-; $-OCH_2-$; $-OCH_2CH_2-$; $-OCH_2CH_2O-$; $-OCH_2CH_2OCH_2-$; $-NR^7-$; $-NR^7CH_2-$; $-NR^7$cycloC_{3-7}; $-OCH_2CH_2N(R^7)CH_2-$; $-CH_2CH_2-$; $-C\equiv C-$; -C=O-; and -CH=CH-; wherein each of R^7, independently of each other, is selected from the group of hydrogen and C_{1-3}alkyl;

R^2 and R^3 are each independently of each other hydrogen, halo or alkyl;

A is selected from the group of phenyl, piperazinyl, and piperidinyl, wherein each radical is optionally substituted with n radicals R^4, wherein n is an integer equal to zero or 1;

R^4 is selected from the group of halo; cyano; hydroxy; ethanoyl; alkyl; alkyloxy; alkyloxyalkyl; alkyloxycarbonyl; alkyloxycarbonylalkyl; alkylcarbonyl; alkylcarbonyloxy; alkylcarbonylalkyloxy; polyhaloC_{1-3}alkyl; polyhaloC_{1-3}alkyloxy; polyhaloC_{1-3}alkylthio; alkylthio; alkylsulfonyl; Het^3; Het^3-alkyl; Het^3-oxy; Het^3-oxyalkyl; Het^3-alkyloxy; Het^3-oxyalkyloxy; Het^3-carbonyl; Het^3-thioalkyl; aryl; arylalkyl; aryloxy; aryloxyalkyl; arylalkyloxy; arylalkenyl; arylcarbonylalkyl; arylsulfonyl; $-NR^aR^b$; alkyl-NR^aR^b; O-alkyl-NR^aR^b; $-C(=O)-NR^aR^b$; $-C(=O)$-alkyl-NR^aR^b; and O-alkyl-$C(=O)-NR^aR^b$; wherein

R^a and R^b are selected from the group of hydrogen, alkyl, alkylcarbonyl, arylalkyl, alkyloxyalkyl, Het^3, Het^3alkyl, alkylsulfonyl, alkyl-NR^cR^d, and C(=O)alkyl-NR^cR^d, wherein R^c and R^d are selected from the group of hydrogen, alkyl and alkylcarbonyl ; or two radicals R^4 may be combined to form a bivalent radical selected from the group of $-CH_2CH_2-O-$; $-O-CH_2-O-$; and $-O-CH_2CH_2-O-$;

Het^1 is selected from the group of tetrahydropyranyl and pyridinyl ; wherein each radical Het^1 is optionally substituted with 1, 2 or 3 polyhaloC_{1-3}alkyl substituents ;

Het^2 is selected from the group of piperazinyl ; piperidinyl ; thienyl ; furanyl ; 1*H*-indazolyl ; 1*H*-benzimidazolyl ; 1,2,3,4-tetrahydro-isoquinolinyl ; 2,5-diaza-bicyclo[2.2.1]heptyl ; pyrrolidinyl ; azetidinyl ; 2,7-diaza-spiro[3.5]-nonyl ; pyridinyl ; pyrazolyl ; indolinyl ; 1*H*-indolyl ; 1*H*-indazolyl ; benzomorpholinyl ; thiazolyl ; 1,2,3,4- tetrahydroquinolinyl ; 3,9-diazaspiro[5.5]undecyl ; 1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolinyl ; 1,2,3,4,4a,10a-hexahydro-benzo[5,6][1,4]dioxino[2,3-c]pyridinyl ; 2,3,4,9-tetrahydro-1*H*-indeno[2,1-c]-pyridinyl ; 2,3,4,9-tetrahydro-1*H*-β-carbolinyl; 1,2,3,4-tetrahydro-benzo[4,5]-furo[2,3-c]pyridinyl ; 1,2,3,4-tetrahydrobenzo[4,5]thieno[2,3-c]pyridinyl ; [1,4]diazepyl ; isoxazolyl ; indanyl ; and indolyl ;

Het^3 is selected from the group of pyridinyl ; pyrimidinyl ; pyridazilyl ; pyrazinyl ; piperidinyl ; pyrrolidinyl ; piperazinyl ; triazolyl ; tetrahydropyranyl ; tetrahydro-thiopyran-1,1-dioxide ; thiazolyl ; oxazolyl ; morpholinyl ; oxadiazolyl ; imidazolyl ; benzoxazolyl; benzothienyl ; benzofuranyl ; 1,2,3,4-tetrahydro-isoquinolinyl ; indolyl ; indolinyl ; phthalazyl ; and benzo[1,3]dioxyl ; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, C_{1-6}alkyl, polyhaloC_{1-3}alkyl, cyano, hydroxy, oxo, ethanoyl, phenyl, pyrrolidinyl, piperidinyl, pyridinyl, morpholinyl, mono- and di(alkyl)amino, and C_{1-3}alkyloxy ;

aryl is phenyl or biphenyl ; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other selected from the group of halo, C_{1-3}alkyl, polyhaloC_{1-3}alkyl, polyhaloC_{1-3}alkyloxy, cyano, nitro, ethyloxy-

carbonyl, and C_{1-3}alkyloxy ; and

alkyl is a saturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms ; or is a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms ; or is saturated hydrocarbon radical from 4 to 12 carbonatoms, comprising at least one saturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and at least one saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms ; wherein each carbon atom may optionally be substituted with one or more radicals selected from the group of cyano, hydroxy, carboxyl, carbamoyl, phenyl, and a bivalent radical $-OCH_2CH_2O-$.

In further embodiment, the invention relates to a compound according to general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein the compound is selected from the group of :

- 4-(4-(*N*-acetylmethyl)phenyl)-3-cyano-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-179);
- 4-(3,4-dimethoxyphenyl)-3-cyano-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-110);
- 3-cyano-4-(3-fluoro-4-methoxyphenyl)-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-114);
- 3-cyano-4-(4-hydroxypropylphenyl)-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-095);
- 3-cyano-4-(4-methoxymethylphenyl)-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-103);
- 3-cyano-4-(2-fluoro-4-methoxyphenyl)-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-113);
- 3-cyano-4-(4-(*N*-morpholyl)phenyl)-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-223);
- 3-cyano-1-(3-methylbutyl)-4-(phenylethynyl)pyridine-2(1*H*)-one (compound 1-267);
- 3-cyano-1-butyl-4-[4-(2-methyl-pyridin-4-yloxy)-phenyl]-pyridine-2(1*H*)-one

(compound 1-064); and

- 3-cyano-1-cyclopropylmethyl-4-(4-phenyl-piperidin-1-yl)-pyridine-2(1*H*)-one (compound 4-047).

In the framework of this application, alkyl is a saturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms ; or is a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms ; or is a saturated hydrocarbon radical from 4 to 12 carbonatoms, comprising at least one saturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and at least one saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms ; wherein each carbon atom may optionally be substituted with one or more radicals selected from the group of halo, polyhaloC_{1-3}alkyl, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl, ethanoyl, carbamoyl, phenyl, and a bivalent radical -OCH_2CH_2O-. In one embodiment, alkyl is methyl, ethyl, *n*-propyl, isopropyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In one embodiment, each carbon atom is optionally substituted with one or more radicals selected from the group of cyano, hydroxy, carboxyl, carbamoyl, phenyl, and the bivalent radical -OCH_2CH_2O-.

The notation C_{1-6}alkyl defines a saturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms, such as C_6alkyl ; C_5alkyl ; C_4alkyl ; C_3alkyl ; C_2alkyl ; and C_1alkyl. Examples of C_{1-6}alkyl are methyl, ethyl, *n*-propyl, iso-propyl, butyl, isobutyl, pentyl, and heptyl.

The notation cycloC_{3-7}alkyl defines a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms, such as cycloC_7alkyl ; cycloC_6alkyl ; cycloC_6alkyl ; cycloC_5alkyl ; cycloC_4alkyl ; cycloC_3alkyl ; and cycloC_3alkyl. Examples of cycloC_{3-7}alkyl are cyclopropyl, cyclobutyl, cyclopentyl, cycloheptyl, and cyclohexyl.

The notation C_{1-3}alkyl defines a saturated, straight or branched hydrocarbon radical having from 1 to 3 carbon atoms, such as methyl, ethyl, n-propyl and iso-propyl.

In one preferred embodiment, alkyl is C_{1-6}alkyl ; in another preferred embodiment alkyl is C_{3-7}cycloalkyl.

In the framework of this application, alkenyl is alkyl, additionally containing

one or more double bonds.

In the framework of this application, aryl is naphthyl, phenyl or biphenyl; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other selected from the group of halo, C_{1-3}alkyl, polyhaloC_{1-3}alkyl, polyhaloC_{1-3}alkyloxy, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl, ethanoyl, ethyloxycarbonyl, and C_{1-3}alkylox. More preferred, aryl is phenyl or biphenyl. More preferred, aryl is optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, C_{1-3}alkyl, polyhaloC_{1-3}alkyl, polyhaloC_{1-3}alkyloxy, cyano, nitro, ethyloxycarbonyl, and C_{1-3}alkyloxy. More preferred, aryl is phenyl or biphenyl, optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, C_{1-3}alkyl, polyhaloC_{1-3}alkyl, polyhaloC_{1-3}alkyloxy, cyano, nitro, ethyloxycarbonyl, and C_{1-3}alkyloxy.

In the framework of this application, halo is a substituent selected from the group of fluoro, chloro, bromo and iodo. Preferably, halo is bromo, fluoro or chloro.

In the framework of this application, polyhaloC_{1-3}alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 3 carbon atoms, wherein one or more carbon atoms is substituted with one or more halo-atoms. Preferably, polyhaloalkyl is trifluoromethyl.

In the framework of this application, with "compounds according to the invention" is meant a compound according to the general Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof.

The pharmaceutically acceptable acid addition salts are defined to comprise the therapeutically active non-toxic acid addition salts forms that the compounds according to Formula (I) are able to form. Said salts can be obtained by treating the base form of the compounds according to Formula (I) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methane-

sulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicylic acid, p-aminosalicylic acid and pamoic acid.

Conversely said acid addition salt forms can be converted into the free base form by treatment with an appropriate base .

The compounds according to Formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salts forms (base addition salts) by treatment with appropriate organic and inorganic bases. Appropriate base salts forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hybramine salts, and salts with amino acids, for example arginine and lysine.

Conversely, said salts forms can be converted into the free forms by treatment with an appropriate acid.

Quaternary ammonium salts of compounds according to Formula (I) defines said compounds which are able to form by a reaction between a basic nitrogen of a compound according to Formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, in particular methyliodide and benzyliodide. Other reactants with good leaving groups may also be used, such as, for example, alkyl trifluoromethanesulfonates, alkyl methanesulfonates and alkyl p-toluenesulfonates. A quaternary ammonium salt has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate ions.

The term addition salt as used in the framework of this application also comprises the solvates that the compounds according to Formula (I) as well as the salts thereof, are able to form. Such solvates are, for example, hydrates and alcoholates.

The *N*-oxide forms of the compounds according to Formula (I) are meant to comprise those compounds of Formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one or more tertiary nitrogens (e.g. of the piperazinyl or piperidinyl radical) are *N*-oxidized. Such *N*-oxides can easily be obtained by a skilled person without any inventive skills and they are obvious alternatives for the compounds according to Formula (I) since these

compounds are metabolites, which are formed by oxidation in the human body upon uptake . As is generally known, oxidation is normally the first step involved in drug metabolism (Textbook of Organic Medicinal and Pharmaceutical Chemistry, 1977, pages 70- 75). As is also generally known, the metabolite form of a compound can also be administered to a human instead of the compound per se, with much the same effects.

The compounds of Formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of Formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

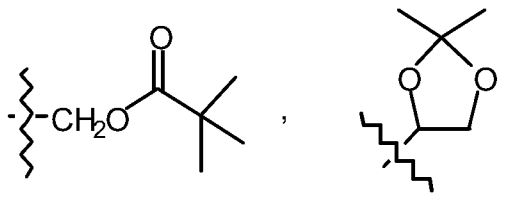
The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms that the compounds of Formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of Formula (I) are obviously intended to be embraced within the scope of this invention.

Following CAS nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned

(based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using relative descriptors [*R**,*R**] or [*R**,*S**], where R* is always specified as the reference center and [*R**,*R**] indicates centers with the same chirality and [*R**,*S**] indicates centers of unlike chirality. For example, if the lowest-numbered chiral center in the molecule has an *S* configuration and the second center is *R*, the stereo descriptor would be specified as *S*-[*R**,*S**]. If "α" and "β" are used : the position of the highest priority substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the "α" position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric carbon atom in the ring system (hydrogen atom in compounds according to Formula (I)) relative to the position of the highest priority substituent on the reference atom is denominated "α", if it is on the same side of the mean plane determined by the ring system, or "β", if it is on the other side of the mean plane determined by the ring system.

The invention also comprises derivative compounds (usually called "pro-drugs") of the pharmacologically-active compounds according to the invention, which are degraded *in vivo* to yield the compounds according to the invention. Pro-drugs are usually (but not always) of lower potency at the target receptor than the compounds to which they are degraded. Pro-drugs are particularly useful when the desired compound has chemical or physical properties that make its administration difficult or inefficient. For example, the desired compound may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion on pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs,* 1985, **29**, pp. 455-473.

Pro-drugs forms of the pharmacologically-active compounds according to the invention will generally be compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the *N*-oxide form thereof, having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the formula $-COOR^x$, where R^x is a C_{1-6}alkyl, phenyl, benzyl or one of the following groups :



Amidated groups include groups of the formula $-CONR^yR^z$, wherein R^y is H, C_{1-6}alkyl, phenyl or benzyl and R^z is –OH, H, C_{1-6}alkyl, phenyl or benzyl. Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as, for example, formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

In the framework of this application, with "compounds according to the invention" is meant a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof.

In the framework of this application, an element, in particular when mentioned in relation to a compound according to Formula (I), comprises all isotopes and isotopic mixtures of this element, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. In particular, when hydrogen is mentioned, it is understood to refer to ^{1}H, ^{2}H, ^{3}H and mixtures thereof; when carbon is mentioned, it is understood to refer to ^{11}C, ^{12}C, ^{13}C, ^{14}C and mixtures thereof; when nitrogen is mentioned, it is understood to refer to ^{13}N, ^{14}N, ^{15}N and mixtures thereof; when oxygen is mentioned, it is understood to refer to ^{14}O, ^{15}O, ^{16}O, ^{17}O, ^{18}O and mixtures thereof; and when fluor is mentioned, it is understood to refer to ^{18}F, ^{19}F and mixtures thereof.

The compounds according to the invention therefore also comprise compounds with one or more isotopes of one or more element, and mixtures thereof, including radioactive compounds, also called radiolabelled compounds, wherein one or more non-radioactive atoms has been replaced by one of its radioactive isotopes. By the term "radiolabelled compound" is meant any compound according to Formula (I), an *N*-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, which contains at least one radioactive atom. For example, compounds can be labelled with positron or with gamma emitting radioactive isotopes. For

radioligand-binding techniques (membrane receptor assay), the ^{3}H-atom or the ^{125}I-atom is the atom of choice to be replaced. For imaging, the most commonly used positron emitting (PET) radioactive isotopes are ^{11}C, ^{18}F, ^{15}O and ^{13}N, all of which are accelerator produced and have half-lives of 20, 100, 2 and 10 minutes respectively. Since the half-lives of these radioactive isotopes are so short, it is only feasible to use them at institutions which have an accelerator on site for their production, thus limiting their use. The most widely used of these are ^{18}F, ^{99m}Tc, ^{201}Tl and ^{123}I. The handling of these radioactive isotopes, their production, isolation and incorporation in a molecule are known to the skilled person.

In particular, the radioactive atom is selected from the group of hydrogen, carbon, nitrogen, sulfur, oxygen and halogen. Preferably, the radioactive atom is selected from the group of hydrogen, carbon and halogen.

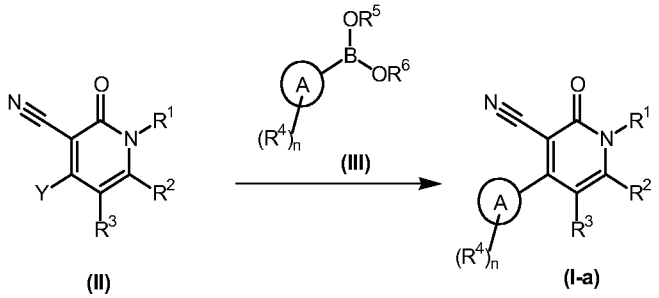
In particular, the radioactive isotope is selected from the group of ^{3}H, ^{11}C, ^{18}F, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br. Preferably, the radioactive isotope is selected from the group of ^{3}H, ^{11}C and ^{18}F.

A. Preparation of the final compounds

Experimental procedure 1 (L is a covalent bond)

The final compounds according to Formula (I-a), wherein L is a covalent bond, can be prepared by reacting an intermediate compound of Formula (II) with a compound of Formula (III) according to reaction scheme (1), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane or mixtures of inert solvents such as, for example, 1,4-dioxane/DMF, in the presence of a suitable base, such as, for example, aqueous $NaHCO_3$ or Na_2CO_3, a Pd-complex catalyst such as, for example, $Pd(PPh_3)_4$ under thermal conditions such as, for example, heating the reaction mixture at 150 °C under microwave irradiation, for example for 10 min. In a reaction suitable for Pd mediated coupling with boronic acids or boronic esters, such as, for example, a halo, triflate or pyridinium moiety. Such intermediate compounds may be prepared according to reaction schemes (8), (9) and (10) (see below). R^5 and R^6 may be hydrogen or alkyl, or may be taken together to form for example the bivalent radical of formula $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-C(CH_3)_2C(CH_3)_2-$.

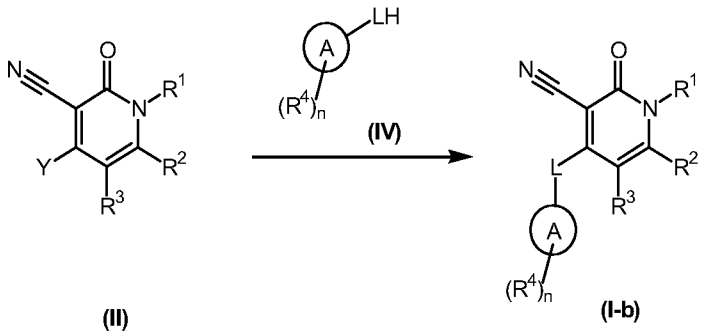
Reaction Scheme 1



Experimental procedure 2 (L is oxygen or sulfur)

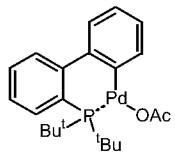
The final compounds according to Formula (I-b), wherein L is oxygen or sulfur, can be prepared by reacting an intermediate compound of Formula (II) with a compound of Formula (IV) according to reaction scheme (2), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, THF, in the presence of a suitable base, such as, for example, NaH, under thermal conditions such as, for example, heating the reaction mixture for example at 80 °C under microwave irradiation for 10 minutes. In reaction scheme (2), all variables are defined as in Formula (I), R^1 is V^1-M^1 and Y is a suitable leaving group, such as, for example, pyridinium.

Reaction Scheme 2



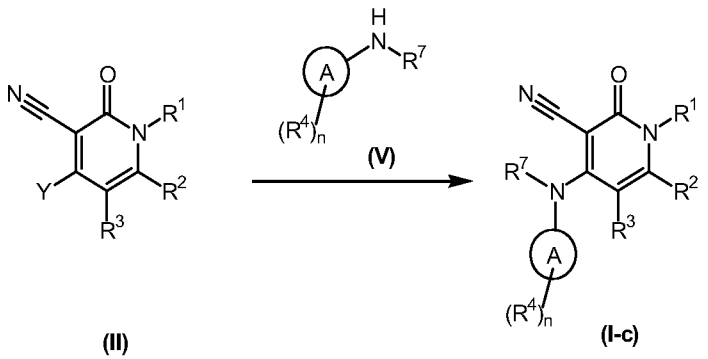
Experimental procedure 3 (L is aminoalkyl)

The final compounds according to Formula (I-c), wherein L is $-NR^7-$; $-NR^7CH_2-$; or $-NR^7CH_2CH_2-$ wherein each of R^7, independently of each other, is selected from the group of hydrogen and alkyl, can be prepared by reacting an intermediate compound of Formula (II) with a compound of Formula (V) according to reaction scheme (3), a reac-

tion that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane, in the presence of a suitable base, such as, for example, K_3PO_4, a Pd-complex catalyst such as, for example,  , under thermal conditions such as, for example, heating the reaction mixture for example at 80 °C for 12 hours. In reaction scheme (3), all variables are defined as in Formula (I), R^1 is V^1-M^1 and Y is a suitable group for Pd-mediated coupling with amines, such as, for example, halo.

Alternatively, compounds according to Formula (I-c) can be prepared by reacting an intermediate compound of Formula (II) with a compound of Formula (V) according to reaction scheme (3), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, dimethoxyethane or acetonitrile, in the presence of a suitable base, such as, for example, Cs_2CO_3 or *N,N*-diisopropylethylamine, under thermal conditions such as, for example, heating the reaction mixture for example at 160 °C under microwave irradiation for 30 minutes.

Reaction Scheme 3

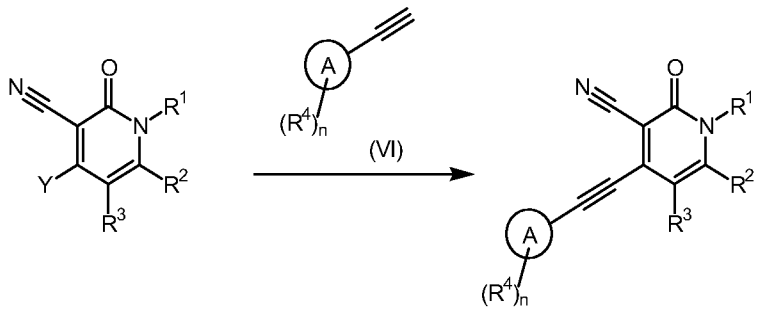


Experimental procedure 4 (L is alkynyl)

The final compounds according to Formula (I-d), wherein L is -C≡C-, can be prepared by reacting an intermediate compound of Formula (II) with a compound of Formula (VI) according to reaction scheme (4), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, THF, in the presence of a suitable base, such as, for example, NEt_3, a Pd-complex catalyst such as, for example, $PdCl_2(PPh_3)_2$ a phosphine such as, for example, PPh_3, a copper salt such as, for example, CuI and un-

der thermal conditions such as, for example, heating the reaction mixture for example at 80 °C for 12 hours. In reaction scheme (4), all variables are defined as in Formula (I), R^1 is V^1-M^1 and Y is a group suitable for Pd-mediated coupling with alkynes, such as, for example, halo.

Reaction Scheme 4

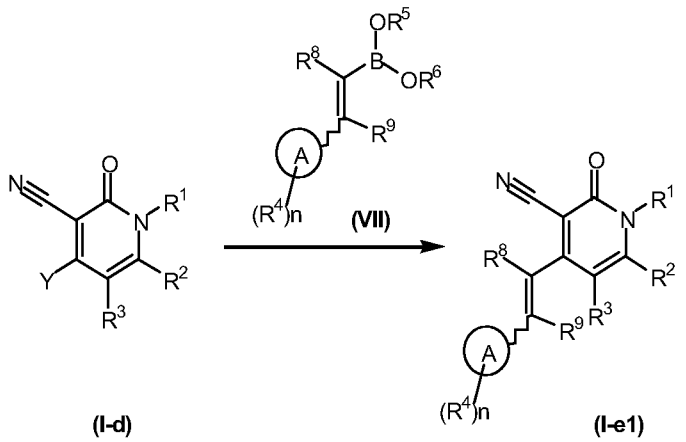


(II) (I-d)

Experimental procedure 5 (L is alkenyl)

The final compounds according to Formula (I-e), wherein L is -C(R^8)=C(R^9)- can be prepared by reaction of an intermediate of Formula (II) with an intermediate of Formula (VII) in an inert solvent such as, for example, 1,4-dioxane, in the presence of a suitable base, such as, for example, $NaHCO_3$ or Na_2CO_3, a Pd-complex catalyst such as, for example, $Pd(PPh_3)_4$ under thermal conditions such as, for example, heating the reaction mixture at 85 °C, for example for 8 hours. In reaction scheme (5), all variables are defined as in Formula (I) and Y is a group suitable for Pd-mediated coupling with boronic acids or boronic esters, such as, for example, a halo, trifluoromethanesulphonyl or pyridinium moiety. Such intermediate compounds may be prepared according to reaction schemes (8), (9) and (10) (see below). R^5 and R^6 may be hydrogen or alkyl, or may be taken together to form for example the bivalent radical of formula $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-C(CH_3)_2C(CH_3)_2-$. In reaction scheme (5), all variables are defined as in Formula (I) and R^1 is V^1-M^1.

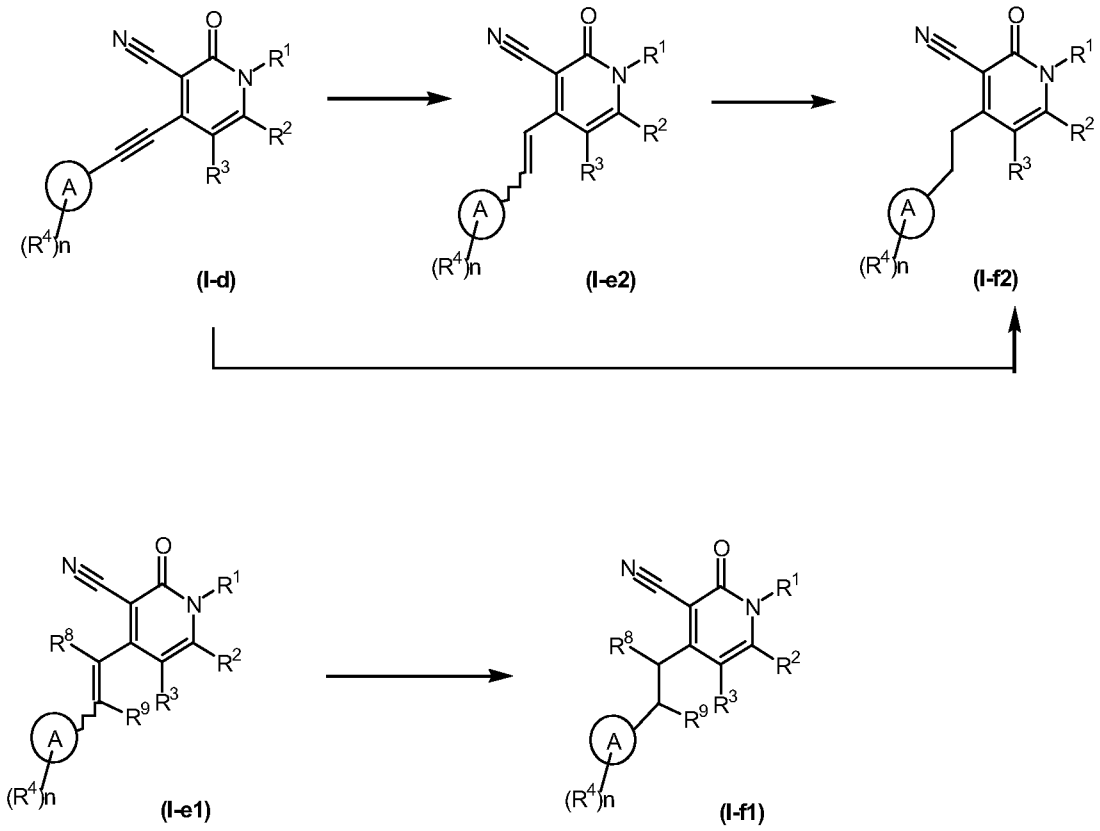
Reaction Scheme 5



Experimental procedure 6

The final compounds according to Formula (I-e2), wherein L is -CH=CH- and Formula (I-f2), wherein L is $-CH_2CH_2-$, can be prepared by art-known procedures such as, for example, hydrogenation of a final compound of Formula (I-d), prepared according to reaction scheme (6). Additionally, final compounds of Formula (I-f1) and Formula (I-f2) can be prepared from final compounds of Formula (I-e1) and Formula (I-e2) by art-known hydrogenation methods according to reaction scheme (6). Additionally, final compounds of Formula (I-e2) can be prepared by partial reduction of the triple bond of final compounds of Formula (I-d) by art known procedures. In reaction scheme (6), all variables are defined as in Formula (I) and R^1 is V^1-M^1.

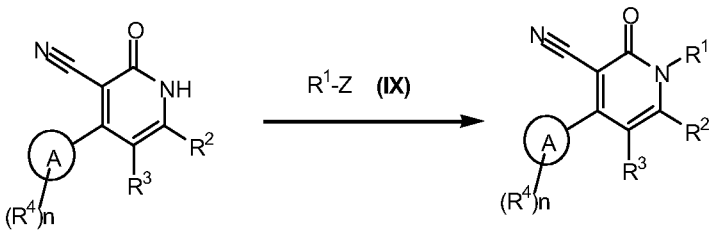
Reaction Scheme 6



Experimental procedure 7

The compounds according to Formula (I) can be prepared by art known procedures by reacting a compound of Formula (VIII) with an alkylating agent of Formula (IX), such as, for example, isopentylbromide, using a suitable base such as, for example, K_2CO_3, and an iodine salt such as, for example, KI, in an inert solvent such as, for example, acetonitrile at a moderately high temperature such as, for example, 120 °C. In reaction scheme (7), all variables are defined as in Formula (I), R^1 is V^1-M^1 and Z is a suitable leaving group such as, for example, halo.

Reaction Scheme 7



(VIII) (I)

Additionally, final compounds according to Formula (I) can be prepared by a skilled person using art known procedures by further modifications of final compounds of Formula (I-a), (I-b), (I-c), (I-d), (I-e) and (I-f) such as, for example:

- Alkylation of final compounds of Formula (I-a), (I-b), (I-c), (I-d), (I-e) and (I-f) that contain in their structure one or more hydroxy- or amino-substituents with a suitable alkylating agent under thermal conditions using a suitable base.

- Saponification of final compounds of Formula (I-a), (I-b), (I-c), (I-d), (I-e) and (I-f) that contain in their structure one or more alkyloxycarbonyl function by using a suitable saponificating agent such as, for example, NaOH or LiOH.

- Reaction of final compounds of Formula (I-a), (I-b), (I-c), (I-d), (I-e) and (I-f) that contain in their structure one or more carboxylic acid function with ammonia or a primary or secondary amine by using a suitable coupling agent such as, for example *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate, to yield the corresponding final compounds of Formula (I), bearing a primary, secondary or tertiary carboxamide function in their structures.

- Reaction of final compounds of Formula (I-a), (I-b), (I-c), (I-d), (I-e) and (I-f) that contain in their structure a primary or secondary amine function with a carboxylic acid by using a suitable coupling agent such as, for example, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate to yield the corresponding

final compounds of Formula (I), bearing a primary, secondary or tertiary carboxamide function in their structures.

- Reductive amination of final compounds of Formula (I-a), (I-b), (I-c), (I-d), (I-e) and (I-f) that contain in their structure one or more amino-substituents with a suitable aldehyde under thermal conditions using a suitable reducing agent such as, for example, sodium cyanoborohydride.

- Reaction of final compounds of Formula (I-a), (I-b), (I-c), (I-d), (I-e) and (I-f) that contain in their structure one or more hydroxy-substituents with an alcohol derivative by using a suitable coupling system such as, for example, di-tert-butylazodicarboxylate/triphenylphosphine under thermal conditions.

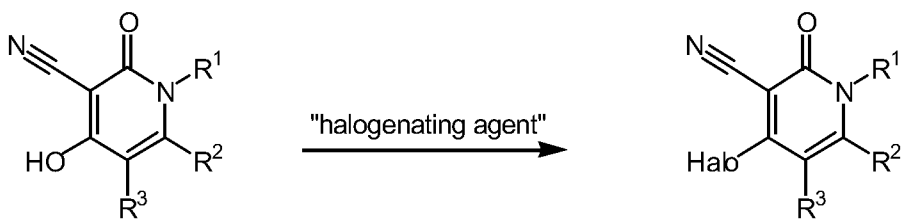
- 1,3-Dipolar cycloaddition of final compounds of Formula (I-a), (I-b), (I-c), (I-d), (I-e) and (I-f) that contain in their structure a reactive double or triple bond with a suitable dipole to yield the corresponding [3+2] adduct final compounds.

B. Preparation of the intermediate compounds

Experimental procedure 8

Intermediate compounds of Formula (II-a) can be prepared by reacting an intermediate of Formula (X) with a suitable halogenating agent such as, for example, $P(=O)Br_3$, a reaction that is performed in a suitable reaction-inert solvent such as, for example, DMF, at a moderately elevated temperature such as, for example, 110 °C. In reaction scheme (8), all variables are defined as in Formula (I) and R^1 is V^1-M^1.

Reaction Scheme 8

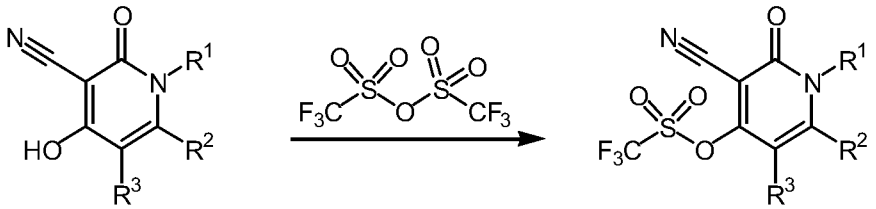


(X) (II-a)

Experimental procedure 9

Intermediate compounds of Formula (II-b) can be prepared by reacting an intermediate of Formula (X) with triflic anhydride (also called trifloromethanesulfonic anhydride), a reaction that is performed in a suitable reaction-inert solvent such as, for example, dichloromethane, in the presence of a base such as, for example, pyridine at a low temperature such as, for example, -78 °C. In reaction scheme (9), all variables are defined as in Formula (I) and R^1 is V^1-M^1.

Reaction Scheme 9

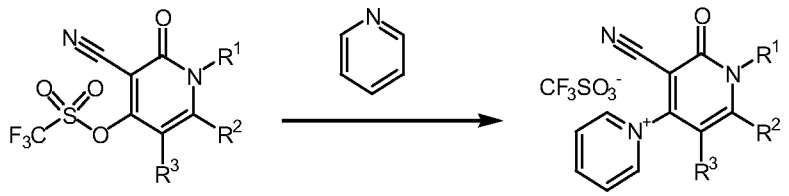


(X) (II-b)

Experimental procedure 10

Intermediate compounds of Formula (II-c) can be prepared by reacting an intermediate compound of Formula (II-b) with pyridine, at a moderately low temperature such as, for example, 40 °C. In reaction scheme (10), all variables are defined as in Formula (I) and R^1 is V^1-M^1.

Reaction Scheme 10



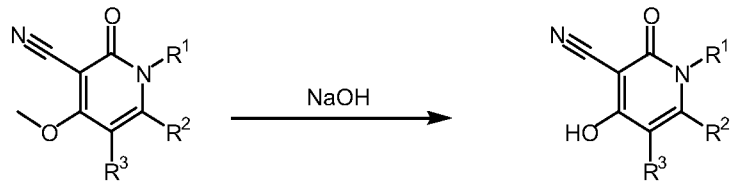
(II-b) (II-c)

Experimental procedure 11

Intermediate compounds of Formula (X) can be prepared by art known procedures by reacting an intermediate compound of Formula (XI) with a suitable reagent for me-

thylether-cleavage, such as, for example, NaOH, in a solvent such as, for example, water at a moderately high temperature such as, for example, 100 °C. In reaction scheme (11), all variables are defined as in Formula (I) and R^1 is V^1-M^1.

Reaction Scheme 11

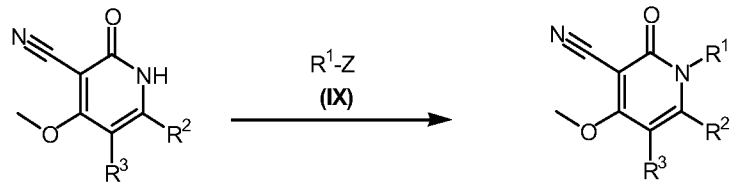


(XI) (X)

Experimental procedure 12

Intermediate compounds of Formula (XI) can be prepared by art known procedures by reacting an intermediate of Formula (XII) with an alkylating agent of Formula (IX), such as, for example, isopentylbromide, using a base such as, for example, K_2CO_3, and, optionally an iodine salt such as, for example, KI, in an inert solvent such as, for example, acetonitrile at a moderately high temperature such as, for example, 120 °C. In reaction scheme (12), all variables are defined as in Formula (I), R^1 is V^1-M^1 and Z is a suitable leaving group such as, for example, halo.

Reaction Scheme 12



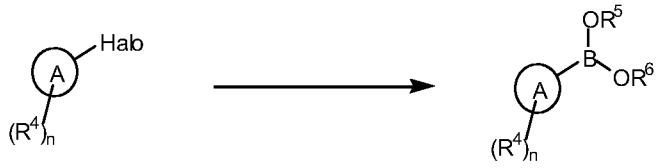
(XII) (XI)

Experimental procedure 13

Intermediate compounds of Formula (III) can be prepared by art known procedures by reacting an intermediate of Formula (XIII) with a suitable boron source such as, for example, bis(pinacolato)diboron in the presence of a Palladium catalyst such as, for

example, 1,1′-bis(diphenylphosphino)ferrocenepalladium(II)dichloride in a inert solvent such as, for example, dichloromethane, in the presence of a suitable salt such as, for example, potassium acetate at moderately high temperature such as, for example, 110°C for as for example 16 hours. Additionally, compounds of Formula (III) can be prepared by art known procedures of metal-halogen exchange and subsequent reaction with an appropriate boron source from compounds of Formula (XIII). Thus for example reaction of an intermediate compound of Formula (XIII) with an organolithium compound such as, for example, *n*-butyllithium at a moderately low temperature such as, for example, –40 °C in an inert solvent such as, for example, THF followed by subsequent reaction with an appropriate boron source such as, for example, trimethoxyborane. In reaction scheme (13), all variables are defined as in Formula (I) and R^5 and R^6 may be hydrogen or alkyl, or may be taken together to form for example the bivalent radical of formula $–CH_2CH_2$-, $-CH_2CH_2CH_2$-, or $-C(CH_3)_2C(CH_3)_2$-.

Reaction Scheme 13



(XIII) (III)

The starting materials of Formula (X) and the intermediate compounds according to Formula (III), (IV), (V), (VI), (VII), (IX), (XII) and (XIII) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art.

It is evident that in the foregoing and in the following reactions, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art, such as, for example, extraction, crystallization and chromatography. It is further evident that reaction products that exist in more than one enantiomeric form, may be isolated from their mixture by known techniques, in particular preparative chromatography, such as, for example, preparative HPLC.

Pharmacology

The compounds provided in this invention are positive allosteric modulators of metabotropic receptors, in particular they are positive allosteric modulators of mGluR2. The compounds of the present invention do not appear to bind to the glutamate recognition site, the orthosteric ligand site, but instead to an allosteric site within the seven transmembrane region of the receptor. In the presence of glutamate or an agonist of mGluR2, the compounds of this invention increase the mGluR2 response. The compounds provided in this invention are expected to have their effect at mGluR2 by virtue of their ability to increase the response of such receptors to glutamate or mGluR2 agonists, enhancing the response of the receptor. Hence, the present invention relates to a compound for use as a medicine, as well as to the use of a compound according to the invention or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 allosteric modulators, in particular positive mGluR2 allosteric modulators.

Also, the present invention relates to the use of a compound according to the invention or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating, or preventing, ameliorating, controlling or reducing the risk of various neurological and psychiatric disorders associated with glutamate dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 positive allosteric modulators.

Where the invention is said to relate to the use of a compound or composition according to the invention for the manufacture of a medicament for e.g. the treatment of a mammal, it is understood that such use is to be interpreted in certain jurisdictions as a method of e.g. treatment of a mammal, comprising administering to a mammal in need of such e.g. a treatment, an effective amount of a compound or composition according to the invention.

In particular, the neurological and psychiatric disorders associated with glutamate dysfunction, include one or more of the following conditions or diseases: acute

neurological and psychiatric disorders such as, for example, cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia (including AIDS-induced dementia), Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine (including migraine headache), urinary incontinence, substance tolerance, substance withdrawal (including substances such as, for example, opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), psychosis, schizophrenia, anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), mood disorders (including depression, mania, bipolar disorders), trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain (including acute and chronic states, severe pain, intractable pain, neuropathic pain, and post-traumatic pain), tardive dyskinesia, sleep disorders (including narcolepsy), attention deficit/hyperactivity disorder, and conduct disorder.

In particular, the condition or disease is a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.

Preferably, the central nervous system disorder is an anxiety disorder, selected from the group of agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), social phobia and other phobias.

Preferably, the central nervous system disorder is a psychotic disorder selected from the group of schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform disorder and substance-induced psychotic disorder

Preferably, the central nervous system disorder is a personality disorder selected from the group of obsessive-compulsive personality disorder and schizoid, schizotypal disorder.

Preferably, the central nervous system disorder is a substance-related disorder selected from the group of alcohol abuse, alcohol dependence, alcohol withdrawal, alcohol withdrawal delirium, alcohol-induced psychotic disorder, amphetamine dependence, amphetamine withdrawal, cocaine dependence, cocaine withdrawal, nicotine dependence, nicotine withdrawal, opioid dependence and opioid withdrawal.

Preferably, the central nervous system disorder is an eating disorder selected from the group of anorexia nervosa and bulimia nervosa.

Preferably, the central nervous system disorder is a mood disorder selected from the group of bipolar disorders (I & II), cyclothymic disorder, depression, dysthymic disorder, major depressive disorder and substance-induced mood disorder.

Preferably, the central nervous system disorder is migraine.

Preferably, the central nervous system disorder is epilepsy or a convulsive disorder selected from the group of generalized nonconvulsive epilepsy, generalized convulsive epilepsy, petit mal status epilepticus, grand mal status epilepticus, partial epilepsy with or without impairment of consciousness, infantile spasms, epilepsy partialis continua, and other forms of epilepsy.

Preferably, the central nervous system disorder is attention-deficit/hyperactivity disorder.

Preferably, the central nervous system disorder is a cognitive disorder selected from the group of delirium, substance-induced persisting delirium, dementia, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, dementia of the Alzheimer's type, substance-induced persisting dementia and mild cognitive impairment.

Of the disorders mentioned above, the treatment of anxiety, schizophrenia, migraine, depression, and epilepsy are of particular importance.

At present, the fourth edition of the Diagnostic & Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association provides a diagnostic tool for the identification of the disorders described herein. The person skilled in the art will recognize that alternative nomenclatures, nosologies, and classification systems for

neurological and psychiatric disorders described herein exist, and that these evolve with medical and scientific progresses.

Because such positive allosteric modulators of mGluR2, including compounds of Formula (I), enhance the response of mGluR2 to glutamate, it is an advantage that the present methods utilize endogenous glutamate.

Because positive allosteric modulators of mGluR2, including compounds of Formula (I), enhance the response of mGluR2 to agonists, it is understood that the present invention extends to the treatment of neurological and psychiatric disorders associated with glutamate dysfunction by administering an effective amount of a positive allosteric modulator of mGluR2, including compounds of Formula (I), in combination with an mGluR2 agonist.

The compounds of the present invention may be utilized in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula (I) or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone.

Pharmaceutical compositions

The invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a therapeutically effective amount of a compound according to the invention, in particular a compound according to Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof.

The compounds according to the invention, in particular the compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof , or any subgroup or combination thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering

drugs.

To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally, rectally, percutaneously, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as, for example, suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as, for example, starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary

dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, ininjectable solutions or suspensions and the like, and segregated multiples thereof. Since the compounds according to the invention are potent orally administrable dopamine antagonists, pharmaceutical compositions comprising said compounds for administration orally are especially advantageous.

As already mentioned, the invention also relates to a pharmaceutical composition comprising the compounds according to the invention and one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula (I) or the other drugs may have utility as well as to the use of such a composition for the manufacture of a medicament.

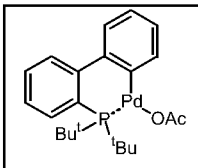
The following examples are intended to illustrate but not to limit the scope of the present invention.

Experimental part

Several methods for preparing the compounds of this invention are illustrated in the following Examples. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification :

AcOEt (ethyl acetate)	M (molar)
AcOH (acetic acid)	MeOH (methanol)
BBr_3 (boron tribromide)	mg (milligrams)
BINAP (±)-1,1'-Bi(2-naphthol)	$MgSO_4$ (magnesium sulphate)
Br_2 (bromine)	MHz (megahertz)
$CDCl_3$ (deuterated chloroform)	min (minutes)
CCl_4 (carbon tetrachloride)	µl (microliters)
DCM (dichloromethane)	ml (milliliters)
MCPBA (3-chloroperbenzoic acid)	mmol (millimol)
DEAD (diethyl azodicarboxylate)	m.p. (melting point)

DIBAL (diisobutyl aluminium hydride)	$NaBH(OAc)_3$ (Sodium triacetoxyboro-hydride)
DME (dimethoxyethane)	Na_2CO_3 (sodium carbonate)
DMF (dimethylformamide)	NaH (sodium hydride)
DMSO (dimethyl sulfoxide)	$NaHCO_3$ (sodium bicarbonate)
Dppf (1,1'-bis(diphenylphosphanyl)ferrocene)	NaHMDS (sodium hexamethyldisilazane)
EDCI.HCl (1-3(dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride)	NaI (sodium iodide)
Et_3N (triethylamine)	NaO^tBu (sodium *tert*-butoxide)
Et_2O (diethyl ether)	Na_2SO_4 (sodium sulphate)
EtOH (ethanol)	NBS (*N*-bromosuccinimide)
g (grams)	NH_4Cl (ammonium chloride)
^1H (proton)	NH_4OH (ammonium hydroxide)
H_2 (hydrogen)	NMR (Nuclear Magnetic Reasonance)
HCl (hydrochloric acid)	$Pd_2(dba)_3$ (palladium (II)dibenzylideneacetone)
HPLC (High Pressure Liquid Chromatography)	$PdCl_2(dppf)_2$ (Bis(1,1'-bis(diphenyl-phosphanyl)ferrocene palladium (II) di-chloride)
Hz (Hertz)	$PdCl_2(PPh_3)_2$ (Bis(triphenylphosphine) palladium (II) dichloride
KBr (potassium bromide)	$Pd(OAc)_2$ (Palladium acetate)
K_2CO_3 (potassium carbonate)	$Pd(PPh_3)_4$ (tetrakis(triphenylphosphine)palladium(0))
KOAc (potassium acetate)	$P(=O)Br_3$ (phosphorousoxybromide)
KI (potassium iodide)	PPh_3 (triphenylphosphine)
KO*t*Bu (potassium *tert*-butoxide)	TFA (trifluoroacetic acid)
KOH (potassium hydroxide)	THF (tetrahydrofuran)
K_3PO_4 (potassium phosphate)	TLC (thin layer chromatography)
LCMS (Liquid Chromatography Mass Spectrum)	Tf_2O (trifloromethanesulfonic anhydride)
$LiAlH_4$ (lithium aluminium hydride)	Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

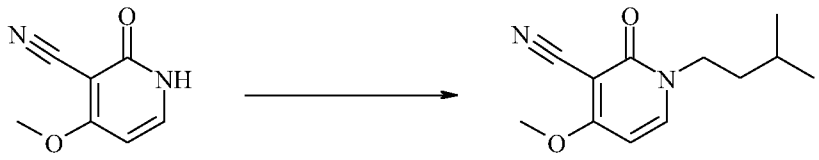
 ([577971-19-8] CAS)	

All references to brine refer to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Celsius). All reactions are conducted not under an inert atmosphere at room temperature, unless otherwise noted.

Microwave assisted reactions were performed in a single-mode reactor: Emrys™ Optimizer microwave reactor (Personal Chemistry A.B., currently Biotage). Description of the instrument can be found in www.personalchemistry.com. And in a multimode reactor: MicroSYNTH Labstation (Milestone, Inc.). Description of the instrument can be found in www.milestonesci.com.

A. Preparation of the intermediate compounds

A1. Intermediate compound 1



Intermediate compound 1

The reaction was carried out under N_2 atmosphere. To a solution of commercially available 4-methoxy-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (1.00 g, 6.60 mmol, 1 eq) in acetonitrile (45 ml) was added K_2CO_3 (2.73 g, 19.8 mmol, 3 eq) and isopentylbromide (441 mg, 8.65 mmol, 1.3 eq). The resulting solution was heated at 100 °C for 12 hours. The reaction was then cooled to room temperature and filtered through a pad of celite. The filtrate was then concentrated *in vacuo*. Subsequently, the crude residue thus obtained was purified by flash chromatography (SiO_2, eluting with a gradient elution of between 0 - 2 % MeOH in DCM) to yield intermediate compound 1 as a creamy solid (82 %, 5.40 mmol).

A2. Intermediate compounds 2 and 2'

Intermediate compound 2

A solution of **intermediate compound 1** (1.5 g, 6.81 mmol) in aqueous NaOH (0.1 N, 75 ml) and THF (20 ml) was heated to 100 °C for 1 hour. The reaction was cooled to 0 °C and acidified by the addition of 1M HCl, adjusting the pH to about 3, at which point a white solid precipitated. The solid was filtered off and dried *in vacuo* to yield the *N*-isopentyl substituted intermediate compound 2 as a white solid (1.3 g, 6.30 mmol). In an equal manner was prepared the *N*-*n*-butyl substituted intermediate compound 2'.

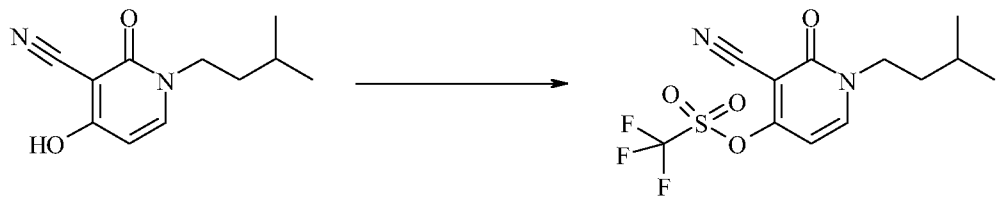
A3. Intermediate compounds 3, 3' and 3"

Intermediate compound 3

The reaction was carried out under N_2 atmosphere. To a solution of **intermediate compound 2** (2.00 g, 9.66 mmol, 1 eq) in DMF (10 ml) was added cautiously $P(=O)Br_3$ (5.54 g, 19.0 mmol, 2 eq), the resulting solution was then heated at 100 °C into a sealed tube for 2 hours. The reaction was then cooled to room temperature and diluted by H_2O (30 ml), the resulting solution was subsequently extracted with AcOEt (3 x 30 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to yield an oil. The crude product was purified by flash chromatography (SiO_2, eluting with DCM) to yield *N*-isopentyl substituted intermediate compound 3 as a creamy solid (2.13 g, 82 %, 7.92

mmol). In an equal manner was prepared the *N*-*n*-butyl substituted intermediate compound 3' and the *N*-methylcyclopropyl substituted intermediate compound 3".

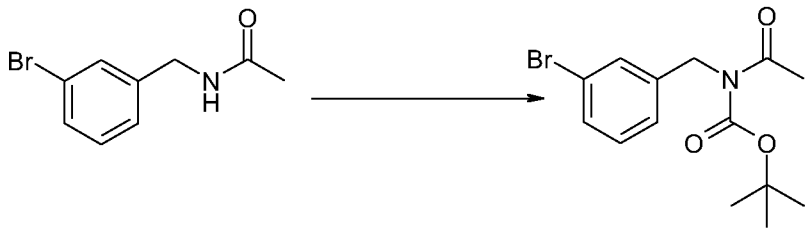
A4. Intermediate compound 4



Intermediate compound 4

In a round flask containing **intermediate compound 2** (100 mg, 0.48 mmol) in DCM (5 ml), were added 3 eq of pyridine (0.118 ml, 1.44 mmol). The mixture was cooled to -78 °C and Tf_2O (0.217 ml, 0.528 mmol) was added slowly. The solution was warmed to room temperature and stirred for 1/2 hour. The mixture was hydrolized with cold water, extracted with DCM (3 x 10 ml),washed twice with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to yield intermediate compound 4 (133 mg).

A6. Intermediate compound 6

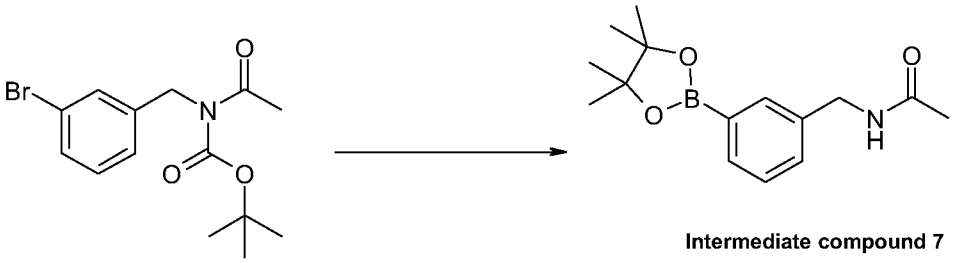


Intermediate compound 6

The reaction was carried out under nitrogen atmosphere. To a solution of *N*-(2-bromobenzyl)-acetamide (468 mg, 2.02 mmol) in acetonitrile (45 ml) was added di-*tert*-butyl dicarbonate (1.34 g, 6.15 mmol) and *N*,*N*-dimethaminopyridine (501 mg, 4.1 mmol). The reaction mixture was then stirred at room temperature for 20 min, after which time it was diluted with AcOEt (40 ml) and washed with a saturated solution of $NaHCO_3$ (2 x 40 ml) and a saturated solution of NH_4Cl (3 x 40 ml). The organic layer was then

dried over Na_2SO_4 and concentrated *in vacuo* to yield a crude solid. This was purified by short open column chromatography (SiO_2, eluting with 2 % MeOH in DCM) to yield intermediate compound 6 as a yellow oil (590.00 mg, 89 %, 1.79 mmol).

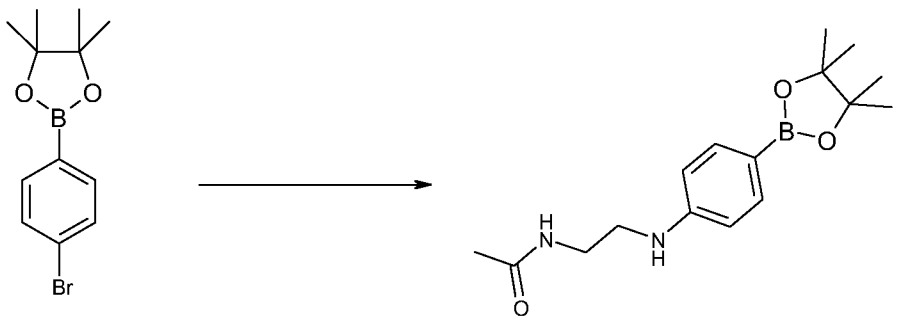
A7. Intermediate compound 7



Intermediate compound 7

To a solution of **intermediate compound 6** (200 mg, 0.61 mmol) in DMSO (4 ml) was added bis(pinacolato)diboron (232 mg, 0.913 mmol) and potassium KOAc (180 mg, 1.83 mmol) the solution was then degassed using a stream of nitrogen and then to the reaction mixture was added 1,1'-bis(diphenylphosphino)ferrocenepalladium (II) dichloride, DCM (20.0 mg, 0.0183 mmol). The reaction mixture was then heated at 110 °C under a nitrogen atmosphere for 16 hours. The reaction was then cooled to room temperature and diluted with AcOEt (30 ml) and the resulting solution was washed with water (3 x 15 ml), the organic fraction was then dried over Na_2SO_4 and concentrated *in vacuo* to yield the desired compound. The product was purified by short open column chromatography (SiO_2, eluting with DCM) to yield intermediate compound 7 as yellow oil (149.0 mg, 89 %, 0.054 mmol).

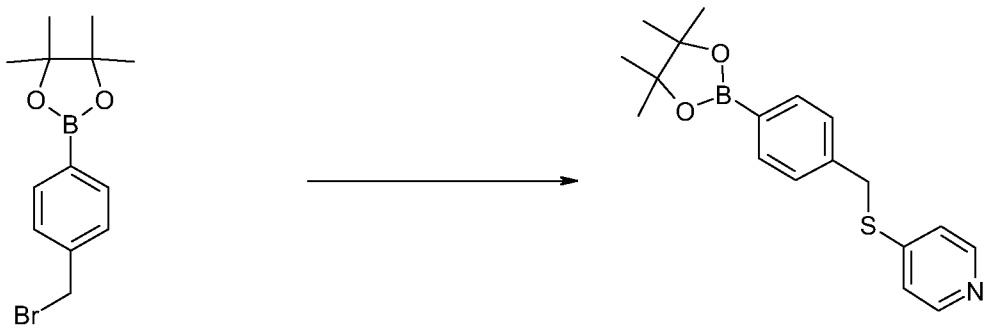
A8. Intermediate compound 8



Intermediate compound 8

The reaction was carried out under N_2 atmosphere. 4-Bromobenzeneboronic acid pinacol cyclic ester (300 mg, 1.06 mmol), *N*-acetylethylenediamine (0.155 ml, 1.59 mmol), Xantphos (123 mg, 0.21 mmol), and Cs_2CO_3 (518 mg, 1.59 mmol) were added to a mixture of 1,4-dioxane (5.88 ml) and DMF (0.12 ml) at room temperature, and N_2 was fluxed through the mixture for 5 min. $Pd(OAc)_2$ (24 mg, 0.1 mmol) was added and the mixture was irradiated under microwave conditions at 170 °C for 10 min into a sealed tube. The reaction was then cooled to room temperature and filtered through a pad of celited. The volatiles were evaporated in vacumm and the residues thus obtained was purified by short open column chromatography (SiO_2, eluting with DCM/MeOH(NH_3) to yield intermediate compound 8 (80 mg).

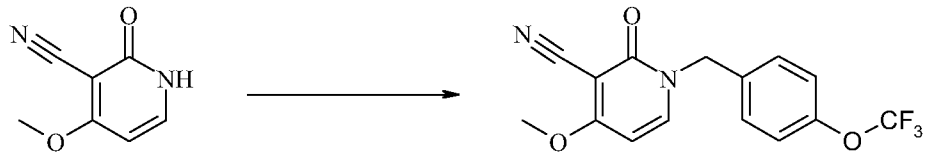
A9. Intermediate compound 9



Intermediate compound 9

To a solution of 4-pyridinethiol (149 mg, 1.35 mmol) in dimethyformamide (5 ml) was added K_2CO_3 (186 mg, 1.35 mmol) ; the resulting solution was stirred for 12 min and to this subsequently was added a solution of 2-(4-bromomethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (400 mg, 1.35 mmol) and the resulting solution was stirred for 2 hours. The mixture was then diluted by the addition of water (30 ml) and extracted with AcOEt (3 x 15 ml) ; the organic layer was subsequently dried over Na_2SO_4 and concentrated *in vacuo* to yield the crude product. The crude reaction mixture was subsequently purified by *Biotage* purification (eluting with DCM) to yield intermediate compound 9. (406.0 mg, 1.24 mmol, 92 %).

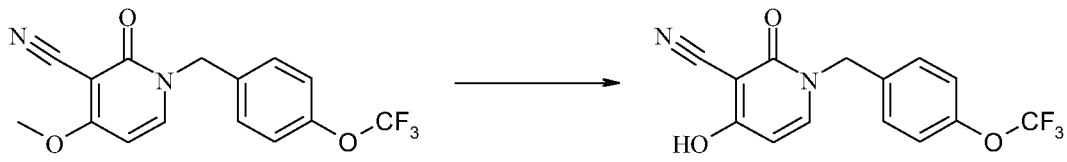
A10. Intermediate compound 10



Intermediate compound 10

Commercially available 4-methoxy-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (4.70 g, 31.29 mmol, 1 eq), 4-(trifluoromethoxy)benzylbromide (5.44 ml, 32.86 mmol, 1.05 eq) and K_2CO_3 (12.9 g, 93.8 mmol, 3 eq) were mixed in acetonitrile (200 ml). The mixture was heated at 140 °C for 16 hours into a sealed tube. The reaction was then cooled to room temperature and the solvents were evaporated in vacuum. The resulting residue was dissolved in DCM and filtered through a pad of celite. The filtrate was then concentrated *in vacuo*. Subsequently, the white solid thus obtained was triturated with diethylether to yield intermediate compound 10 as a white solid (9.20 g, 91 %).

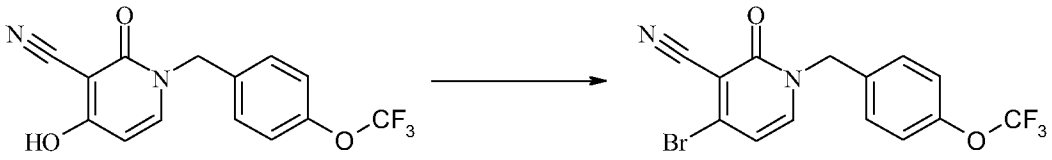
A11. Intermediate compound 11



Intermediate compound 11

To a solution of **intermediate compound 10** (9.20 g, 28.37 mmol) in THF (100 ml) was added aqueous NaOH (0.1 N, 300 ml). The reaction mixture was heated at 100 °C for 4 hours. The reaction was then cooled to room temperature and the THF was evaporated in vacuum. The resulting basic aqueous phase was acidified by the addition of 2 N HCl, adjusting the pH to about 3, at which point a white solid precipitated. The solid was filtered off, washed with diethylether and dried *in vacuo* to yield the intermediate compound 11 as a white solid (8.05 g, 91 %).

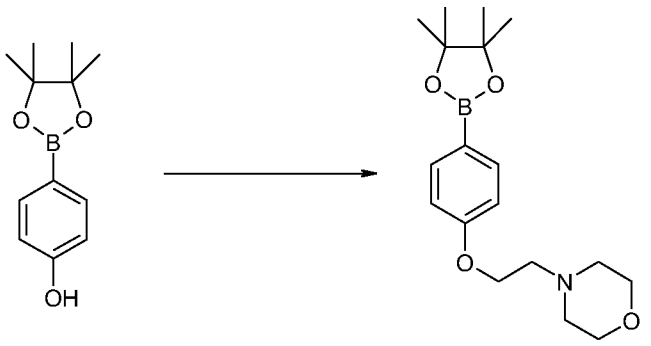
A12. Intermediate compound 12



Intermediate compound 12

Intermediate compound 11 (6.57 g, 21.19 mmol, 1 eq) and $P(=O)Br_3$ (12.15 g, 42.39 mmol, 2 eq) were mixed in DMF (125 ml) and the resulting mixture was then heated at 110 °C for 1 hour. The reaction was then cooled to room temperature and diluted with H_2O (200 ml), the resulting solution was subsequently extracted with AcOEt (3 x 75 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, eluting with DCM) to yield intermediate compound 12 as a white solid (6.75 g). In a similar manner was made **intermediate compound 12'** wherein the phenyl moiety in the para-position is substituted with a fluor instead of a trifluoromethoxy moiety.

A13. Intermediate compound 13

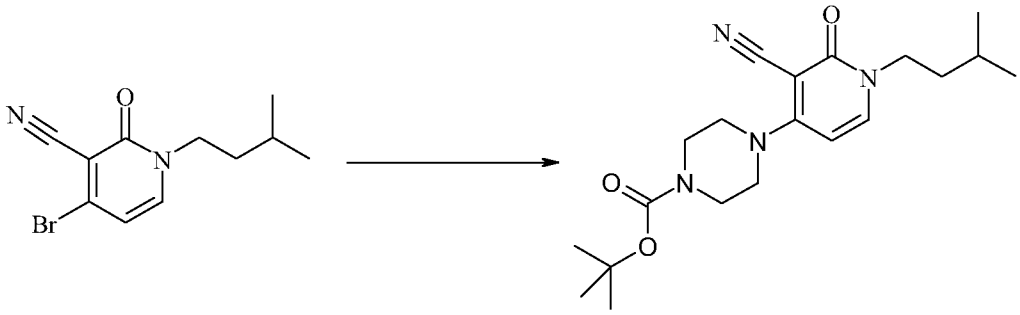


Intermediate compound 13

To a mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (500 mg, 2.27 mmol), *N*-(2-hydroxyethyl)morpholine (330.8 mg, 2.72 mmol) and PPh_3 polymer bound (loading 2.15 mmol/g) (2.11 g, 4.54 mmol) in dry DCM (30 ml) at 0 °C was added di-tert-butylazodicarboxylate (784.0 mg, 3.40 mmol). The reaction mixture was stirred at room temperature for 2 hours. Then, the resin was filtered off, washed with

DCM and the filtrate concentrated *in vacuo*. The residue (756.45 mg) was used in the next reaction step without further purification

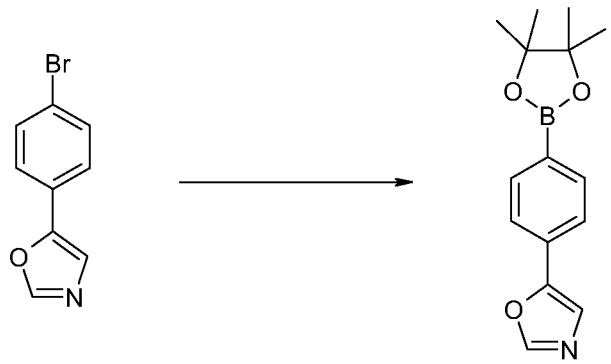
A14. Intermediate compound 14



Intermediate compound 14

Intermediate compound 3 (200 mg, 0.74 mmol), 1-tert-butoxycarbonylpiperazine (151 mg, 0.81 mmol), K_3PO_4 (236 mg, 1.1 mmol) and catalyst [577971-19-8] CAS (10 mg) were mixed in 1,4-dioxane (3 ml) at room temperature. The corresponding mixture was heated at 85 °C in a sealed tube for 16 hours. The mixture was cooled to room temperature, filtered through a pad of celite and washed with DCM. The filtrate was concentrated *in vacuo* and the residue thus obtained was purified by flash chromatography to yield intermediate compound 14 (200 mg, 72 %).

A16. Intermediate compound 16

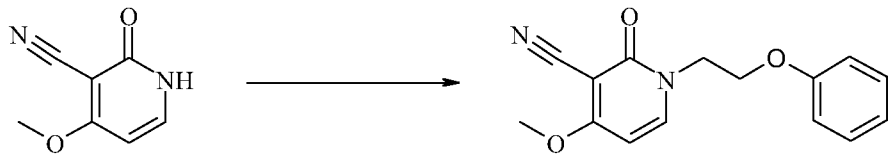


Intermediate compound 16

A mixture of 5-(4-bromophenyl)-1,3-oxazole (220 mg, 0.98 mmol), bis(pinacolato)-diboron (372 mg, 1.47 mmol), 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) di-

chloride, DCM (24 mg, 0.0294 mmol), KOAc (288 mg, 2.93 mmol) in DMSO (7 ml) was heated at 110 °C for 16 hours. The mixture was cooled to room temperature, diluted with AcOEt (30 ml) and washed with water (3 x 15 ml). The combined organic layers were dried over Na_2SO_4, evaporated in vacuum and the residue thus obtained (200 mg) was used in the next reaction step without further purification.

A17. Intermediate compound 17



Intermediate compound 17

A solution of commercially available 4-methoxy-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (4.0 g, 0.0266 mol), beta-bromophenetole (5.62 g, 0.0279 mol) and K_2CO_3 (11.0 g, 0.0799 mol) in CH_3CN (150 ml) was heated at reflux for 16 hours. The reaction mixture was then filtered off and the filtrate concentrated *in vacuo*. The residue was recrystallised from ethylether to yield intermediate compound 17 (7 g, 97 %).

A18. Intermediate compound 18

Intermediate compound 18

To a solution of **intermediate compound 17** (7.0 g, 0.0259 mol) in MeOH (100 ml) was added aqueous NaOH (0.1 N, 200 ml). The reaction mixture was heated to 100 °C for 3 hours. The reaction was then cooled to room temperature and the MeOH was evaporated in vacuum. The resulting basic aqueous phase was acidified by the addition of 2 N HCl, adjusting the pH to about 3, at which point a white solid precipitated. The

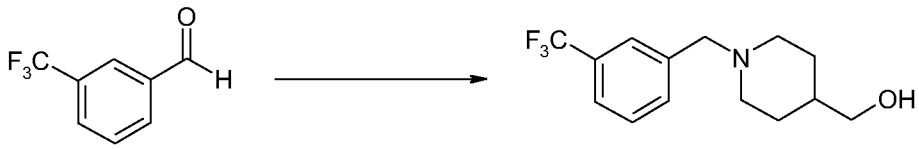
solid was collected using a sintered funnel, washed with ethylether and dried *in vacuo* to yield intermediate compound 18 as white solid (5.78 g, 87 %).

A19. Intermediate compound 19

Intermediate compound 19

Intermediate compound 18 (7.10 g, 0.027 mol) and $P(=O)Br_3$ (15.886 g, 0.055 mol) were mixed in DMF (150 ml) and the resulting mixture was then heated at 110 °C for 3 hours. The reaction was then cooled to room temperature and diluted by H_2O (100 ml), the resulting solution was subsequently extracted with AcOEt (3 x 150 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, eluting with DCM) to yield intermediate compound 19 (7.67 g, 89 %).

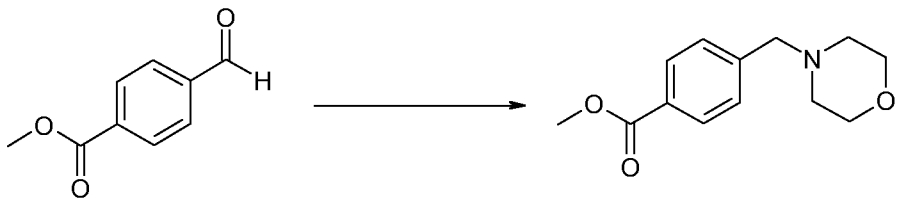
A20. Intermediate compound 20



Intermediate compound 20

In a round flask containing 3-(trifluoromethyl)benzaldehyde ([454-89-7] CAS) (0.872 ml, 0.0065 mol) and 4-piperidinemethanol (0.5 g, 0.0043 mol) in DCE (20-30 ml) and a few drops of AcOH, $NaBH(OAc)_3$ (2.2 g, 0.0107 mol) was added. The mixture was stirred overnight at room temperature , after which time it was washed with a saturated solution of $NaHCO_3$ and extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography to yield intermediate compound 20 (0.610 g, 56 %).

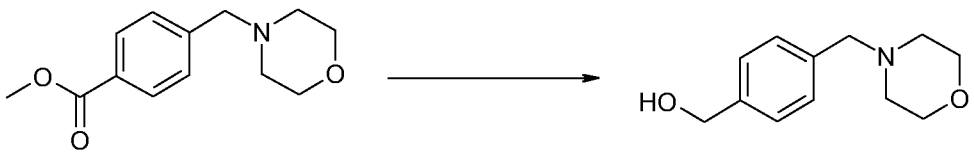
A23. Intermediate compound 23



Intermediate compound 23

In a round flask containing methyl-4-formylbenzoate (5.6 g, 0.034 mol) and morpholine (2 g, 0.023 mol) in DCE (20 ml), few drops of AcOH and molecular sieves (4A) were added. The reaction mixture was stirred at room temperature for 40 min and $NaBH(OAc)_3$ (5 g, 0.023 mol) was added. The mixture was stirred overnight at room temperature, after which time another equivalent of $NaBH(OAc)_3$ (5 g, 0.023 mol) was added. The mixture was stirred at room temperature for 5 hours and was subsequently washed with HCl (1 N) and extracted with DCM. The organic layer was finally washed with a saturated solution of $NaHCO_3$. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (DCM / $MeOH(NH_3)$ mixtures) to yield intermediate compound 23 (3 g, 60 %)

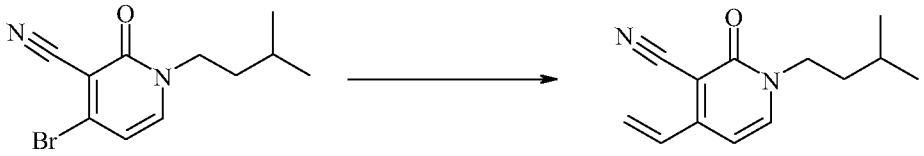
A24. Intermediate compound 24



Intermediate compound 24

The reaction was carried out under N_2 atmosphere. To a solution of **intermediate compound 23** (2 g, 0.0085 mol) in THF (12 ml), lithium aluminum hydride (1 M in THF) (17 ml, 0.017 mol) was slowly added. The reaction mixture was stirred at room temperature for 2 hours. Then, a saturated solution of $NaHCO_3$ was carefully added and the mixture was extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield intermediate compound 24 (1.75 g, 100 %) which was used in the next reaction step without further purification.

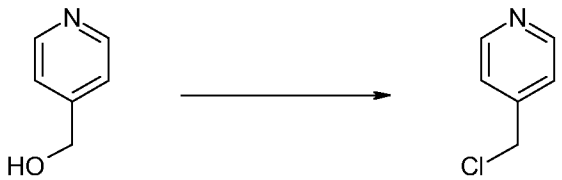
A28. Intermediate compound 28



Intermediate compound 28

A mixture of **intermediate compound 3** (250 mg, 0.93 mmol), tributyl(vinyl)tin (0.325 ml, 1.11 mmol) and $Pd(PPh_3)_4$ (22 mg, 0.0186 mmol) in degassed toluene (10 ml) was microwaved at 130 °C for 25 min. The mixture was then cooled to room temperature and solvents were evaporated in vacuum. The residue was purified by flash chromatography (SiO_2, DCM / $MeOH(NH_3)$ mixtures) to yield intermediate compound 28 (100 mg, 50 %) as pale yellow solid.

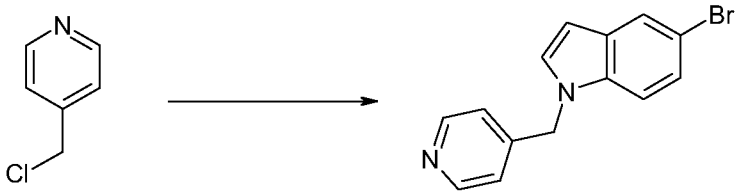
A29. Intermediate compound 29



Intermediate compound 29

To a solution of 4-pyridylcarbinol (15 g, 137.4 mmol) in DCM (200 ml) was added thionyl chloride (43.6 ml) and the resulting reaction mixture was stirred at room temperature for 4 h. The mixture was cooled to room temperature and the solvent was evaporated *in vacuo*. The residue was diluted with DCM and washed with a saturated solution of $NaHCO_3$. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield intermediate compound 29 (17.18 g, 99 %).

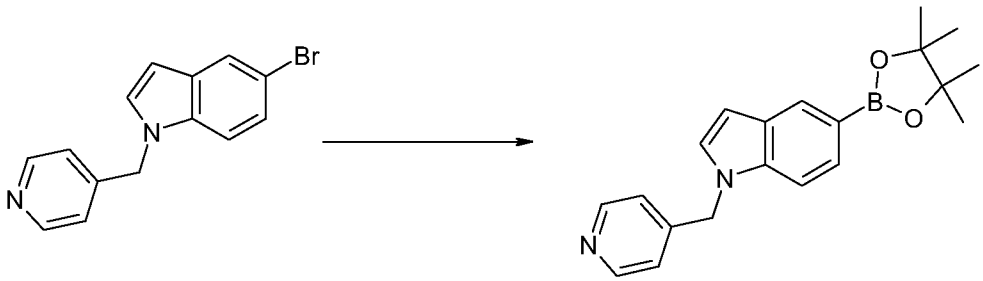
A30. Intermediate compound 30



Intermediate compound 30

To a mixture of NaH (60 % in mineral oil) (0.718 g, 17.96 mmol) in THF (20 ml), a solution of 5-bromoindole (2.34 g, 11.8 mmol) in THF (17 ml) was added dropwise. The resulting mixture was stirred at room temperature for 1 h. Then, **intermediate compound 29** (1.81 g, 14.2 mmol) was added and the mixture was heated at 80 °C overnight. The cooled reaction mixture was washed with H_2O and extracted with AcOEt. The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash chromatography (SiO_2, DCM / MeOH mixtures) to yield intermediate compound 30 (2.73 g, 80 %).

A31. Intermediate compound 31

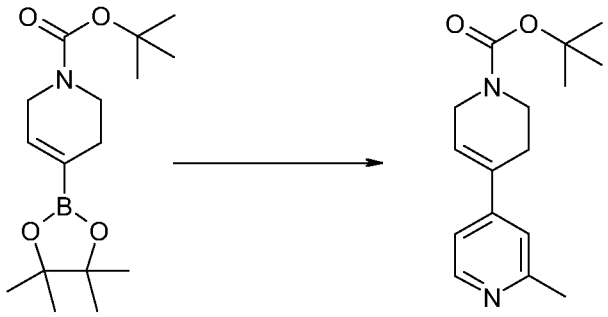


Intermediate compound 31

To a solution of **intermediate compound 30** (2.73 g, 9.5 mmol) in DMSO (27 ml) was added bis(pinacolato)diboron (2.414 g, 9.5 mmol) and KOAc (2.8 g, 28.5 mmol). The solution was then degassed using a stream of nitrogen and then to the reaction mixture was added 1,1'-bis(diphenylphosphino)ferrocenepalladium (II) dichloride, DCM (0.23 g, 0.28 mmol). The reaction mixture was then heated at 110 °C overnight under a nitrogen atmosphere. The reaction was then cooled to room temperature and additional amounts of bis(pinacolato)diboron (1.63 g, 6.4 mmol), KOAc (1.89 g, 19.2 mmol) and 1,1'-bis(diphenylphosphino)ferrocenepalladium (II) dichloride, DCM (0.155 g, 0.19

mmol) were added and the mixture was heated at 130 °C overnight. The cooled reaction mixture was diluted with AcOEt, filtered through a pad of celite and the filtrate was washed with water. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield intermediate compound 31 (4.5 g, quant.) used in the next reaction step without further purification.

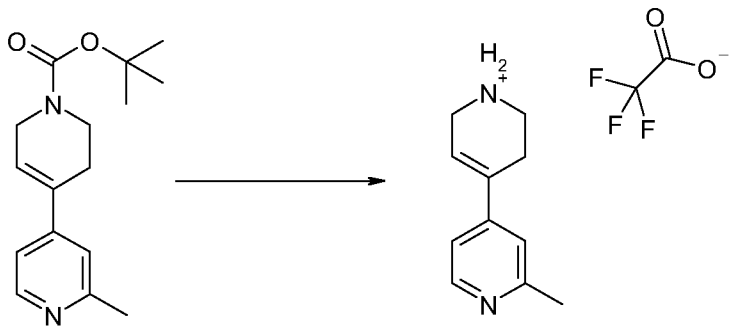
A32. Intermediate compound 32



Intermediate compound 32

To a mixture of (*N*-tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester ([286961-14-6] CAS) (1.5 g, 4.8 mmol) in a mixture of 1,4-dioxane (8 ml) and DMF (2 ml) were added 4-chloro-2-picoline (0.308 g, 2.4 mmol), 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride, DCM (0.293 g, 0.36 mmol) and potasium carbonate (0.993 g, 7.2 mmol). The mixture was then degassed using a stream of nitrogen and then microwaved at 160 °C for 90 min. The cooled reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, DCM / MeOH(NH_3) mixtures) to yield intermediate compound 32 (0.5 g, 38 %).

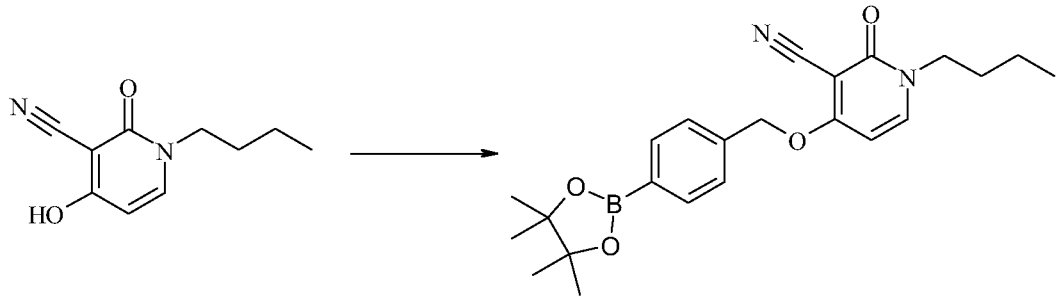
A33. Intermediate compound 33



Intermediate compound 33

A solution of **intermediate compound 32** (0.5 g, 1.82 mmol) in a 20 % solution of TFA in DCM (10 ml) was stirred at room temperature for 4 hours, after which time the solvent was evaporated. The residue (0.5 g) was used in the next reaction step without further purification.

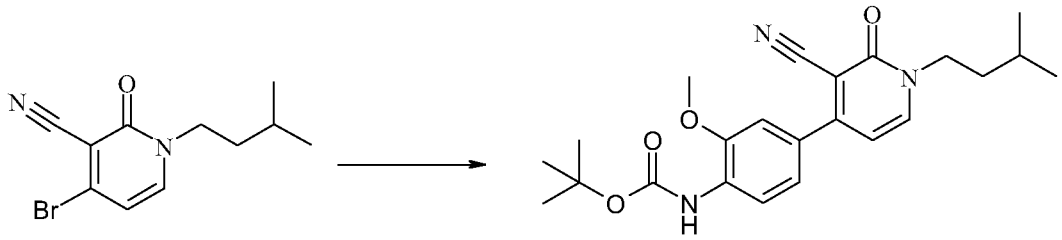
A35. Intermediate compound 35



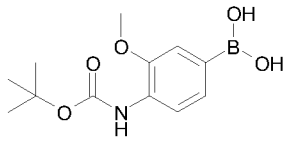
Intermediate compound 2' Intermediate compound 35

To a solution of **intermediate compound 2'** (1.5 g, 7.8 mmol) in acetonitrile (13 ml), (4-bromomethylphenyl)boronic acid, pinacol ester (3.0 g, 9.76 mmol) ([138500-85-3] CAS) and cesium carbonate (5.92 g, 15.6 mmol) were added. The reaction mixture was microwaved at 160 °C for 30 min. Then, solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (SiO_2, DCM / MeOH mixtures) to yield intermediate compound 35 (2.93 g, 92 %).

A36. Intermediate compound 36

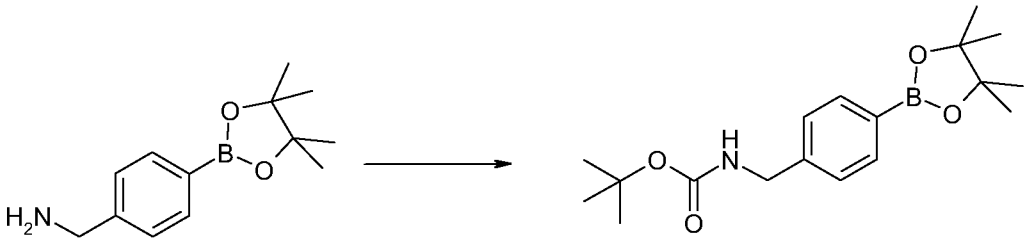


Intermediate compound 36



A mixture of **intermediate compound 3** (0.366 g, 1.36l mmol), (compound described in US 2005187277 A1) (0.436 g, 1.63 mmol, $Pd(PPh_3)_4$ (0.157 g, 0.136 mmol) in 1,4-dioxane (2 ml) and a saturated solution of Na_2CO_3 (2 ml) was microwaved at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and the filtrate evaporated *in vacuum*. The residue was subsequently purified by flash chromatography (SiO_2, DCM / MeOH(NH_3) mixtures) to yield intermediate compound 36 (0.55 g, 98 %).

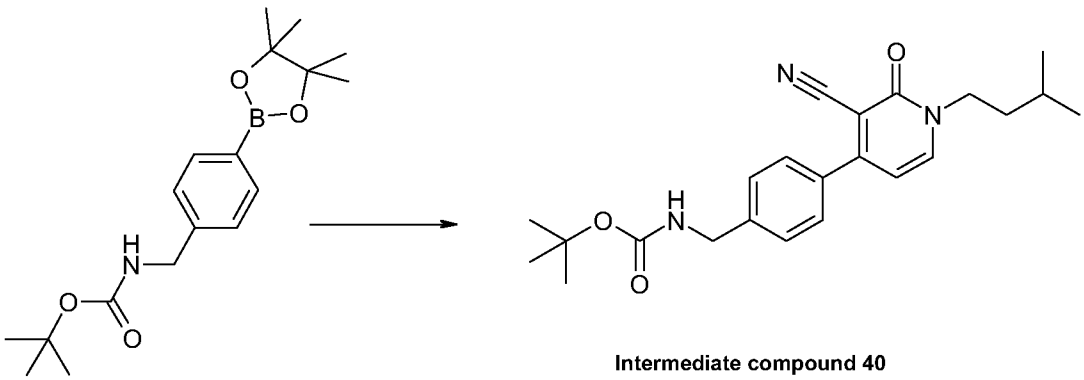
A39. Intermediate compound 39



Intermediate compound 39

To a solution of 4-aminomethylphenylboronic acid, pinacol ester (CAS 138500-88-6) (1.2 g, 5.14 mmol) and Et_3N (1.42 ml, 10.28 mmol) in DCM (50 ml) stirred at room temperature, di-tert-butyldicarbonate (1.68 g, 7.72 mmol) was added. The mixture was stirred at room temperature for 2 hours. The solvent was evaporated *in vacuum* to yield a residue which was treated with diethylether to yield intermediate compound 39 (1.7 g) as a solid, 99 %) used in the next reaction step without further purification.

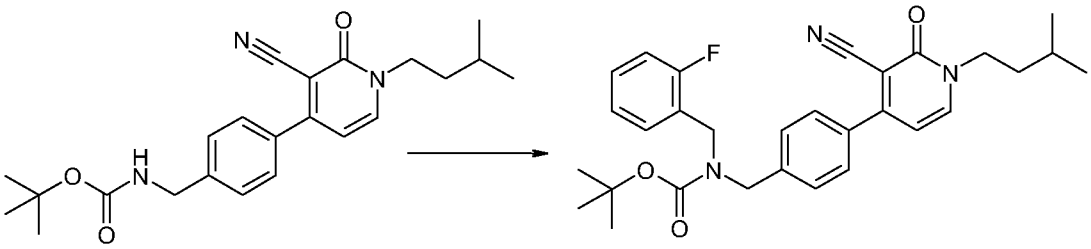
A40. Intermediate compound 40



Intermediate compound 40

To a solution of **intermediate compound 39** (1.7 g, 5.14 mmol) in 1,4-dioxane (3 ml) and a saturated solution of $NaCO_3$ (3 ml) was added intermediate compound 3 (1.15 g, 4.28 mmol). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (485.0 mg, 0.42 mmol). The reaction was then microwaved into a sealed tube at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and the filtrate concentrated *in vacuo*. The crude reaction mixture was then purified by flash chromatography (SiO_2, DCM / $MeOH(NH_3)$ 9:1) to yield intermediate compound 40 (1.3 g, 77 %).

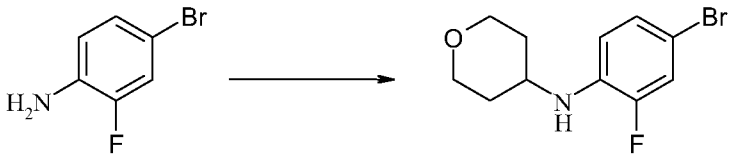
A41. Intermediate compound 41



Intermediate compound 41

To a solution of **intermediate compound 40** (0.125 g, 0.316 mmol) in DMF (dried, 5 ml) at 0 °C, NaH (60 % mineral oil; 0.019 mg, 0.474 mmol) was added. The resulting suspension was stirred at 0 °C (under nitrogen atmosphere) for 30 min. Then, 3-fluorobenzylbromide (0.059 ml, 0.474 mmol) was added. The reaction mixture was stirred at room temperature for 3 hours. Then, water was added and the resulting aqueous mixture was extracted with AcOEt. The organic layer was washed with a saturated solution of NaCl. The combined organic layers were dried over Na_2SO_4. The crude reaction mixture was then purified by flash chromatography (SiO_2, DCM / $MeOH(NH_3)$ 9:1) to yield intermediate compound 41 (0.082 g, 51 %) as a yellow oil.

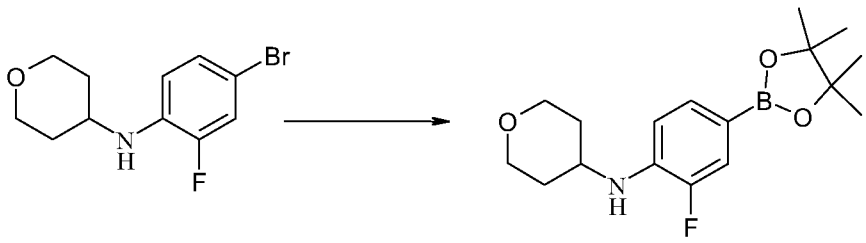
A42. Intermediate compound 42



Intermediate compound 42

To a mixture of 4-bromo-2-fluoroaniline (0.6 g, 3.15 mmol), tetrahydro-4*H*-pyran-4-one (0.68 g, 6.31 mmol) and $NaBH(OAc)_3$ (0.96 g, 4.72 mmol) in DCE (20 ml), molecular sieves (4A) (1g) were added. The mixture was stirred at room temperature for 16 h. Then, additional amounts of tetrahydro-4*H*-pyran-4-one (0.34 g, 3.15 mmol) and $NaBH(OAc)_3$ (0.66 g, 3.15 mmol) were added and the mixture was stirred at room temperature for 48 h. Then, the reaction mixture was filtered through a pad of celite and washed with DCM. The filtrate was concentrated *in vacuo* to yield intermediate compound 42 (0.86 g, quant.) used in the next reaction step without further purification.

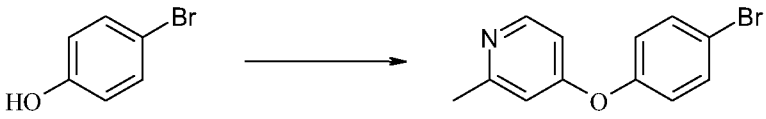
A43. Intermediate compound 43



Intermediate compound 43

To a solution of **intermediate compound 42** (0.86 g, 3.15 mmol) in DMSO (3 ml) was added bis(pinacolato)diboron (0.80 g, 3.15 mmol) and KOAc (0.93 g, 9.45 mmol) the solution was then degassed using a stream of nitrogen and then to the reaction mixture was added 1,1'-bis(diphenylphosphino)ferrocenepalladium (II) dichloride, DCM (0.07 g, 0.09 mmol). The reaction mixture was then heated at 120 °C under a nitrogen atmosphere for 16 hours. The reaction was then cooled to room temperature and diluted with water (50 ml) and the resulting solution was extracted with AcOEt, the organic fraction was then dried over Na_2SO_4 and concentrated *in vacuo* to yield intermediate compound 43 (1.01 g, 100 %) used in the next reaction step without further purification.

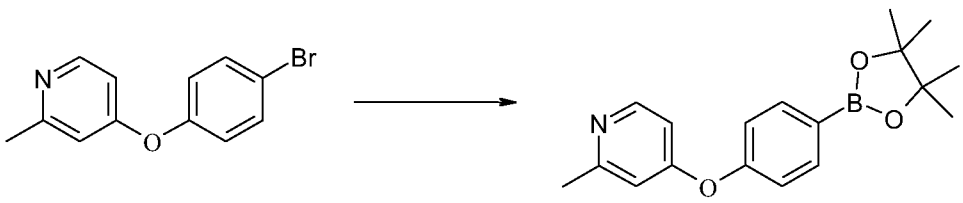
A44. Intermediate compound 44



Intermediate compound 44

To a solution of NaH (60 % in mineral oil) (0.13 g, 3.25 mmol) in DMF (5 ml) was added commercially available 4-bromophenol (0.50 g, 2.89 mmol) and the reaction was stirred at room temperature for 10 min. Then, 4-chloro-2-picoline (0.30 g, 2.40 mmol) was added and the resulting reaction mixture was then microwaved at 150ºC for 10 min. After cooling, the mixture was diluted with water and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue thus obtained was purified by flash chromatography (DCM) to yield intermediate compound 44 (0.52 g, 81%).

A45. Intermediate compound 45

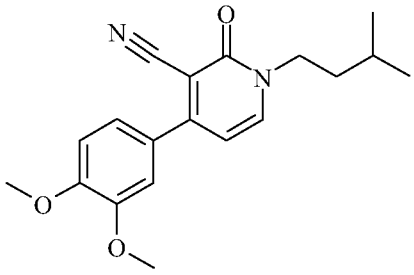


Intermediate compound 45

To a solution of **intermediate compound 44** (0.50 g, 1.89 mmol) in DMSO (5 ml) was added bis(pinacolato)diboron (0.72 g, 2.84 mmol) and KOAc (0.56 g, 5.68 mmol) the solution was then degassed using a stream of nitrogen and then to the reaction mixture was added 1,1'-bis(diphenylphosphino)ferrocenepalladium (II) dichloride, DCM (0.05 g, 0.06 mmol). The reaction mixture was then heated at 110 ºC under a nitrogen atmosphere for 16 hours. The reaction was then cooled to room temperature and diluted with water and the resulting solution was extracted with AcOEt, the organic fraction was then dried over Na_2SO_4 and concentrated *in vacuo* to yield intermediate compound 45 (0.58 g, 100 %) used in the next reaction step without further purification.

B. Preparation of the final compounds

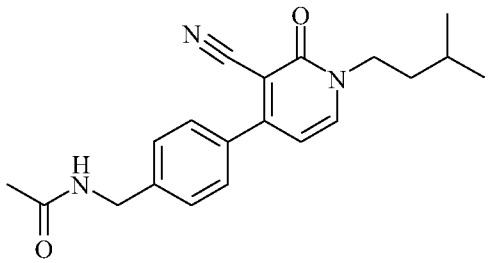
B1. Final compound 1-110



Final compound 1-110

To a solution of 3,4-dimethoxyphenylboronic acid (740.0 mg, 4.08 mmol) in 1,4-dioxane (14 ml) and a saturated solution of $NaHCO_3$ (14 ml) was added **intermediate compound 3** (1.00 g, 3.70 mmol). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (641.0 mg, 0.55 mmol). The reaction was then microwaved into a sealed tube at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and the filtrate concentrated *in vacuo*. The crude reaction mixture was then purified by flash chromatography (eluting with a solvent gradient 0-2 % MeOH in DCM) to yield the desired compound. The compound was then recrystallised from diethylether to yield the final compound **1-110** (940.0 mg, 2.88 mmol, 78 %).

B2. Final compound 1-179

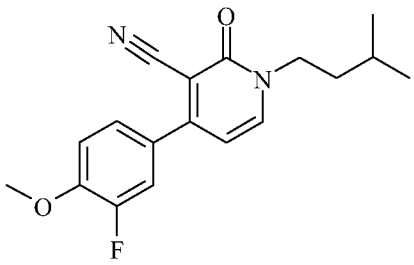


Final compound 1-179

Intermediate compound 4 (150 mg, 0.44 mmol), and 4-(acetamidomethyl)phenylboronic acid (129 mg, 0.67 mmol) were mixed in 1,4-dioxane (5 ml) and Et_3N (0.12 ml, 0.89 mmol) at room temperature and N_2 was flushed through the mixture for 5 min. $Pd(PPh_3)_4$ (77 mg, 0.067 mmol) was added and the resulting mixture was heated at 90 °C for 2 hours. The mixture was cooled to room temperature, diluted with AcOEt and brine. The aqueous phase was extracted with AcOEt (3 x 20ml). The combined organ-

ics layers were dried over Na_2SO_4, evaporated in vacuum and the residue thus obtained was purified by column chromatography (SiO_2, DCM / AcOEt) to yield 16 mg of final compound **1-179** as a white solid.

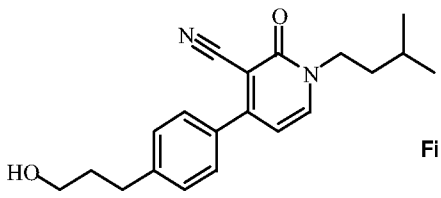
B3. Final compound 1-114



Final compound 1-114

Intermediate compound 4 (150 mg, 0.44 mmol), 3-fluoro-4-methoxyphenylboronic acid (110 mg, 0.67 mmol) were mixed in 1,4-dioxane (5 ml) and Et_3N (0.12 ml, 0.89 mmol) at room temperature and N_2 was flushed through the mixture for 5 min. $Pd(PPh_3)_4$ (77 mg, 0.067 mmol) was added and the resulting mixture was heated at 90 °C for 2 hours. The mixture was cooled to room temperature, diluted with AcOEt and brine. The aqueous phase was extracted with AcOEt (3 x 20ml). The combined organics layers were dried over Na_2SO_4, evaporated in vacuum and the residue thus obtained was purified by column chromatography (SiO_2, DCM / AcOEt) to yield 43 mg of final compound **1-114** as a yellow solid.

B4. Final compound 1-095

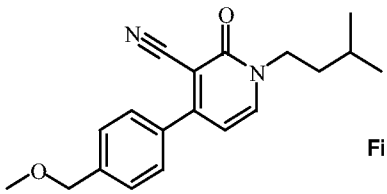


Final compound 1-095

Intermediate compound 4 (150 mg, 0.44 mmol) and 4-(3-hydroxypropyl)-phenylboronic acid (120 mg, 0.67 mmol) were mixed in 1,4-dioxane (5 ml) and Et_3N (0.12 ml, 0.89 mmol) at room temperature and N_2 was flushed through the mixture for 5 min. $Pd(PPh_3)_4$ (77 mg, 0.067 mmol) was added and the resulting mixture was heated at 90 °C for 2 hours. The mixture was cooled to room temperature, diluted with AcOEt

and brine. The aqueous phase was extracted with AcOEt (3 x 20 ml). The combined organics layers were dried over Na_2SO_4, evaporated in vacuum and the residue thus obtained was purified by column chromatography (SiO_2, DCM / AcOEt) to yield 40 mg of final compound **1-095** as a white solid.

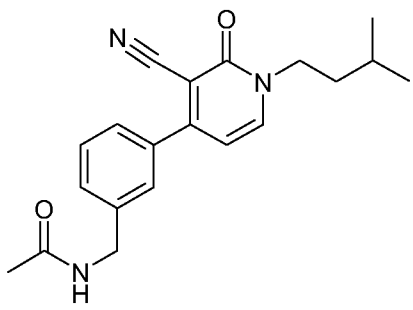
B5. Final compound 1-103



Final compound 1-103

Intermediate compound 4 (150 mg, 0.44 mmol), 4-(methoxymethyl)phenylboronic acid (110 mg, 0.67mmol) were mixed in 1,4-dioxane (5 ml) and Et_3N (0.12 ml, 0.89 mmol) at room temperature and N_2 was flushed through the mixture for 5 min. $Pd(PPh_3)_4$ (77 mg, 0.067 mmol) was added and the resulting mixture was heated at 90 °C for 2 hours. The mixture was cooled to room temperature, diluted with AcOEt and brine. The aqueous phase was extracted with AcOEt (3 x 20 ml). The combined organics layers were dried over Na_2SO_4, evaporated in vacuum and the residue thus obtained was purified by column chromatography (SiO_2, DCM/AcOEt) to yield 52 mg of final compound **1-103** as a white solid.

B6. Final compound 1-178

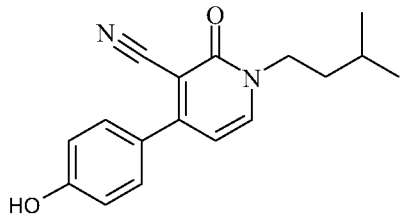


Final compound 1-178

To a solution of **intermediate compound 7** (220.0 mg, 0.58 mmol), in 1,4-dioxane (6 ml) and a saturated solution of Na_2CO_3 (6 ml) was added **intermediate compound 3** (173 mg, 0.65 mmol). The resulting solution was degassed using a stream of nitrogen

and to this was added $Pd(PPh_3)_4$ (101.0 mg, 0.088 mmol). The reaction was then microwaved at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and the filtrate concentrated *in vacuo*. The crude reaction mixture was then purified by preperative HPLC to yield the pure final compound **1-178** (51 mg, 0.15 mmol, 26 %).

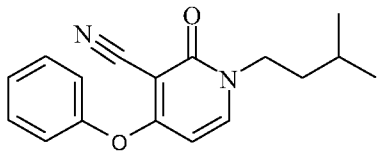
B7. Final compound 1-097



Final compound 1-097

To a solution of 4-hydroxyphenylboronic acid (336 mg, 2.44 mmol), in 1,4-dioxane (20 ml) and a saturated solution of NEt_3 (0.615 ml, 4.43 mmol) was added **final compound 5-052** (750 mg, 1.79 mmol). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (384 mg, 0.33 mmol). The reaction was heated at 90 °C for 2 hours into a sealed tube. The resulting reaction mixture cooled to room temperature, was diluted with water and brine and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and vacuum concentrated. The crude reaction mixture was then purified by flash chromatography (SiO_2, eluting with mixtures of heptane / AcOEt) to yield the final compound **1-097** (230 mg, 45 %).

B8. Final compound 1-274

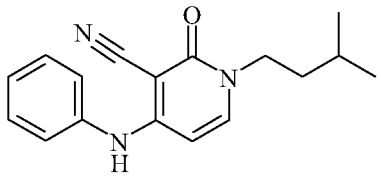


Final compound 1-274

To a solution of phenol (0.042 ml, 0.48 mmol) in dry THF (3 ml) at room temperature, NaH (60 % in mineral oil, 13.83 mg, 0.96 mmol) was added. The resulting mixture was stirred at room temperature for 5 min. **Final compound 5-052** (100 mg, 0.24 mmol) was added. The mixture was microwaved into a sealed tube for 10 min at 80 °C. The

mixture was cooled to room temperature, solvents were evaporated *in vacuo* and the residue thus obtained was purified by column chromatography (SiO_2, DCM / MeOH(NH_3) mixtures) to yield 55 mg of final compound **1-274** as a white solid.

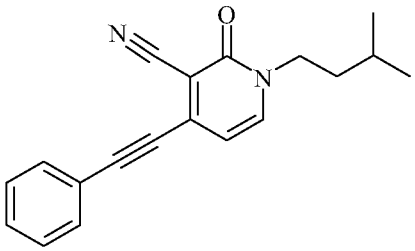
B9. Final compound 1-298



Final compound 1-298

Intermediate compound 3 (100 mg, 0.371 mmol), aniline (0.067 ml, 0.743 mmol) K_3PO_4 (158 mg, 0.745 mmol) and catalyst [577971-19-8] CAS (10 mg) were mixed in 1,4-dioxane (15 ml) at room temperature. The corresponding mixture was stirred at 80 ºC (oil bath temperature) into a sealed tube for 12 hours. The mixture was cooled to room temperature and AcOEt (30 ml) and $NaHCO_3$ (10 ml, aqueous saturated solution) were added to the reaction mixture. Layers were separated and the organic one was dried over Na_2SO_4. Solvents were evaporated in vacuum and the residue thus obtained was purified by flash chromatography to yield final compound **1-298** (50 mg).

B10. Final compound 1-267

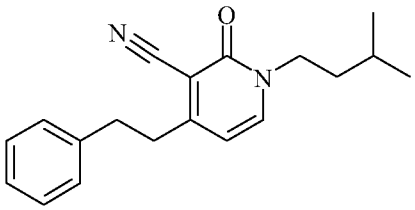


Final compound 1-267

Reaction under nitrogen atmosphere. **Intermediate compound 3** (150 mg, 0.557 mmol), phenylacetylene (0.064 ml, 0.580 mmol), $PdCl_2(PPh_3)_2$ (19.6 mg, 0.028 mmol) PPh_3 (3.7 mg, 0.014 mmol) and NEt_3 (0.078 ml, 2.23 mmol) were mixed in THF (6 ml) at room temperature and N_2 was flushed through the mixture for 5 min. CuI (1.3 mg, 0.007 mmol) was added and the resulting mixture was heated at 90 ºC (oil bath temperature) into a sealed tube for 10 hours. The reaction mixture was cooled to room tem-

perature and aqueous $Na_2S_2O_4$ (saturated solution) was added. DCM (30 ml) was added and the layers were separated. The organic layer was washed with aqueous $NaHCO_3$ (saturated solution), dried over Na_2SO_4 and vacuum concentrated. The residue thus obtained was purified by flash chromatography (SiO_2, DCM / MeOH(NH_3) mixtures) to yield final compound **1-267** (57 mg).

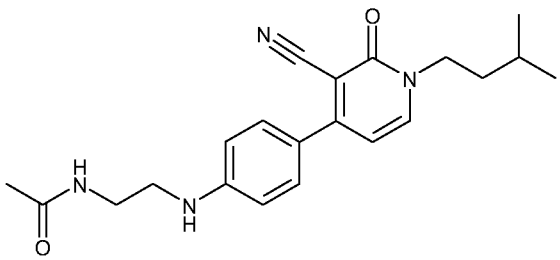
B11. Final compound 1-260



Final compound 1-260

10 % Pd/C (10 mg) was added to a solution of **final compound 1-267** (45 mg, 0.155 mmol) and 1,4-cyclohexadiene (0.22 ml, 2.32 mmol) in MeOH (5 ml) at room temperature. The resulting mixture was stirred into a sealed tube for 12 hours. The catalyst was filtered off and solvents were evaporated *in vacuo*. The residue thus obtained was taken up in MeOH (15 ml) and 10 % Pd/C (10 mg) was added. The resulting mixture was hydrogenated with hydrogen (20 psi) for 3 hours. The catalyst was filtered off and the solvent was evaporated. The residue thus obtained was purified by flash chromatography (SiO_2, DCM / MeOH(NH_3) mixtures) and then by reverse phase HPLC chromatography to yield final compound **1-260** as a white solid (1.63 mg).

B12. Final compound 1-182

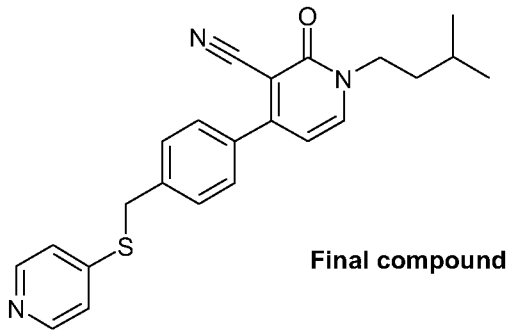


Final compound 1-182

To a solution of **intermediate compound 8** (80 mg, 0.62 mmol), in 1,4-dioxane (1 ml) and a saturated solution of Na_2CO_3 (1 ml) was added **intermediate compound 3** (64.34 mg, 0.239 mmol). The resulting solution was degassed using a stream of nitro-

gen and to this solution was added $Pd(PPh_3)_4$ (41.4 mg, 0.035 mmol). The reaction was then microwaved at 140 °C for 5 min. The resulting reaction mixture was subsequently filtered through a pad of celite and AcOEt (10 ml) was added. H_2O (10 ml) was added and layers were separated. The organic layers were dried (Mg_2SO_4) and vacuum concentrated. The resulting residue was then purified by column chromatography (SiO_2, DCM / $MeOH(NH_3)$ mixtures) to yield the pure final compound **1-182** (28 mg) as bright yellow solid.

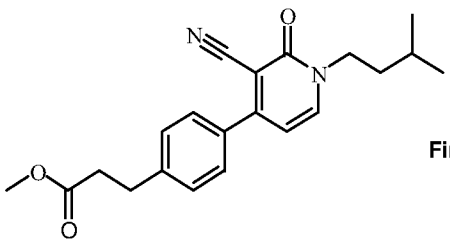
B13. Final compound 1-258



Final compound 1-258

To a solution of **intermediate compound 9** (121 mg, 0.371 mmol), in 1,4-dioxane (3 ml) and a saturated solution of $NaHCO_3$ (3 ml) was added **intermediate compound 3** (100 g, 3.71 mmol). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (64.0 mg, 0.056 mmol). The reaction was then microwaved at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and the filtrate concentrated *in vacuo*. The crude reaction mixture was then purified by HPLC purification to yield final compound **1-258** (13.0 mg, 0.034 mmol, 10 %).

B14. Final compound 1-239

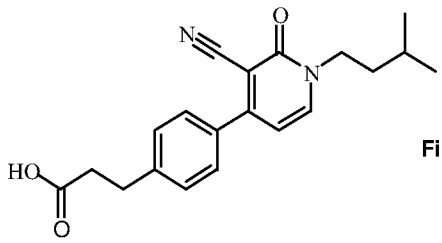


Final compound 1-239

Intermediate compound 4 (150 mg, 0.44 mmol) and 4-(methyl-3-propanoate)phenylboronic acid (140 mg, 0.67 mmol) were mixed in 1,4-dioxane (5 ml) and Et_3N (0.12

ml, 0.89 mmol) at room temperature, and N_2 was flushed through the mixture for 5 min. $Pd(PPh_3)_4$ (77 mg, 0.06 mmol) was added to the mixture and the resulting mixture was heated at 90 °C for 2 hours. The mixture was cooled to room temperature, diluted with AcOEt and brine. The aqueous phase was extracted with AcOEt (3 x 20 ml). The combined organics layers were dried over Na_2SO_4, evaporated in vacuum and the residue thus obtained was purified by column chromatography (SiO_2, DCM / AcOEt) to yield 63 mg of final compound **1-239** as a yellow solid.

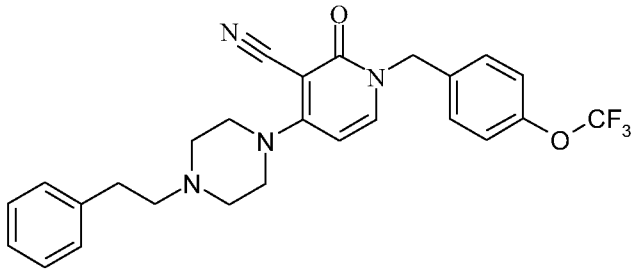
B15. Final compound 1-240



Final compound 1-14

To a solution of **final compound 1-239** (20 mg, 0.057 mmol) in THF/H_2O 1:1 (4 ml) at 0 °C was added lithium hydroxide (24 mg, 0.57 mmol). The reaction mixture was stirred for 30 min and the solution was concentrated. The pH was adjusted to pH = 2 with a 1 N solution of HCl and the precipite thus formed was filtered off and dried, to yield 10 mg of the final compound **1-240** as a white solid.

B16. Final compound 2-043

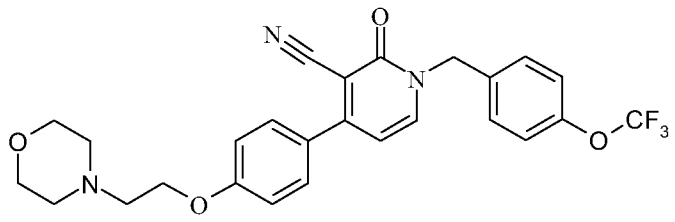


Final compound 2-043

Intermediate compound 12 (300 mg, 0.804 mmol), 1-(2-phenylethyl)piperazine (0.176 ml, 0.964 mmol) K_3PO_4 (341 mg, 1.60 mmol) and catalyst [577971-19-8] CAS (10 mg) were mixed in 1,4-dioxane (6 ml) at room temperature. The corresponding mixture was heated at 110 °C into a sealed tube for 16 hours. The mixture was cooled

to room temperature, filtered through a pad of celite and washed with AcOEt. The filtrate was concentrated *in vacuo* and the residue thus obtained was purified by flash chromatography to yield final compound **2-043** as a pale yellow solid (349 mg, 90 %).

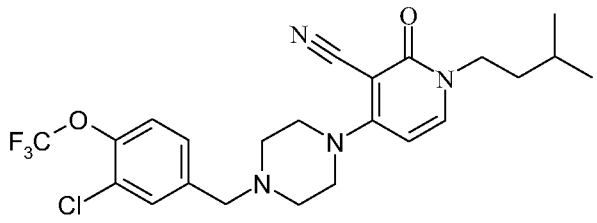
B17. Final compound 1-037



Final compound 1-037

Intermediate compound 12 (350 mg, 0.938 mmol) and **intermediate compound 13** (375 mg, 1.12 mmol) were mixed in 1,4-dioxane (3 ml) and a saturated solution of Na_2CO_3 (3 ml). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (108.3 mg, 0.093 mmol). The reaction was then microwaved into a sealed tube at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and washed with AcOEt. The filtrate was concentrated *in vacuo* and the residue thus obtained was purified by flash chromatography to yield the final compound **1-037** (305.6 mg, 65 %).

B18. Final compound 2-022

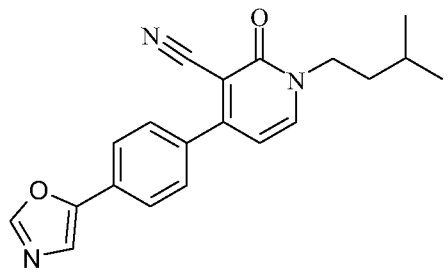


Final compound 2-022

A mixture of **final compound 2-056** (150 mg, 0.55 mmol), 3-chloro-4-(trifluoromethoxy)benzyl bromide (0.16 ml, 0.55 mmol) and K_2CO_3 (150 mg, 1.1 mmol) in DMF (2 ml) was stirred overnight at room temperature . The resulting reaction mixture was then filtered through a pad of celite and washed with AcOEt. The filtrate was concentrated *in vacuo* and the residue thus obtained was purified by flash

chromatography to yield the desired compound. The compound was then recrystallised from diethylether to yield the final compound **2-022** (170 mg, 64 %).

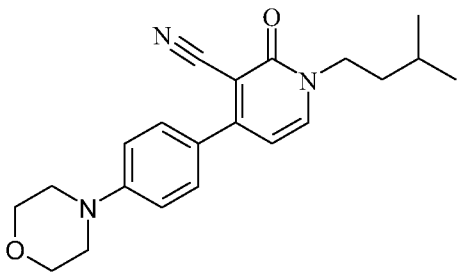
B19. Final compound 1-250



Final compound 1-250

Intermediate compound 3 (198 mg, 0.74 mmol) and **intermediate compound 16** (200 mg, 0.74 mmol) were mixed in 1,4-dioxane (5 ml) and a saturated solution of Na_2CO_3 (5 ml). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (128 mg, 0.115 mmol). The reaction was then microwaved into a sealed tube at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and washed with AcOEt. The filtrate was concentrated *in vacuo* and the residue thus obtained was purified by flash chromatography to yield the final compound **1-250** (63.9 mg, 26 %, yield based on two subsequent reaction steps).

B20. Final compound 1-223

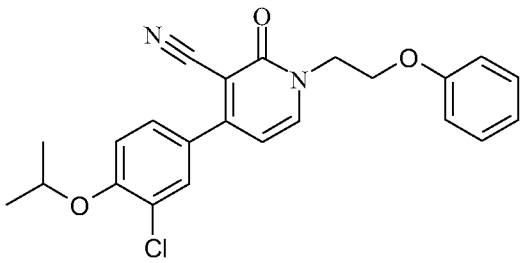


Final compound 1-223

Intermediate compound 3 (727 mg, 2.70 mmol) and commercially available 4-(morpholino)phenylboronic acid (560 mg, 2.70 mmol) were mixed in 1,4-dioxane (10 ml) and a saturated solution of Na_2CO_3 (10 ml). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (468 mg, 0.405 mmol). The reaction was then microwaved into a sealed tube at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and the filtrate was washed

with water (10 ml). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuum. The crude reaction mixture was subsequently purified by flash chromatography to yield the desired compound. The compound was then recrystallised from ethylether to yield the final compound **1-223** (620 mg, 65 %).

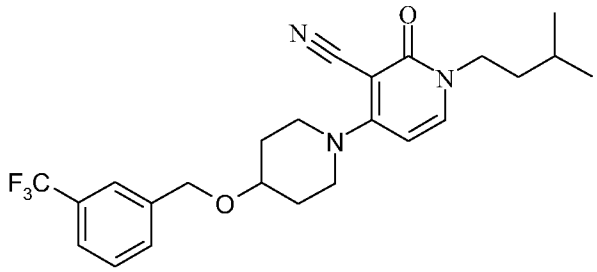
B21. Final compound 1-049



Final compound 1-049

Intermediate compound 19 (250 mg, 0.783 mmol) and 3-chloro-4-isopropoxy-phenylboronic acid (159 mg, 0.86 mmol) were mixed in 1,4-dioxane (2.5 ml) and a saturated solution of $NaHCO_3$ (2.5 ml). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (130 mg, 0.11 mmol). The reaction was then microwaved into a sealed tube at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and the filtrate evaporated in vacuum. The crude reaction mixture was subsequently purified by flash chromatography to yield the desired compound. The compound was then recrystallised from diethylether to yield the final compound **1-049** as a white solid (65 mg, 21 %).

B22. Final compound 4-020

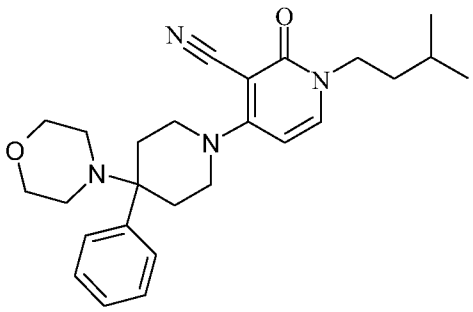


Final compound 4-020

Intermediate compound 3 (100 mg, 0.37 mmol), 4-(3-trifluoromethylbenzyloxy)-piperidine (115.11 mg, 0.444 mmol), K_3PO_4 (150 mg, 0.70 mmol) and catalyst [577971-19-8] CAS (10 mg) were mixed in 1,4-dioxane (5 ml) at room temperature. The corresponding mixture was heated at 85 °C into a sealed tube for 16 hours. The

mixture was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated *in vacuo* and the residue thus obtained was purified by flash chromatography to yield final compound **4-020** as a white gummy solid (90 mg, 55 %).

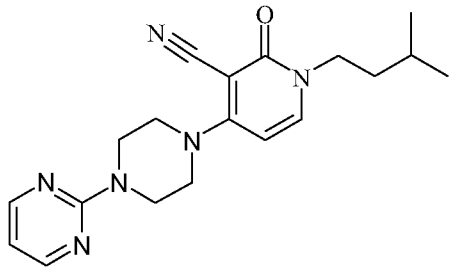
B23. Final compound 4-044



Final compound 4-044

Intermediate compound 3 (150 mg, 0.406 mmol), 4,4-(phenylpiperidin-4-yl)-morpholine (113.3 mg, 0.46 mmol), K_3PO_4 (200 mg, 0.94 mmol) and catalyst [577971-19-8] CAS (10 mg) were mixed in 1,4-dioxane (4 ml) at room temperature. The corresponding mixture was heated at 85 °C into a sealed tube for 36 hours. The mixture was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated *in vacuo* and the residue thus obtained was purified by *prep.* HPLC to yield final compound **4-044** as pale yellow solid (123 mg, 51 %).

B24. Final compound 2-028

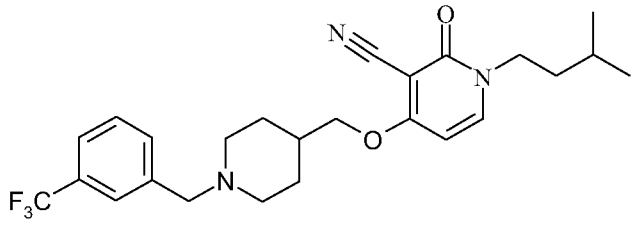


Final compound 2-028

Intermediate compound 3 (226 mg, 0.84 mmol), 1-(2-pyrimidyl)piperazine dihydrochloride (228 mg, 0.96 mmol), K_3PO_4 (612 mg, 2.88 mmol) and catalyst [577971-19-8] CAS (10 mg) were mixed in 1,4-dioxane (5 ml) at room temperature. The corresponding mixture was heated at 85 °C into a sealed tube for 36 hours. The mixture was

cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated *in vacuo* and the residue thus obtained was purified by flash chromatography to yield final compound **2-028** as a pale creamy solid (258 mg, 87 %).

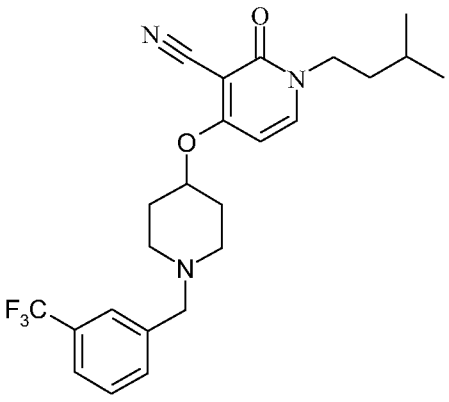
B25. Final compound 3-009



Final compound 3-009

A mixture of **intermediate compound 20** (0.223 g, 0.00081 mol, 1.1 eq.) and NaH (60 % dispersion in mineral oil, 0.035 g, 0.00088 mol, 1.2 eq.) in DME (1.5 ml) was stirred at room temperature over 10 min. Then, **intermediate compound 3** (0.20 g, 0.00074 mol, 1 eq.) was added slowly. The resulting reaction mixture was microwaved at 130 °C for 20 min. The mixture was cooled to room temperature and solvents were evaporated in vacuum. The residue was suspended in DCM, filtered off and the filtrate concentrated *in vacuo*. The crude reaction mixture was then purified by flash chromatography to yield final compound **3-009** (146 mg, 47 %).

B26. Final compound 3-008

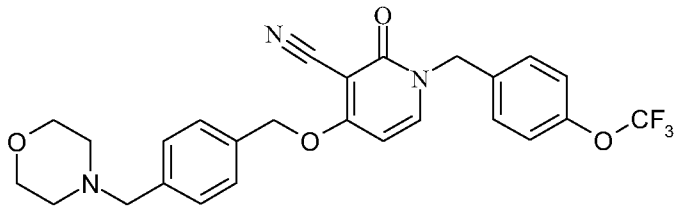


Final compound 3-008

To a solution of **final compound 3-016** (346 mg, 1.19 mmol) and 3-(trifluoromethyl)benzaldehyde ([454-89-7] CAS) (262 mg, 1.5 mmol) in DCE (40 ml), $NaBH(OAc)_3$ (760 mg, 3.6 mmol) was added portionwise. The reaction mixture was

stirred at room temperature for 3 hours. Then, the mixture was quenched with an aqueous solution of NH_4Cl. The combined organic layers were concentrated *in vacuo*. The crude product was purified by flash chromatography to yield final compound **3-008** (370 mg) as a pale brown solid.

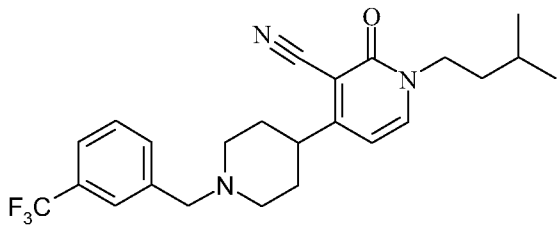
B27. Final compound 1-271



Final compound 1-271

To a mixture of **intermediate compound 11** (200 mg, 0.64 mmol), **intermediate compound 24** (267 mg, 1.28 mmol) and PPh_3 (309 mg, 1.15 mmol) in THF (5 ml) was added di-tert-butylazodicarboxylate (279 mg, 1.21 mmol). The reaction mixture was microwaved at 120 °C over 20 min. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (eluting with a solvent gradient 10-20 % DCM / MeOH(NH_3) to give the final compound **1-271** (219.7 mg, 70 %).

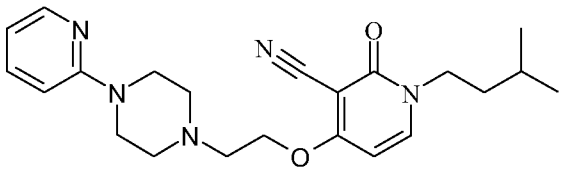
B28. Final compound 3-014



Final compound 3-014

To a solution of **final compound 3-018** (191 mg, 0.70 mmol) and 3-(trifluoromethyl)benzaldehyde ([454-89-7] CAS) (174 mg, 1 mmol) in DCE (16 ml), $NaBH(OAc)_3$ (443 mg, 2.1 mmol) was added portionwise. The mixture was stirred at room temperature for 3 hours, after which time it was quenched with a saturated solution of NH_4Cl. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography to yield final compound **3-014** as white solid (270 mg, 89 %).

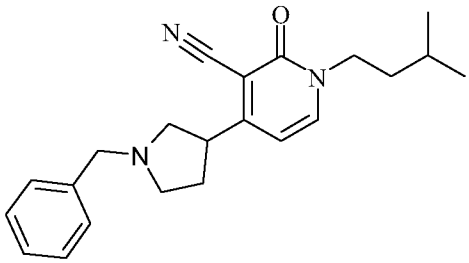
B29. Final compound 2-036



Final compound 2-036

To a mixture of **intermediate compound 2** (0.2 g, 0.971 mmol), K_2CO_3 (0.268 g, 1.942 mmol) and NaI (cat.) in acetonitrile (12 ml), 1-(2-chloroethyl)-4-pyridin-2-yl-piperazine (0.393 g, 1.748 mmol) was added. The reaction mixture was microwaved twice at 150 °C for 10 min. Then, DCM was added and the mixture was filtered off. The filtrate was washed with a saturated solution of $NaHCO_3$. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (DCM / MeOH(NH_3) mixtures) to give final compound **2-036** (152.5 mg, 40 %) as off white solid.

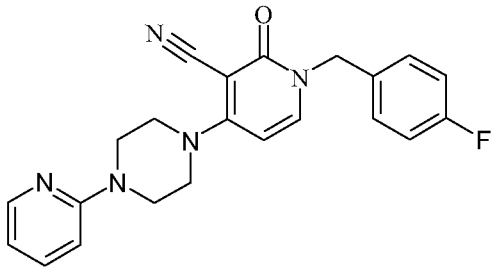
B30. Final compound 5-007



Final compound 1-131

To a solution of **intermediate compound 28** (35 mg, 0.161 mmol) in DCM (6 ml) a drop of TFA was added. Then, *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)-benzylamine (46 mg, 0.193 mmol) was slowly added and the resulting reaction mixture was stirred at room temperature for 2 hours. Then, solvents were evaporated in vacuum and the residue was purified by flash chromatography (SiO_2, DCM / MeOH(NH_3) mixtures) to yield final compound **1-131** (6 mg, 10 %).

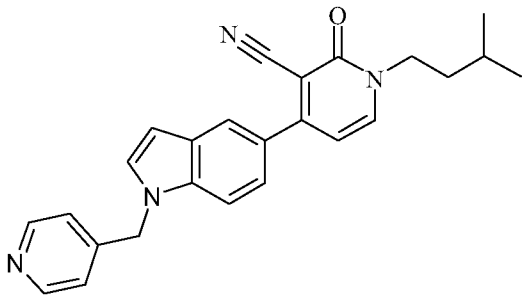
B31. Final compound 2-055



Final compound 2-055

A mixture of **intermediate compound 12'** (250 mg, 0.81 mmol), 1-(2-pyridyl)-piperazine (0.129 ml, 0.85 mmol) and diisopropylethylamine (0.416 ml, 2.4 mmol) in acetonitrile (5 ml) was microwaved at 160 °C for 30 min. The mixture was cooled to room temperature and the solvents were evaporated in vacuum. The residue thus obtained was purified by flash chromatography (SiO_2, DCM / MeOH mixtures) to yield final compound **2-055** (192 mg, 61 %) as a white solid.

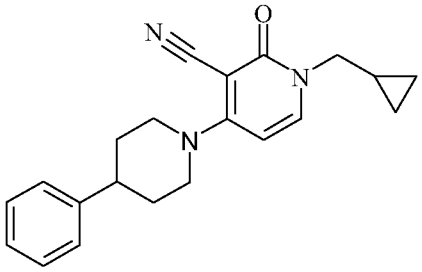
B32. Final compound 5-020



Final compound 5-020

Intermediate compound 3 (0.6 g, 2.20 mmol) and **intermediate compound 31** (3.69 g, 3.79 mmol) were mixed in 1,4-dioxane (7 ml) and a saturated solution of Na_2CO_3 (6 ml). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (0.39 g, 0.33 mmol). The reaction was then microwaved into a sealed tube at 140 °C for 5 min. The resulting reaction mixture was then diluted with AcOEt, filtered through a pad of celite and the filtrate was washed with water (10 ml). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuum*. The crude reaction mixture was subsequently purified by flash chromatography to yield the desired compound. The compound was then recrystallised from diethylether to yield the final compound **5-020** (0.39 g, 44 %).

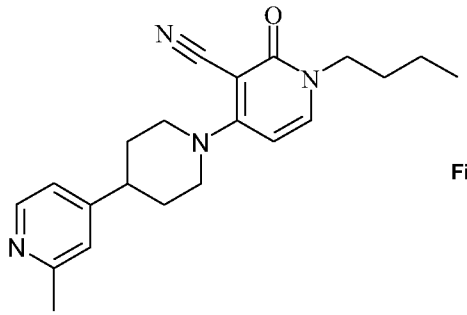
B33. Final compound 4-047



Final compound 4-047

A mixture of **intermediate compound 3''** (0.3 g, 1.18 mmol), 4-phenylpiperidine (0.286 g, 1.77 mmol) and diisopropylethylamine (0.615 ml, 3.54 mmol) in acetonitrile (5 ml) was microwaved at 150 ºC for 20 min. The mixture was cooled to room temperature and the solvents were evaporated *in vacuum*. The residue thus obtained was purified by flash chromatography (SiO_2, DCM / MeOH(NH_3) mixtures) to yield the desired compound. The compound was then recrystallised from ethylether to yield the final compound **4-047** (0.29 g, 73 %)

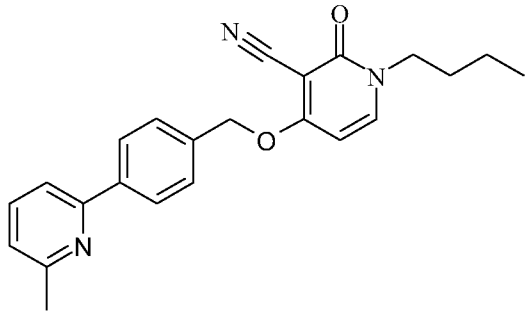
B34. Final compound **4-003**



Final compound 1-196

A mixture of **final compound 5-054** (0.37 g, 1.05 mmol) and palladium (10 % on activated carbon) (catalytic amount) in EtOH (10 ml) was stirred under a hydrogen atmosphere at 50 psi for 3 hours. The catalyst was then filtered off and the filtrate was concentrated *in vacuo*. The residue thus obtained was purified by flash chromatography (SiO_2, DCM / MeOH(NH_3) mixtures) to yield final compound **4-003** (0.21 g, 57 %).

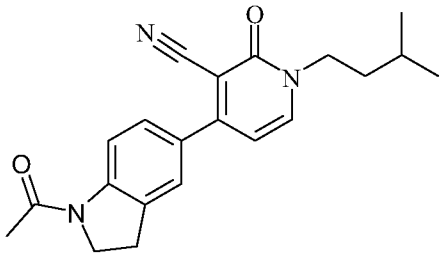
B35. Final compound 1-306



Final compound 1-306

Intermediate compound 35 (0.25 g, 0.61 mmol) and commercially available 2-bromo-6-methylpyridine (0.158 g, 0.92 mmol) were mixed in 1,4-dioxane (2 ml) and a saturated solution of $NaHCO_3$ (2 ml). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (0.10 g, 0.09 mmol). The reaction was then microwaved into a sealed tube at 150 ºC for 10 min. The resulting reaction mixture was then filtered through a pad of celite and the filtrate was washed with water (10 ml). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuum*. The crude reaction mixture was subsequently purified by flash chromatography to yield final compound **1-306** (0.078 g, 34 %).

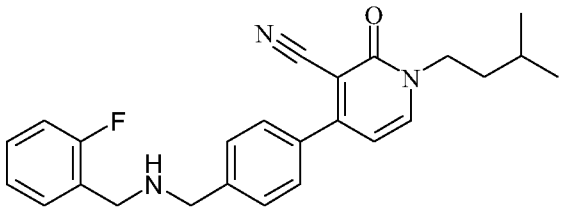
B36. Final compound 5-015



Final compound 5-015

To a solution of **final compound 5-014** (0.04 g, 0.130 mmol), prepared by the reaction pathway B1, and diisopropylethylamine (0.068 ml, 0.392 mmol) in DCM (2 ml), acetyl chloride (0.014 ml, 0.196 mmol) was added. The reaction mixture was stirred at room temperature for 12 hours. Then, the solvents were evaporated *in vacuum* and the residue thus obtained was purified by flash chromatography (SiO_2, DCM / MeOH(NH_3) mixtures) to yield final compound **5-015** (0.045 g, 99 %).

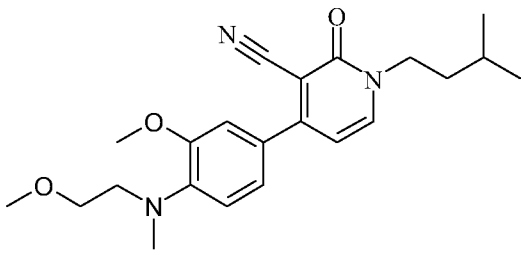
B37. Final compound 1-198



Final compound 1-198

To a solution of **intermediate compound 41** (0.082 mg.0.163 mmol) in DCM (10 ml), TFA (5 ml) was added. The resulting solution was stirred ar room temperature for 3 hours. Then, solvent was evaporated *in vacuo* and the residue was dissolved in DCM, washed with a saturated solution of $NaHCO_3$ and NaCl. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* The residue was purified by flash chromatography (DCM / MeOH(NH_3) mixtures) to give final compound **1-198** (17 mg, 26 %) as a white solid.

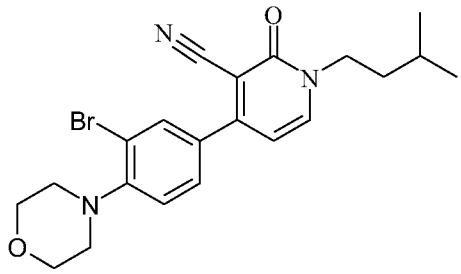
B38. Final compound 1-185



Final compound 1-185

To a mixture of **final compound 1-308** (0.2 g, 0.533 mmol) in 1,4-dioxane (10 ml), *N*-methyl-2-methoxyethylamine (0.0711 mg, 0.8 mmol), Paladium diacetate (0.0118 mg, 0.053 mmol) and Xantphos (0.0616 mg, 0.8 mmol) were added. The reaction mixture was stirred in a sealed tube at 120 ºC for 16 hours. The resulting reaction mixture was then filtered through a pad of celite, washed with AcOEt. The filtrate was washed with a saturated solution of NaCl. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (DCM/MeOH 9:1) to give final compound **1-185** (24 mg, 12 %) as a yellow solid.

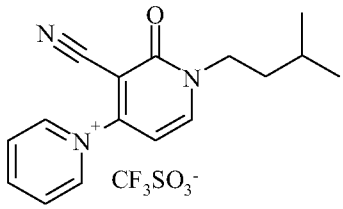
B39. Final compound 1-226



Final compound 1-226

To a solution of **final compound 1-224** (0.147 mg, 0.385 mmol) in DCM (20 ml) at 0 ºC, BBr_3 (0.182 ml, 1.92 mmol) was added. The resulting solution was warmed up to room temperature and stirrred for 16 hours. Then, an aqueous solution of NH_4OH was added. The resulting aqueous solution was extracted with methylenchlorine, washed with a saturated solution of NaCl. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* The residue was purified by flash chromatography (DCM / $MeOH(NH_3)$ 9:1) to give final compound **1-226** (28 mg, 20 %) as yellow solid.

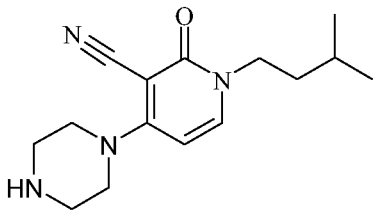
B40. Final compound 5-052



Final compound 5-052

The reaction was carried out under N_2 atmosphere. **Intermediate compound 4** (26 mg, 0.077 mmol) was disolved in pyridine (1 ml, 12.26 mmol). The resulting solution was heated for 1 hour at 40 ºC. The mixture was cooled to room temperature and solvents were evaporated in vacuum. The residue thus obtained was treated with 1,4-dioxane to yield a white solid that was filtered off, dried in vacuum and identified as final compound **5-052** (25 mg; white solid).

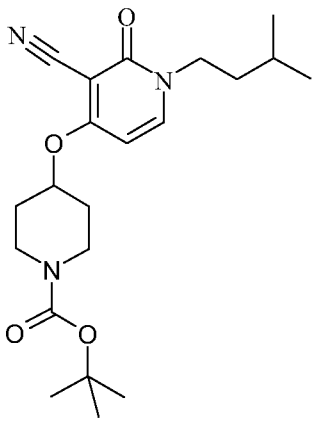
B41. Final compound 2-056



Final compound 2-056

A solution of **intermediate compound 14** (200 mg, 0.53 mmol) in a mixture of TFA/DCM (20 %) (5 ml) was stirred overnight at room temperature. The mixture was basified by the addition of K_2CO_3 (saturated solution). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was identified as final compound **2-056** (150 mg) and was used in the next reaction step without further purification.

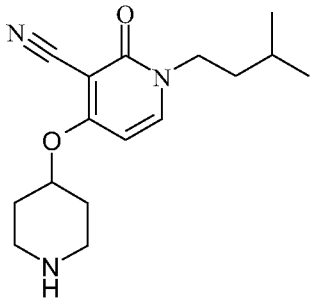
B42. Final compound 3-015



Final compound 3-015

To a mixture of 1-tert-butoxycarbonyl-4-hydroxypiperidine (447 mg, 2.22 mmol) in DME (8 ml), NaH (60 % in mineral oil) was added and the reaction mixture was stirred at room temperature for 5 min. Then, **intermediate compound 3** (500 mg, 1.85 mmol) was added and the resulting reaction mixture was microwaved at 130 °C for 30 min. The reaction was then cooled to room temperature and filtered off. The filtrate was concentrated *in vacuo* to yield final compound **3-015** as brown oil (460 mg).

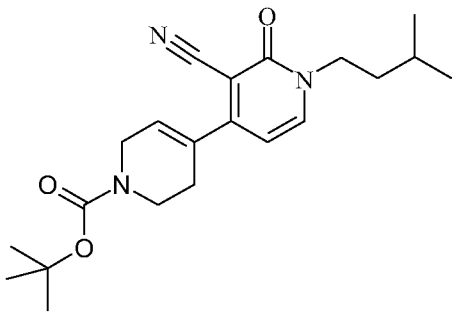
B43. Final compound 3-016



Final compound 3-016

To a solution of **final compound 3-015** (460 mg, 1.18 mmol) in MeOH (50 ml), amberlyst-15 polymer bound (loading 4.6 mmol/g) (0.77 g, 3.54 mmol) was added. The resulting mixture was shaken at room temperature for 12 hours. Then, the resin was filtered off and the solvent was discarded. The resin was suspended in $MeOH/NH_3$ (50 ml) and shaken at room temperature for 3 hours. The resin was filtered off and the filtrate was concentrated *in vacuo* to give the final compound **3-016** (350 mg) as a pale brown solid.

B44. Final compound 5-053

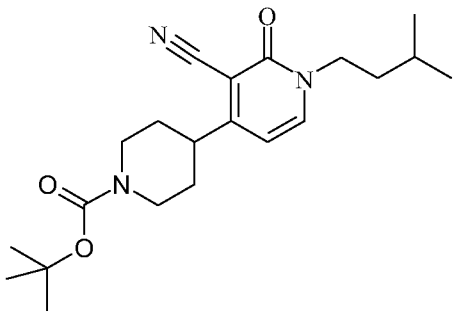


Final compound 5-053

A mixture of **intermediate compound 3** (1 g, 3.71 mmol), (*N*-tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (1.26 g, 4.08 mmol) and $Pd(PPh_3)_4$ (0.642 g, 0.556 mmol) in 1,4-dioxane (6 ml) and a saturated solution of $NaHCO_3$ (6 ml) was microwaved at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and the filtrate evaporated in vacuum. The crude

reaction mixture was subsequently purified by flash chromatography (SiO_2, DCM / MeOH(NH_3) mixtures) to yield final compound **5-053** (0.57 g, 41 %) as a white solid.

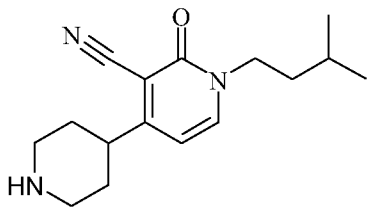
B45. Final compound 3-017



Final compound 3-017

A mixture of **final compound 5-053** (530 mg, 1.42 mmol) and palladium (10 % on activated carbon) (catalytic amount) in AcOEt (50 ml) was stirred under a hydrogen atmosphere at 50 psi for 4 hours. The catalyst was then filtered off and the filtrate was concentrated *in vacuo* to give **final compound 3-017** as colorless oil (540 mg, quant.). The compound thus obtained was used in the next reaction steps without further purification.

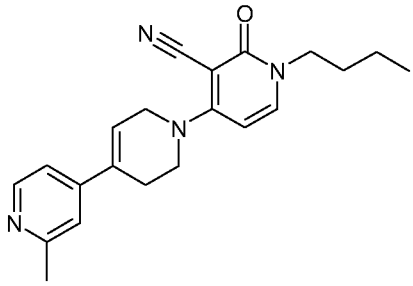
B46. Final compound 3-018



Final compound 3-018

To a solution of **final compound 3-017** (540 mg, 1.44 mmol) in MeOH (50 ml), amberlyst-15 (loading 4.6 mmol/g) (1 g, 4.6 mmol) was added. The resulting mixture was shaken at room temperature for 12 hours. Then, the resin was filtered off and the solvent was discarded. The resin was suspended in MeOH/NH_3 (50 ml) and shaken at room temperature for 3 hours. The resin was filtered off and the filtrate was concentrated *in vacuo* to yield final compound **3-018** (198 mg) as yellow oil.

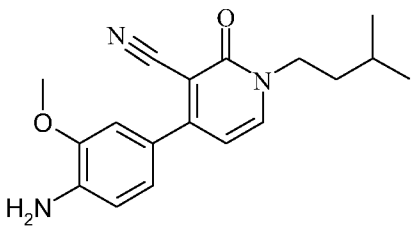
B47. Final compound 5-054



Final compound 5-054

A mixture of **intermediate compound 3'** (0.34 g, 1.33 mmol), **intermediate compound 33** (0.5 g, 1.73 mmol) and diisopropylethylamine (0.925 ml, 5.32 mmol) in acetonitrile (3 ml) was microwaved at 150 ºC for 20 min. The mixture was cooled to room temperature and the solvents were evaporated *in vacuum*. The residue thus obtained was purified by flash chromatography (SiO_2, DCM / MeOH(NH_3) mixtures) to yield final compound **5-054** (0.37 g, 79 %).

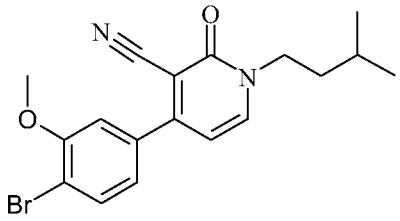
B48. Final compound 1-307



Final compound 1-307

To a solution of **intermediate compound 36** (0.55 mg.1.76 mmol) in DCM (20 ml), TFA (10 ml) was added. The resulting solution was stirred ar room temperature for 2 hours. Then, solvent was evaporated *in vacuo* and the residue was dissolved in DCM, washed with a saturated solution of $NaHCO_3$ and NaCl. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield final compound **1-307** (0.310 g, 74 %) used in the next reaction step without further purification.

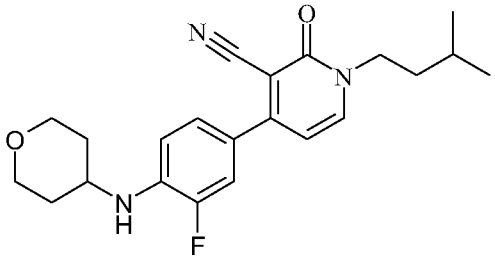
B49. Final compound 1-308



Final compound 1-308

To a suspension of copper (II) bromide (0.2 g, 0.89 mmol) and tert-butylnitrite (0.178 ml, 1.48 mmol) in acetonitrile (29 ml) at 0 °C was added dropwise **final compound 1-307** (0.31 g, 0.99 mmol) within 5 min at 0 °C. The mixture was stirred at 0 °C for 1 hour, then warmed to room temperature and gradually heated at 65 °C for 1 hour. The resulting reaction mixture was then filtered through a pad of celite, washed with acetonitrile and the filtrate evaporated *in vacuum* to yield final compound **1-308** (0.464 g) used in the next reaction step without further purification.

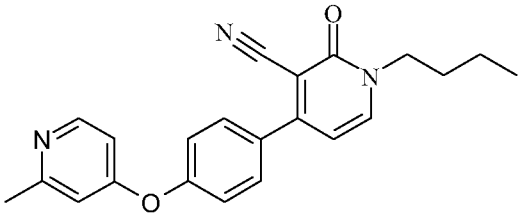
B50. Final compound 1-190



Final compound 1-190

Intermediate compound 43 (0.30 g, 1.11 mmol) and **intermediate compound 3** (0.43 g, 1.33 mmol) were mixed in 1,4-dioxane (3 ml) and a saturated solution of Na_2CO_3 (3 ml). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (0.12 g, 0.1 mmol). The reaction was then microwaved into a sealed tube at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and washed with AcOEt. The filtrate was washed with brine. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue thus obtained was purified by *prep.* HPLC to yield final compound **1-190** (0.04 g, 9 %).

B51. Final compound 1-064

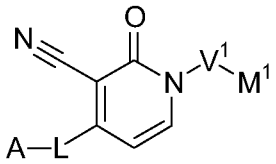


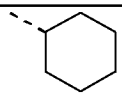
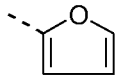
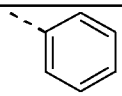
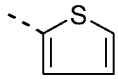
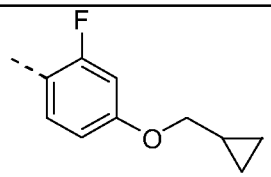
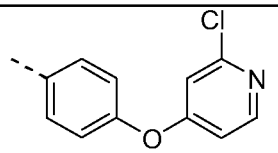
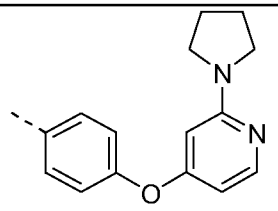
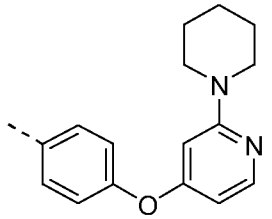
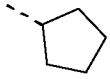
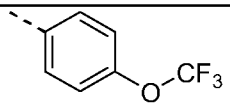
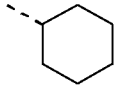
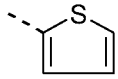
Final compound 1-064

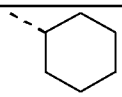
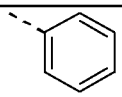
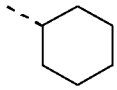
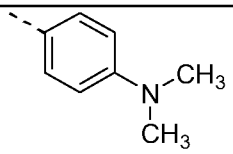
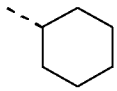
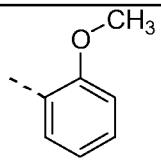
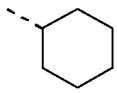
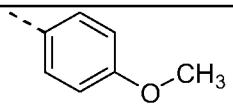
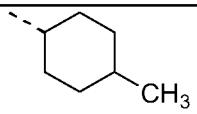
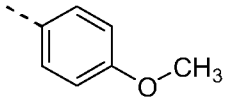
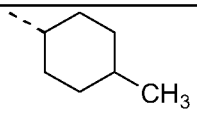
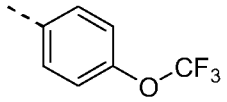
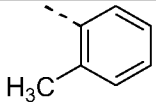
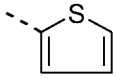
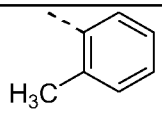
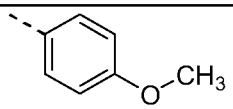
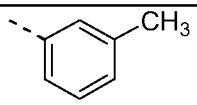
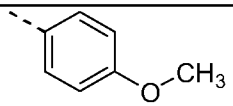
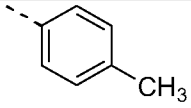
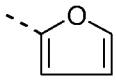
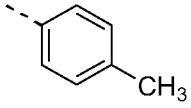
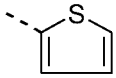
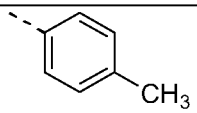
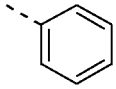
Intermediate compound 3 (0.48 g, 1.89 mmol) and **intermediate compound 45** (0.59 g, 1.89 mmol) were mixed in 1,4-dioxane (4 ml) and a saturated solution of $NaHCO_3$ (4 ml). The resulting solution was degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (0.22 g, 0.19 mmol). The reaction was then microwaved into a sealed tube at 150 °C for 10 min. The resulting reaction mixture was then filtered through a pad of celite and washed with AcOEt. The filtrate was washed with brine. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue thus obtained was purified by flash chromatography (DCM / MeOH mixtures) to yield final compound **1-064** (0.16 g, 25 %).

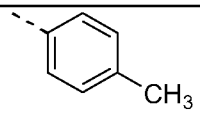
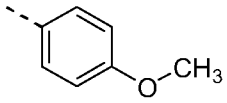
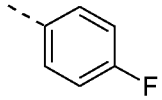
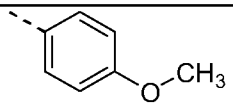
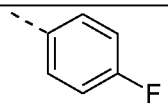
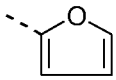
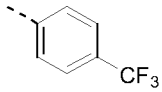
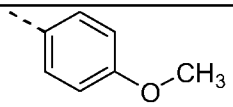
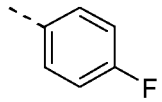
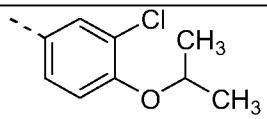
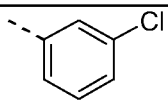
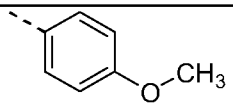
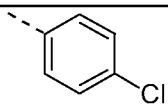
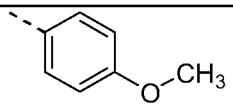
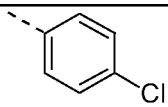
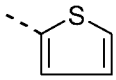
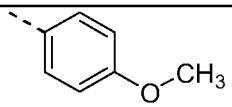
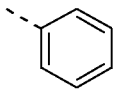
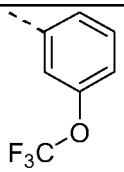
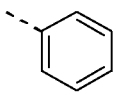
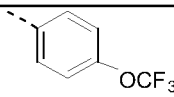
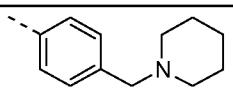
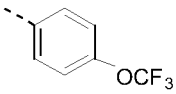
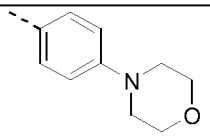
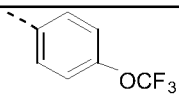
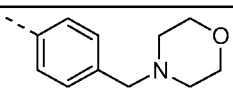
The final compounds in the following Tables have been synthesised according to the previous examples, as denoted in the column denoted as "Exp. Nr". The compound denoted with the asterisk has been exemplified in the Examples.

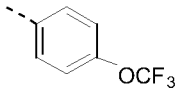
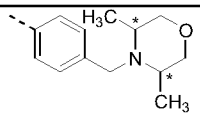
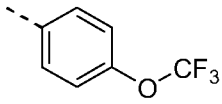
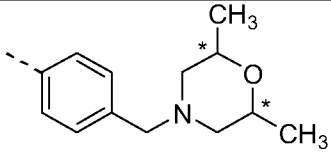
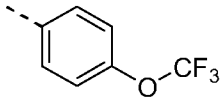
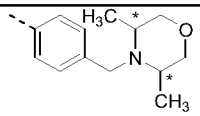
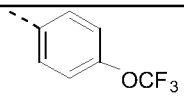
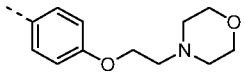
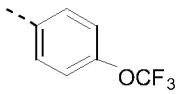
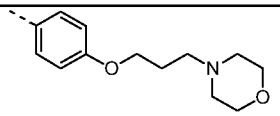
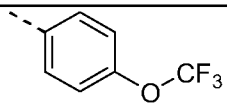
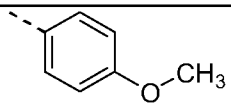
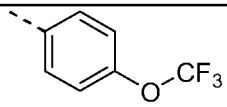
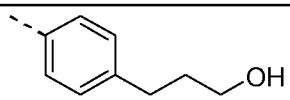
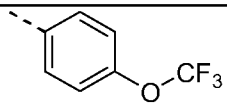
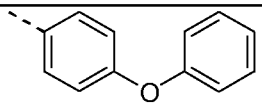
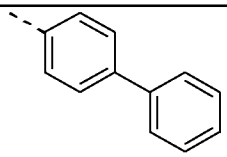
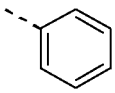
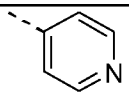
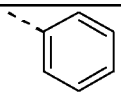
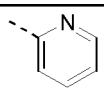
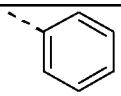
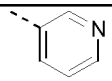
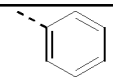
Table 1A : Compounds wherein L is a covalent bond.

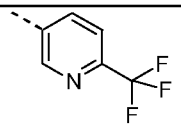
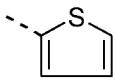
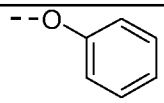
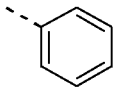
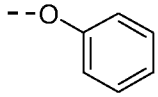
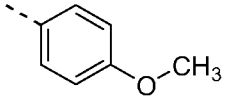
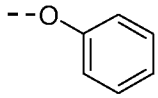
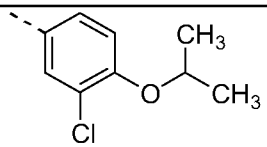
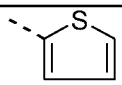
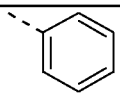
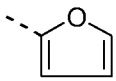
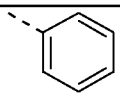
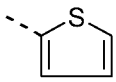
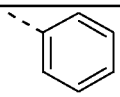
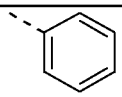
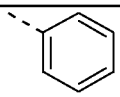
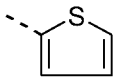
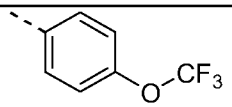
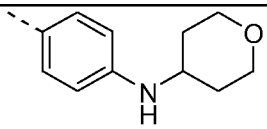
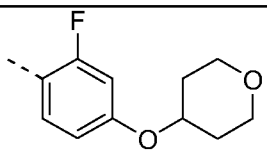


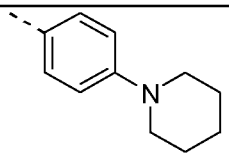
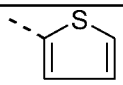
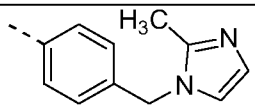
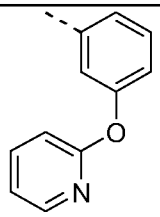
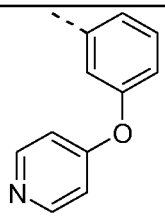
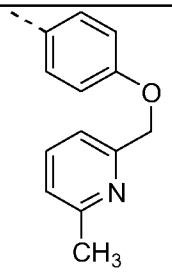
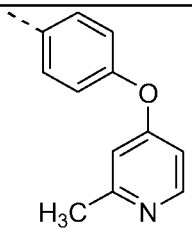
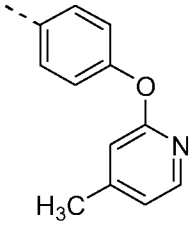
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-001	B2	cb		
1-002	B2	cb		
1-003	B1	--CH_2--		
1-004	B3	--CH_2--		
1-005	B3	--CH_2--		
1-006	B3	--CH_2--		
1-007	B1	--CH_2--		
1-008	B2	--CH_2--		

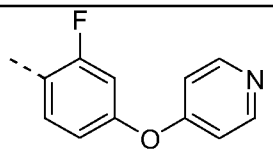
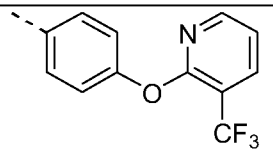
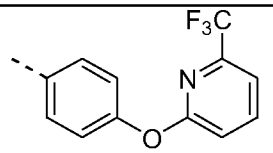
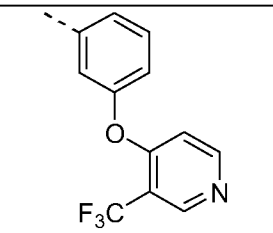
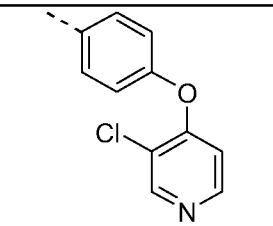
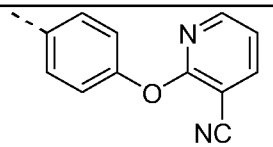
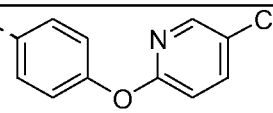
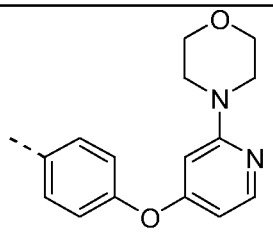
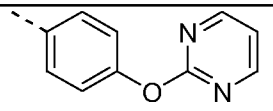
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-009	B2	--CH_2--		
1-010	B1	--CH_2--		
1-011	B1	--CH_2--		
1-012	B1	--CH_2--		
1-013	B1	--CH_2--		
1-014	B1	--CH_2--		
1-015	B2	--CH_2--		
1-016	B1	--CH_2--		
1-017	B1	--CH_2--		
1-018	B2	--CH_2--		
1-019	B2	--CH_2--		
1-020	B2	--CH_2--		

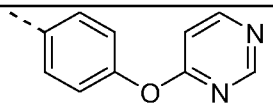
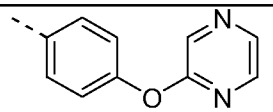
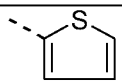
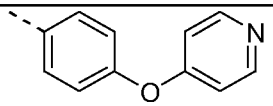
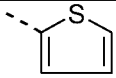
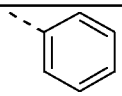
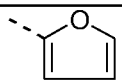
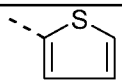
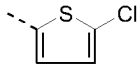
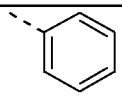
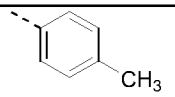
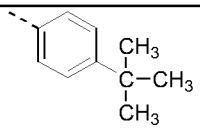
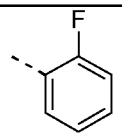
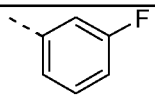
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-021	B1	--CH_2--		
1-022	B1	--CH_2--		
1-023	B2	--CH_2--		
1-024	B1	--CH_2--		
1-025	B1	--CH_2--		
1-026	B1	--CH_2--		
1-027	B1	--CH_2--		
1-028	B2	--CH_2--		
1-029	B2	--CH_2--		
1-030	B1	--CH_2--		
1-031	B1	--CH_2--		
1-032	B1	--CH_2--		
1-033	B1	--CH_2--		

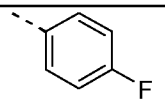
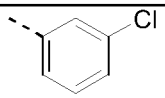
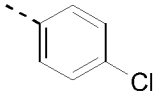
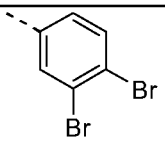
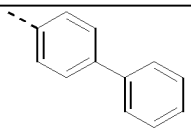
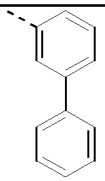
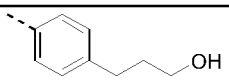
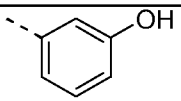
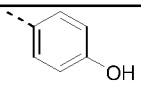
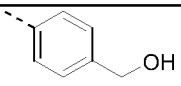
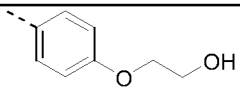
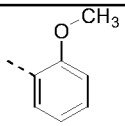
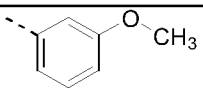
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-034	B1	--CH_2--		 racemic mixture - CIS
1-035	B1	--CH_2--		 racemic mixture - CIS
1-036	B1	--CH_2--		 racemic mixture - TRANS
1-037	B17*	--CH_2--		
1-038	B1	--CH_2--		
1-039	B1	--CH_2--		
1-040	B1	--CH_2--		
1-041	B1	--CH_2--		
1-042	B1	--CH_2--		
1-043	B2	--CH_2--		
1-044	B1	--CH_2--		
1-045	B1	--CH_2--		

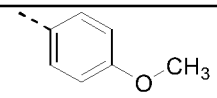
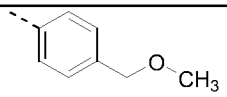
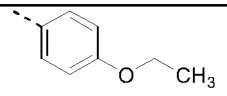
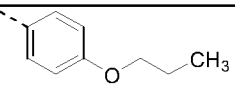
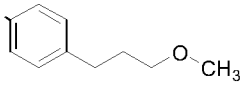
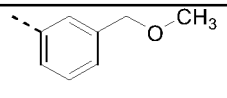
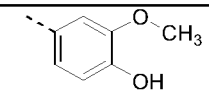
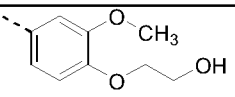
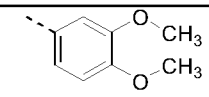
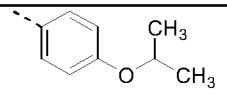
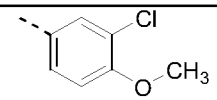
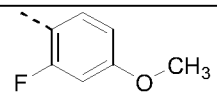
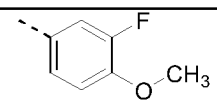
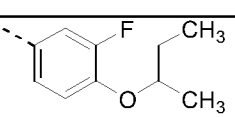
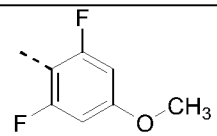
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-046	B2	--CH_2--		
1-047	B2	--CH_2-CH_2--		
1-048	B1	--CH_2-CH_2--		
1-049	B21*	--CH_2-CH_2--		
1-050	B2	--CH_2-CH_2-CH_2--	--H	
1-051	B2	--CH_2-CH_2-CH_2--		
1-052	B2	--CH_2-CH_2-CH_2--		
1-053	B1	--CH_2-CH_2-CH_2--		
1-054	B2	--CH_2-CH=CH--		
1-055	B1	--CH_2-CH_2-CH_2-CH_2--	--H	
1-056	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-057	B3	--CH_2-CH_2-CH_2-CH_2--	--H	

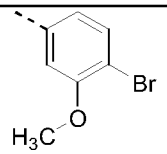
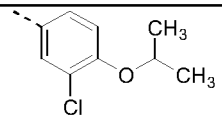
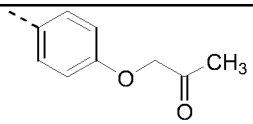
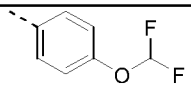
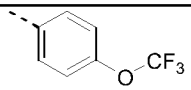
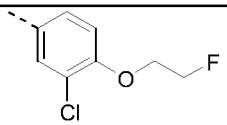
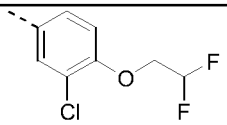
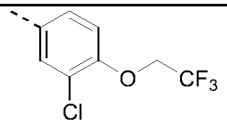
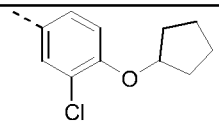
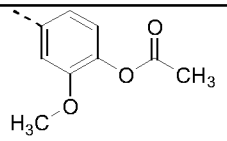
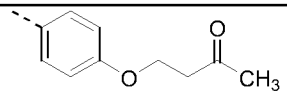
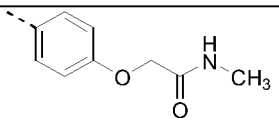
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-058	B1	--CH_2-CH_2-CH_2-CH_2--	--H	
1-059	B2	--CH_2-CH_2-CH_2-CH_2--	--H	
1-060	B1	--CH_2-CH_2-CH_2-CH_2--	--H	
1-061	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-062	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-063	B1	--CH_2-CH_2-CH_2-CH_2--	--H	
1-064	B51*	--CH_2-CH_2-CH_2-CH_2--	--H	
1-065	B3	--CH_2-CH_2-CH_2-CH_2--	--H	

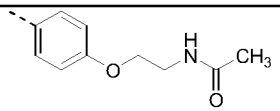
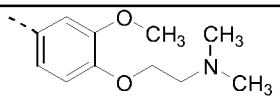
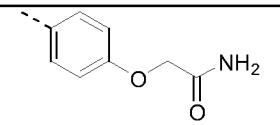
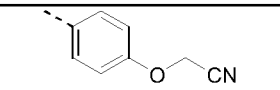
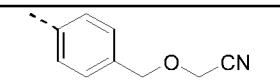
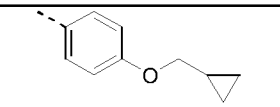
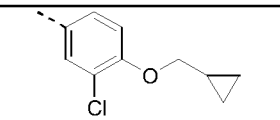
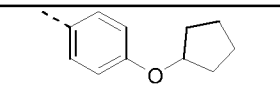
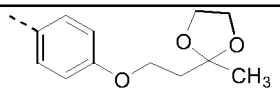
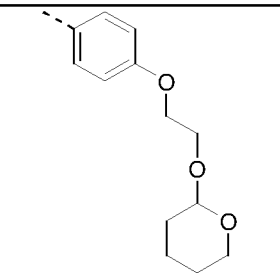
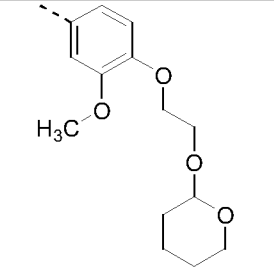
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-066	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-067	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-068	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-069	B29	--CH_2-CH_2-CH_2-CH_2--	--H	
1-070	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-071	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-072	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-073	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-074	B3	--CH_2-CH_2-CH_2-CH_2--	--H	

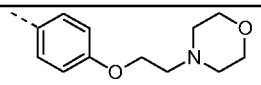
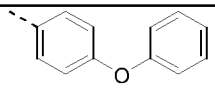
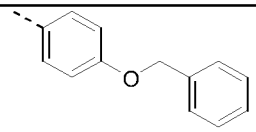
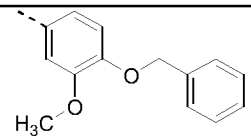
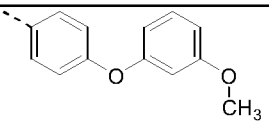
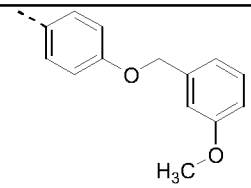
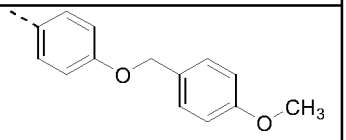
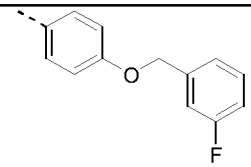
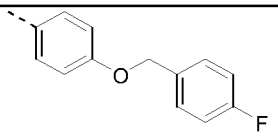
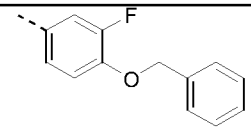
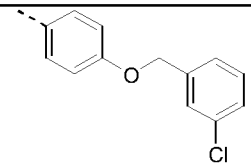
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-075	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-076	B3	--CH_2-CH_2-CH_2-CH_2--	--H	
1-077	B2	--CH_2-$CH(CH_3)$-CH_2--	--H	
1-078	B3	--CH_2-$CH(CH_3)$-CH_2--	--H	
1-079	B2	--$CH(CH_3)$-CH_2-CH_2-CH_2--	--H	
1-080	B2	--CH_2-$CH(CH_3)$-CH_2-CH_2--	--H	
1-081	B2	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-082	B2	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-083	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-084	B2	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-085	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-086	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-087	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-088	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

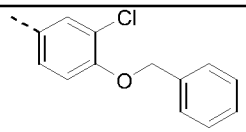
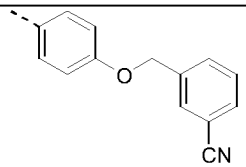
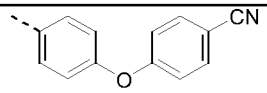
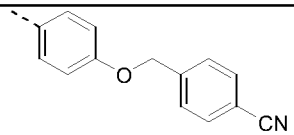
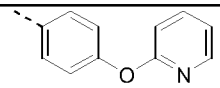
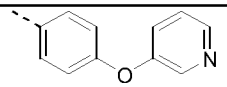
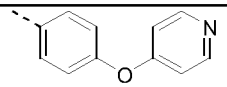
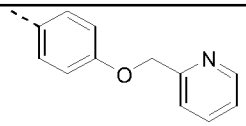
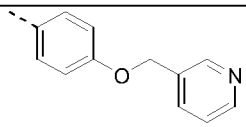
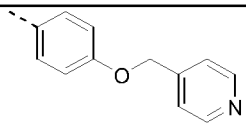
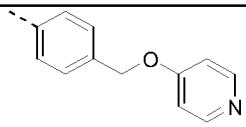
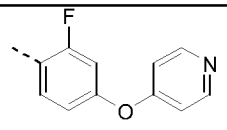
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-089	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-090	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-091	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-092	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-093	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-094	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-095	B4*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-096	B2	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-097	B7*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-098	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-099	B37	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-100	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-101	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

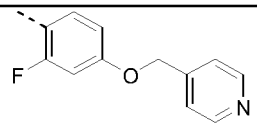
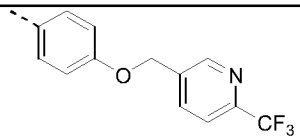
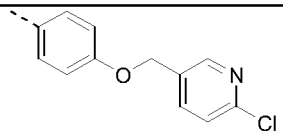
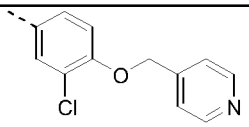
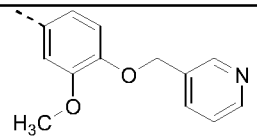
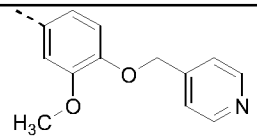
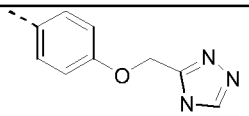
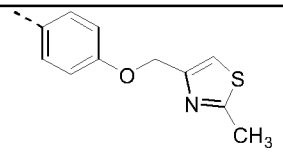
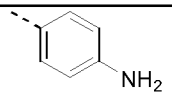
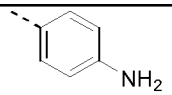
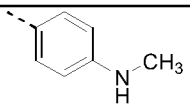
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-102	B2	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-103	B5*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-104	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-105	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-106	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-107	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-108	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-109	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-110	B1*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-111	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-112	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-113	B2	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-114	B3*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-115	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-116	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

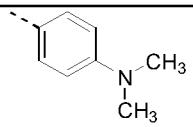
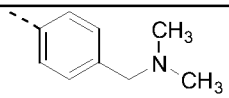
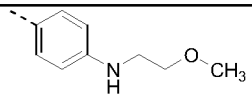
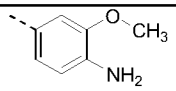
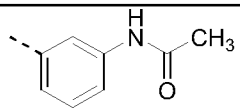
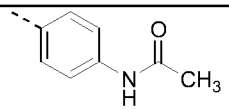
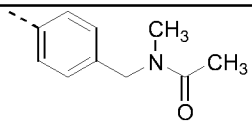
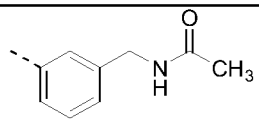
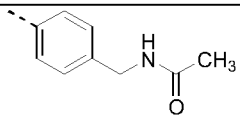
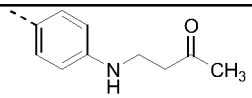
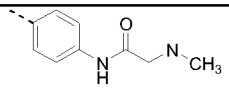
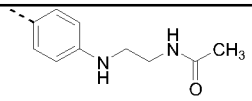
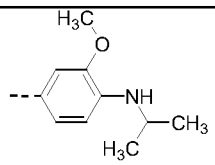
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-308	B49*	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-117	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-118	B2	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-119	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-120	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-121	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-122	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-123	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-124	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-125	B3	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-126	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-127	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	

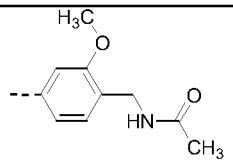
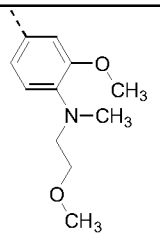
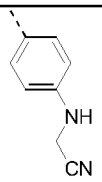
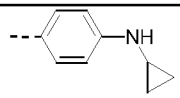
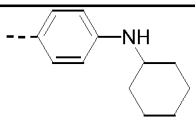
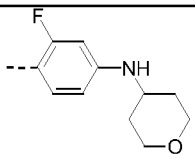
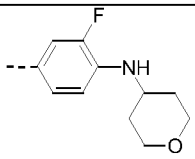
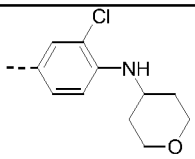
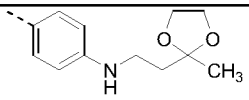
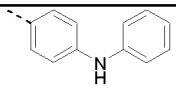
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-128	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-129	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-130	B2	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-131	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-132	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-133	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-134	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-135	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-136	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-137	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-138	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

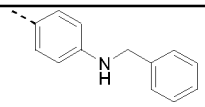
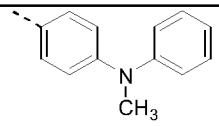
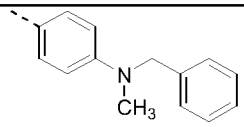
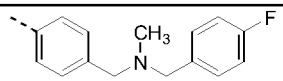
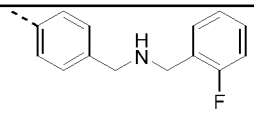
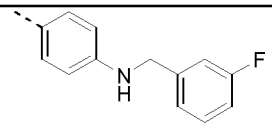
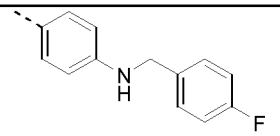
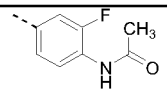
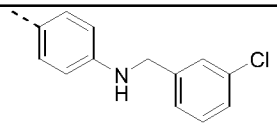
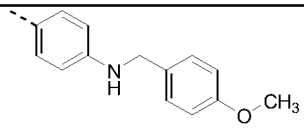
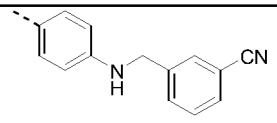
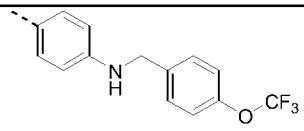
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-139	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-140	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-141	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-142	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-143	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-144	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-145	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-146	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-147	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-148	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-149	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

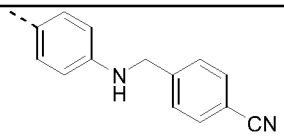
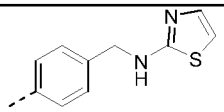
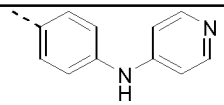
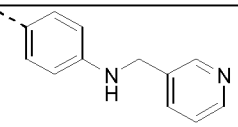
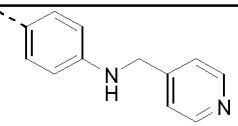
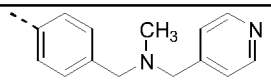
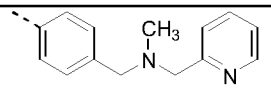
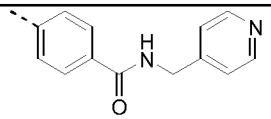
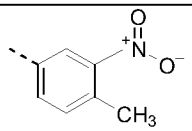
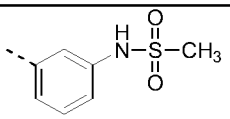
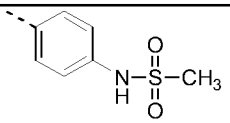
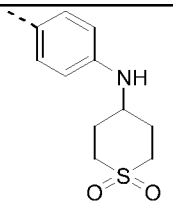
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-150	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-151	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-152	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-153	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-154	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-155	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-156	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-157	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-158	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-159	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-160	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-161	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

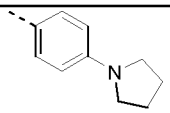
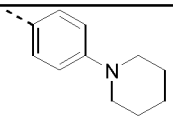
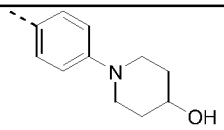
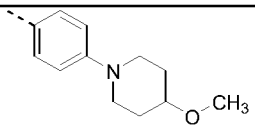
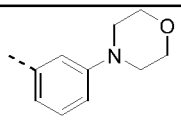
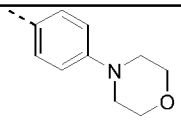
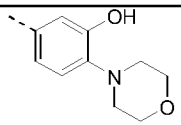
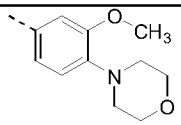
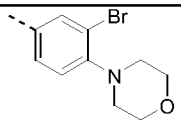
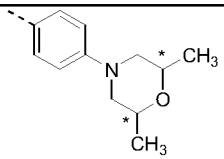
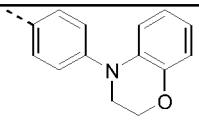
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-162	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-163	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-164	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-165	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-166	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-167	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-168	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-169	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-170	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-305	B37	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	 .CF_3COOH
1-171	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

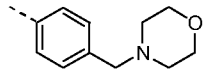
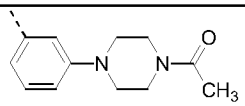
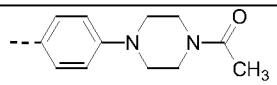
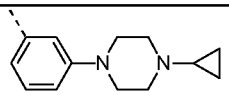
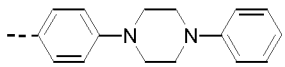
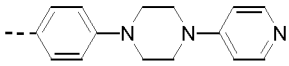
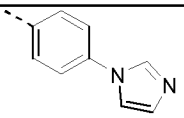
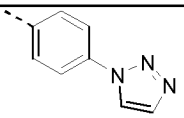
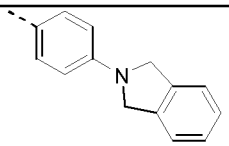
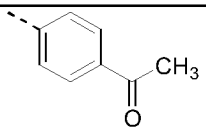
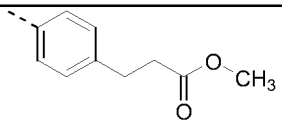
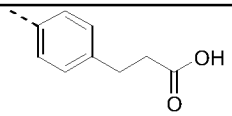
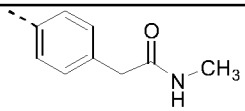
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-172	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-173	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-174	B37	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-307	B48*	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-175	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-176	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-177	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-178	B6*	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-179	B2*	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-180	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-181	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-182	B12*	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-183	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	

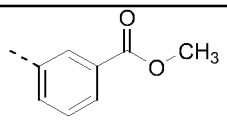
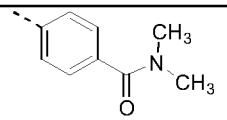
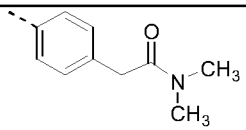
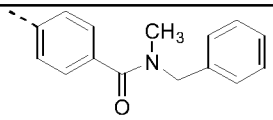
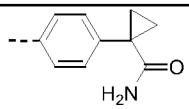
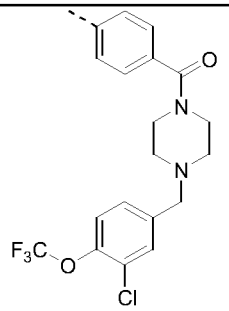
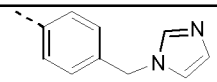
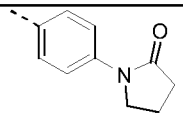
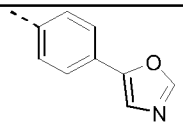
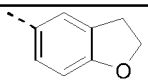
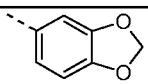
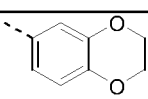
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-184	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-185	B38*	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-186	B3	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-187	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-188	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-189	B3	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-190	B50*	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-191	B3	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-192	B1	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-193	B3	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	

Co. nr.	Exp nr.	V^1	M^1	--L-A
1-194	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-195	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-196	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-197	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-198	B37*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-199	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-200	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-201	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-202	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-203	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-204	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-205	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

Co. nr.	Exp nr.	V^1	M^1	--L-A
1-206	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-207	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-208	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-209	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-210	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-211	B28	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-212	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-213	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-214	B2	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-215	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-216	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-217	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

Co. nr.	Exp nr.	V^1	M^1	--L-A
1-218	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-219	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-220	B9	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-221	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-222	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-223	B20*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-224	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-225	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-226	B39*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-227	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	 CIS–TRANS mixture 80:20
1-228	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

Co. nr.	Exp nr.	V^1	M^1	--L-A
1-229	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-230	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-231	B38	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-232	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-233	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-234	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-235	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-236	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-237	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-238	B2	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-239	B14*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-240	B15*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-241	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

Co. nr.	Exp nr.	V^1	M^1	--L-A
1-242	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-243	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-244	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-245	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-246	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-247	B3	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-248	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-249	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-250	B19*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-251	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-252	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-253	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

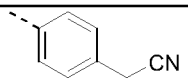
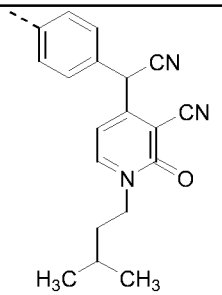
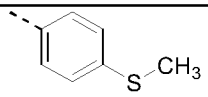
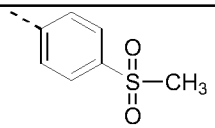
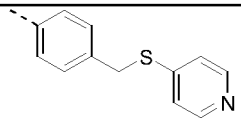
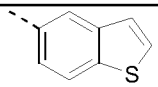
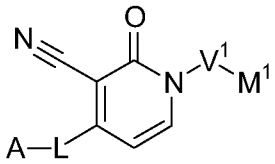
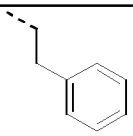
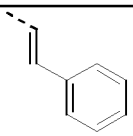
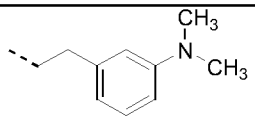
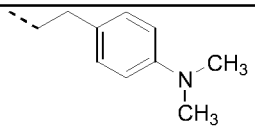
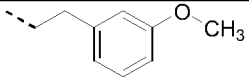
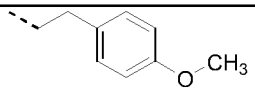
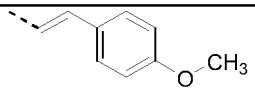
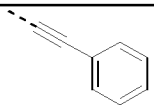
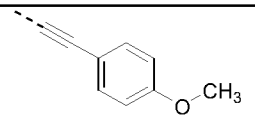
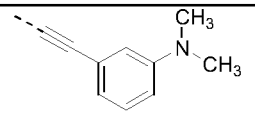
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-254	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-255	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-256	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-257	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-258	B13*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-259	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

Table 1B : Compounds wherein L is a saturated or unsaturated alkyl chain.



Co. nr.	Exp nr.	V^1	M^1	--L-A
1-260	B11*	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-261	B11	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-262	B11	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-263	B11	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-264	B11	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-265	B11	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-266	B11	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-267	B10*	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-268	B10	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	
1-269	B10	--CH_2-CH_2-CH(CH_3)-CH_2--	--H	

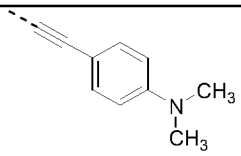
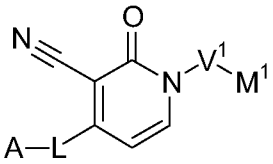
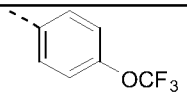
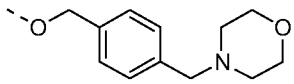
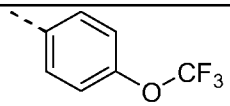
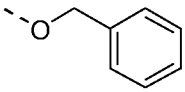
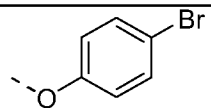
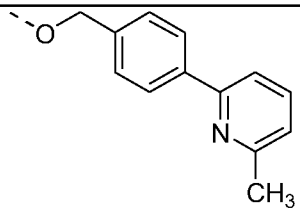
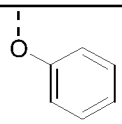
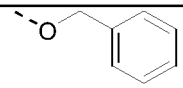
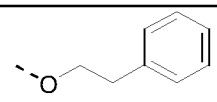
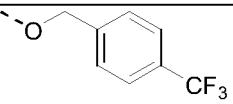
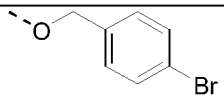
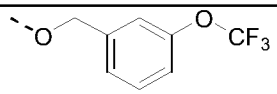
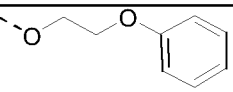
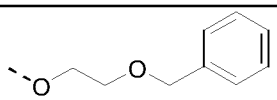
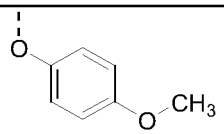
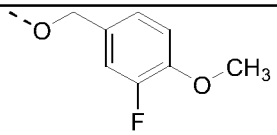
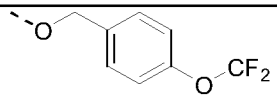
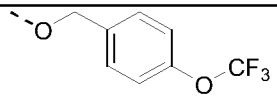
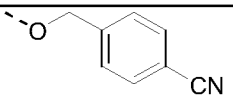
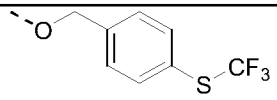
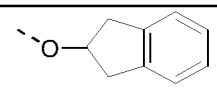
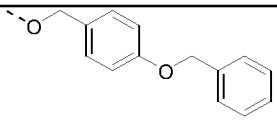
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-270	B10	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

Table 1C : Compounds wherein L contains an O-atom.



Co. nr.	Exp nr.	V^1	M^1	--L-A
1-271	B27*	--CH_2--		
1-272	B29	--CH_2--		
1-273	B8	--CH_2-CH_2-CH_2-CH_2--	--H	
1-306	B35*	--CH_2-CH_2-CH_2-CH_2--	--H	
1-274	B8*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-275	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

Co. nr.	Exp nr.	V^1	M^1	--L-A
1-276	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-277	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-278	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-279	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-280	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-281	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-282	B8	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-283	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-284	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-285	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-286	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-287	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-288	B27	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-289	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	

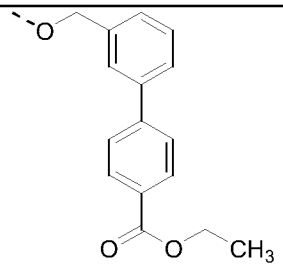
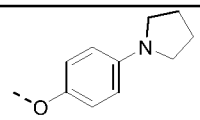
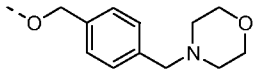
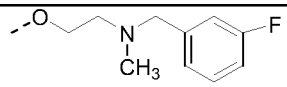
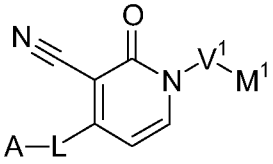
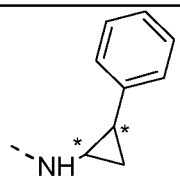
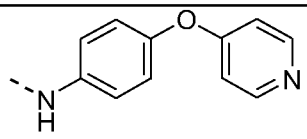
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-290	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-291	B8	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-292	B27	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-293	B29	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	 .HCl

Table 1D : Compounds wherein L contains a *N*-atom.



Co. nr.	Exp nr.	V^1	M^1	--L-A
1-294	B31	--CH_2--		 racemic mixture - TRANS
1-295	B29	--CH_2--		

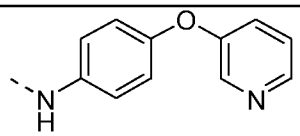
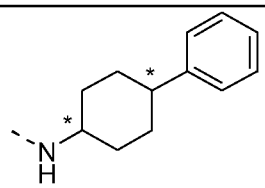
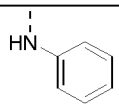
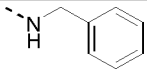
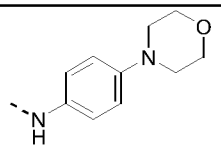
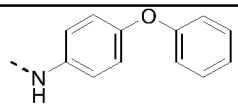
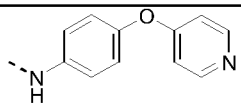
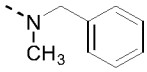
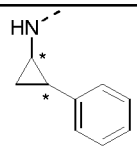
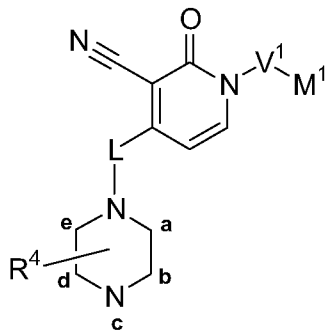
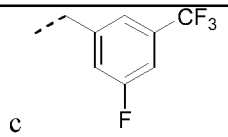
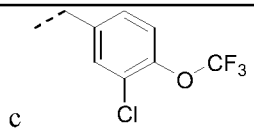
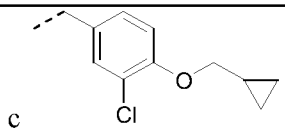
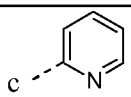
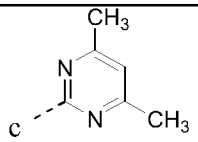
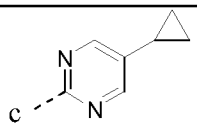
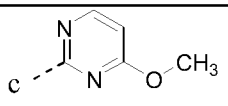
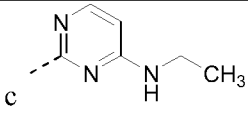
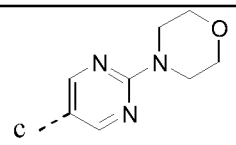
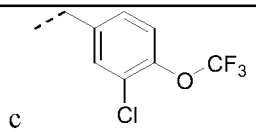
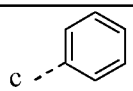
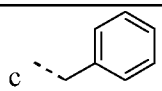
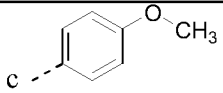
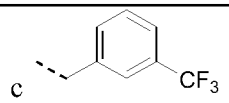
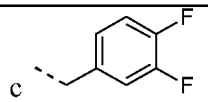
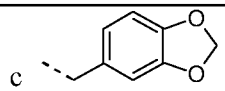
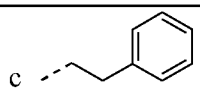
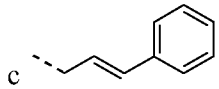
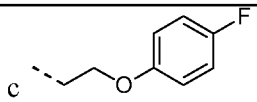
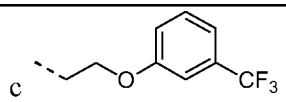
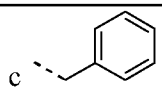
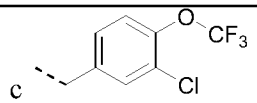
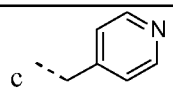
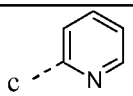
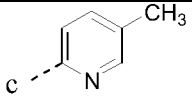
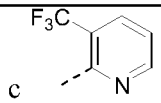
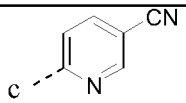
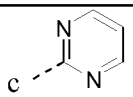
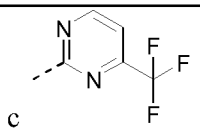
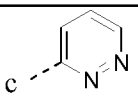
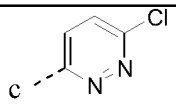
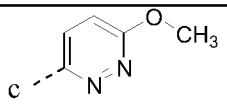
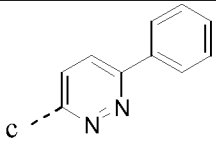
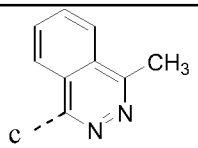
Co. nr.	Exp nr.	V^1	M^1	--L-A
1-296	B29	--CH_2-CH_2-CH_2-CH_2--	--H	 .HCl
1-297	B31	--CH_2-CH_2-CH_2-CH_2--	--H	 racemic mixture - TRANS
1-298	B9*	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-299	B9	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-300	B9	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-301	B9	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-302	B9	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-303	B9	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	
1-304	B9	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	 racemic mixture - TRANS

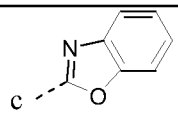
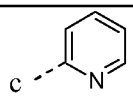
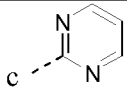
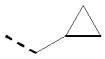
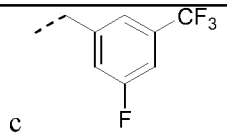
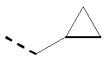
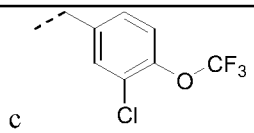
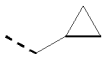
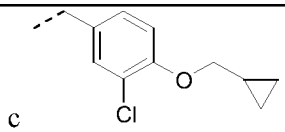
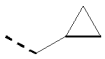
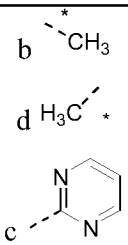
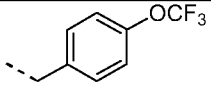
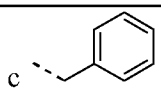
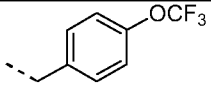
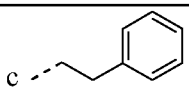
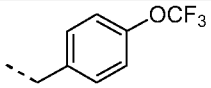
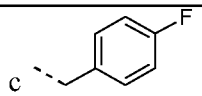
Table 2 : Compounds prepared according to the Examples wherein A is piperazinyl.



Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
2-001	B28	--CH_2-CH_2-CH_2-CH_3	cb	
2-002	B18	--CH_2-CH_2-CH_2-CH_3	cb	
2-003	B28	--CH_2-CH_2-CH_2-CH_3	cb	
2-004	B33	--CH_2-CH_2-CH_2-CH_3	cb	
2-005	B33	--CH_2-CH_2-CH_2-CH_3	cb	
2-006	B33	--CH_2-CH_2-CH_2-CH_3	cb	
2-007	B33	--CH_2-CH_2-CH_2-CH_3	cb	
2-008	B33	--CH_2-CH_2-CH_2-CH_3	cb	

Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
2-009	B33	--CH_2-CH_2-CH_2-CH_3	cb	
2-010	B18	--$CH_2CH(CH_3)_2$	cb	
2-056	B41*	--CH_2-CH_2-$CH(CH_3)_2$	cb	–
2-011	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-012	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-013	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-014	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-015	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-016	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-017	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-018	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-019	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-020	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-021	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	 a --CH_3

Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
2-022	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-023	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-024	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-025	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-026	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-027	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-028	B24*	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-029	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-030	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-031	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-032	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-033	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-034	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	

Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
2-035	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
2-036	B29*	--CH_2-CH_2-$CH(CH_3)_2$	--$O(CH_2)_2$--	
2-037	B33	--CH_2-CH_2-$CH(CH_3)_2$	--(C=O)--	
2-038	B28		cb	
2-039	B28		cb	
2-040	B28		cb	
2-041	B33		cb	 racemix mixture - CIS
2-042	B23		cb	
2-043	B16*		cb	
2-044	B23		cb	

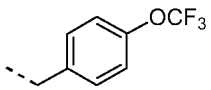
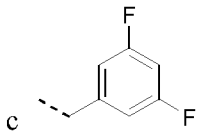
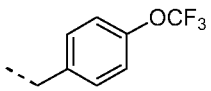
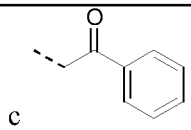
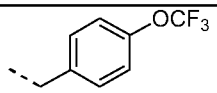
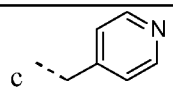
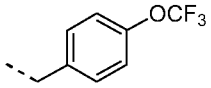
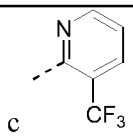
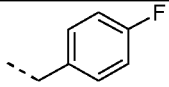
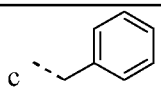
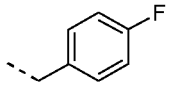
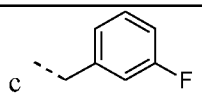
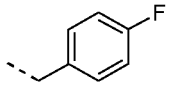
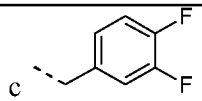
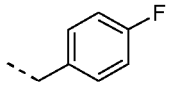
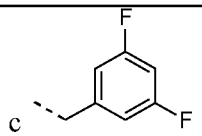
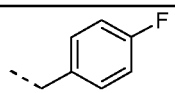
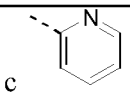
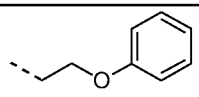
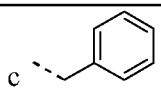
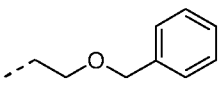
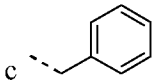
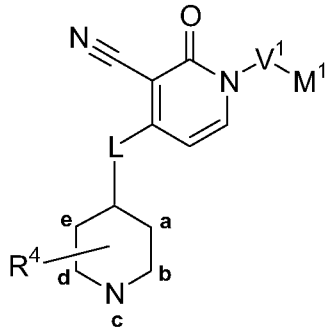
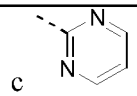
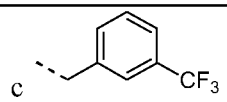
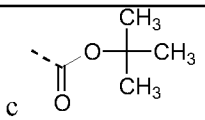
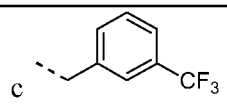
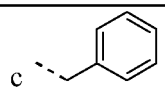
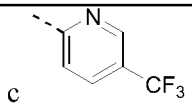
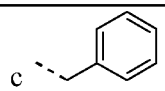
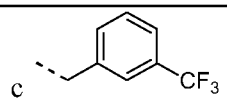
Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
2-045	B33		cb	a --CH_3  .HCl
2-046	B18		cb	
2-047	B23		cb	
2-048	B23		cb	
2-049	B18*		cb	
2-050	B18		cb	
2-051	B18		cb	
2-052	B18		cb	
2-055	B31*		cb	
2-053	B18		cb	
2-054	B18		cb	

Table 3 : Compounds prepared according to the Examples wherein A is 4-piperidinyl.



Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
3-001	B10	--CH_2-CH_2-CH_2-CH_3	cb	
3-002	B18	--CH_2-CH_2-CH_2-CH_3	--O--	
3-018	B46*	--CH_2-CH_2-$CH(CH_3)_2$	cb	–
3-017	B45*	--CH_2-CH_2-$CH(CH_3)_2$	cb	
3-014	B28*	--CH_2-CH_2-$CH(CH_3)_2$	cb	
3-003	B23	--CH_2-CH_2-$CH(CH_3)_2$	--NH--	
3-004	B18	--CH_2-CH_2-$CH(CH_3)_2$	--NH--	
3-005	B23	--CH_2-CH_2-$CH(CH_3)_2$	--$N(CH_3)$--	
3-006	B23	--CH_2-CH_2-$CH(CH_3)_2$	--$N(CH_3)$--	
3-016	B43*	--CH_2-CH_2-$CH(CH_3)_2$	--O--	–

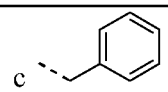
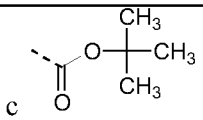
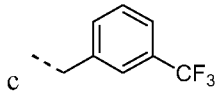
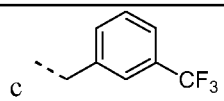
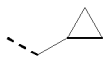
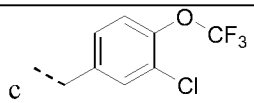
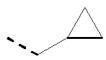
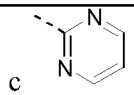
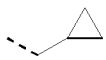
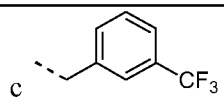
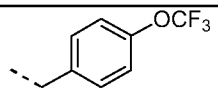
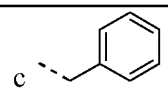
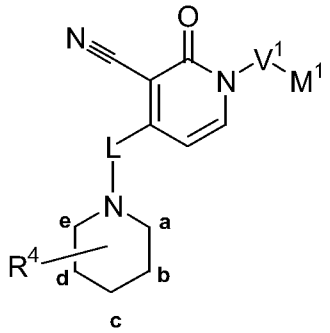
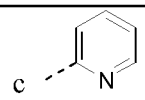
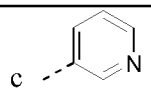
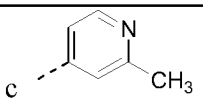
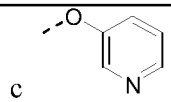
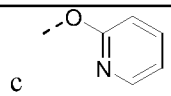
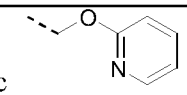
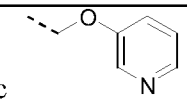
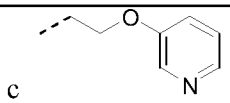
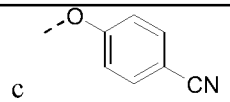
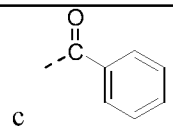
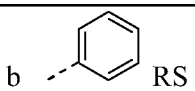
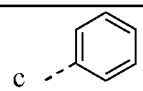
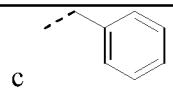
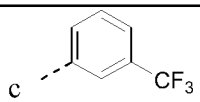
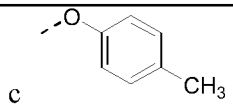
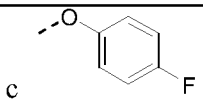
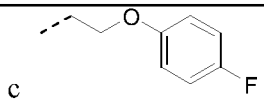
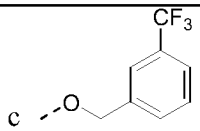
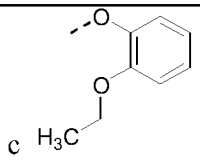
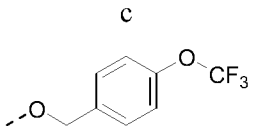
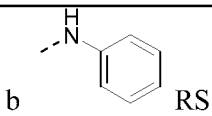
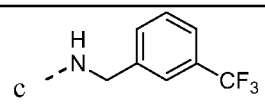
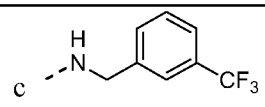
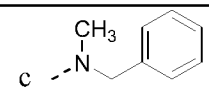
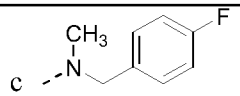
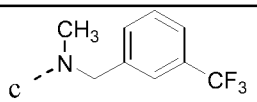
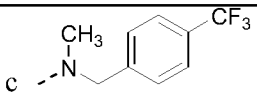
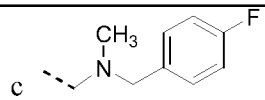
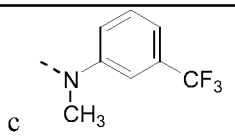
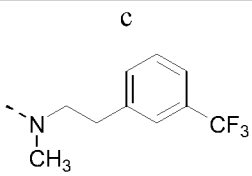
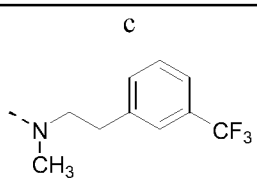
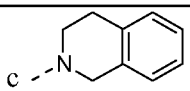
Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
3-007	B25	--CH_2-CH_2-$CH(CH_3)_2$	--O--	
3-015	B42*	--CH_2-CH_2-$CH(CH_3)_2$	--O--	
3-008	B26*	--CH_2-CH_2-$CH(CH_3)_2$	--O--	
3-009	B25*	--CH_2-CH_2-$CH(CH_3)_2$	--OCH_2--	
3-010	B18		--NH--	
3-011	B33		--NH--	
3-012	B18		--O--	
3-013	B23		--$N(CH_3)$--	

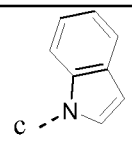
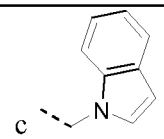
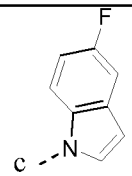
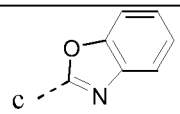
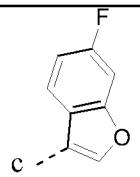
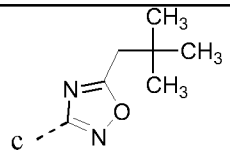
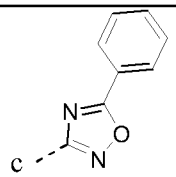
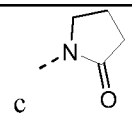
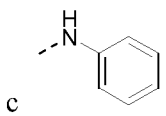
Table 4 : Compounds prepared according to the Examples wherein A is 1-piperidinyl.

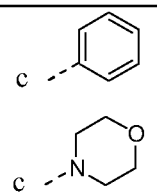
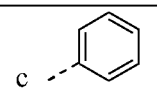
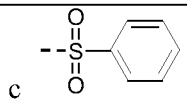
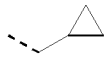
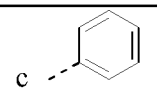
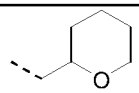
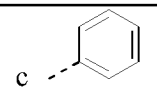
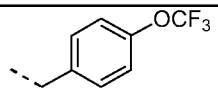
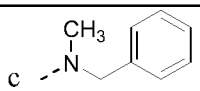
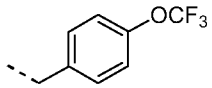
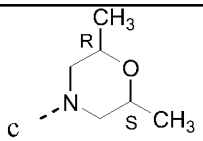
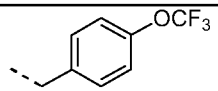
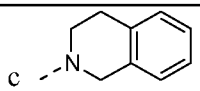
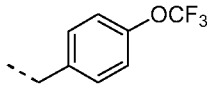
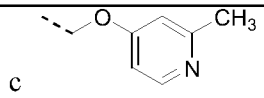
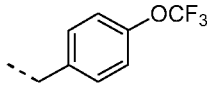
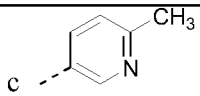
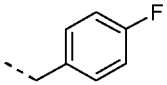
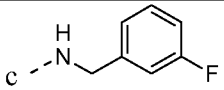
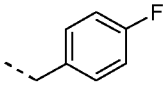
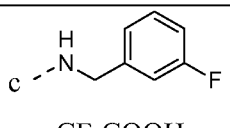


Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
4-001	B10	--CH_2 CH_2 CH_2CH_3	cb	
4-002	B10	--CH_2 CH_2 CH_2CH_3	cb	
4-003	B34*	--CH_2 CH_2 CH_2CH_3	cb	
4-004	B27	--CH_2 CH_2 CH_2CH_3	cb	
4-005	B25	--CH_2 CH_2 CH_2CH_3	cb	
4-006	B33	--CH_2 CH_2 CH_2CH_3	cb	
4-007	B27	--CH_2 CH_2 CH_2CH_3	cb	
4-008	B27	--CH_2 CH_2 CH_2CH_3	cb	 .HCl
4-009	B33	--CH_2 CH_2 CH_2CH_3	cb	

Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
4-010	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	c --CF_3
4-012	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-013	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-014	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-015	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-016	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-017	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-018	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-019	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-020	B22*	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-021	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-022	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-023	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	

Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
4-024	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-025	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	 .HCl
4-026	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-027	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-028	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-029	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-030	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	 .HCl
4-031	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-032	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-033	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	 .HCl
4-034	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	

Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
4-035	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-036	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-037	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-038	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-039	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-040	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-041	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-042	B25	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-043	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb	b --CH_3  racemic mixture - CIS

Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
4-044	B23*	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-045	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	 c --OCH_3
4-046	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb	
4-047	B33*		cb	
4-048	B33		cb	
4-049	B23		cb	
4-050	B23		cb	
4-051	B23		cb	
4-052	B25		cb	 .HCl
4-053	B33		cb	 c --OH
4-054	B33		cb	
4-055	B37		cb	 .CF_3COOH

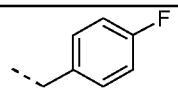
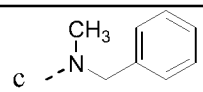
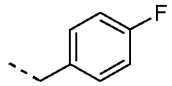
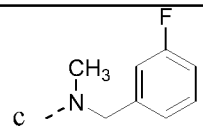
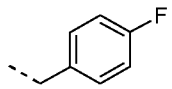
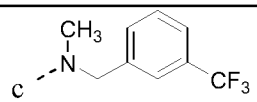
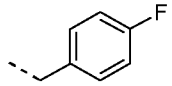
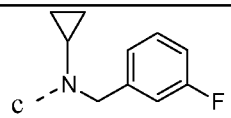
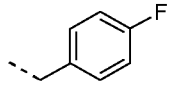
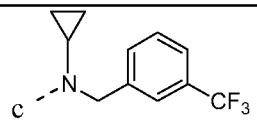
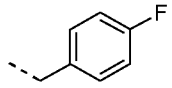
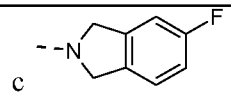
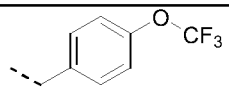
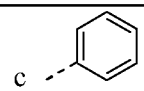
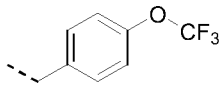
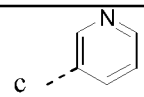
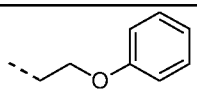
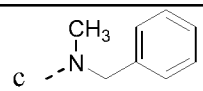
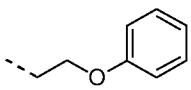
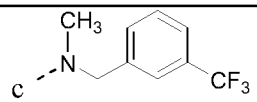
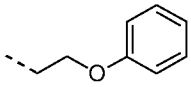
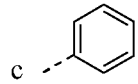
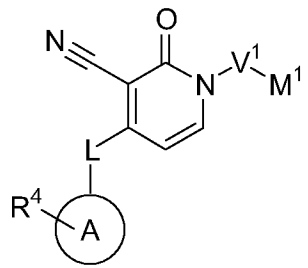
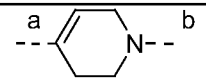
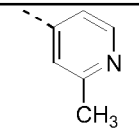
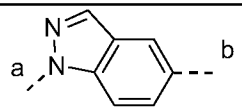
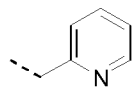
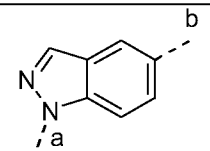
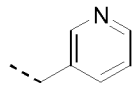
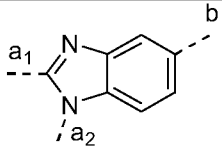
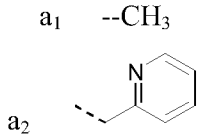
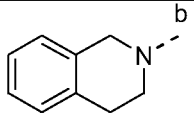
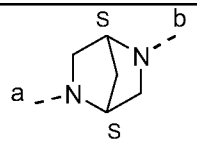
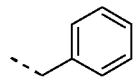
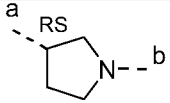
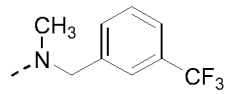
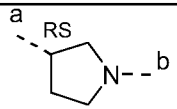
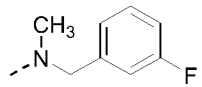
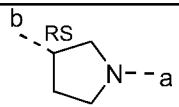
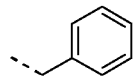
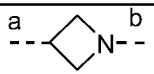
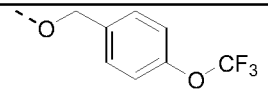
Co. nr.	Exp nr.	--V^1-M^1	--L--	--R^4
4-056	B23		cb	
4-057	B26		cb	
4-058	B23		cb	
4-059	B26		cb	
4-060	B26		cb	 .HCl
4-061	B23		cb	
4-062	B33		cb	
4-063	B33		cb	 c --OH
4-064	B23		cb	
4-065	B23		cb	
4-066	B33		cb	

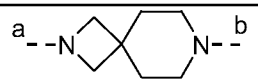
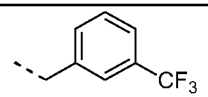
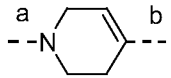
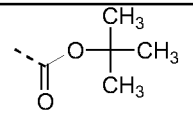
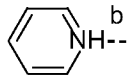
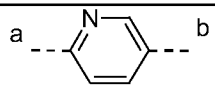
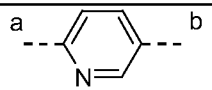
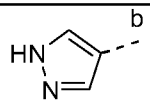
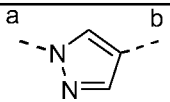
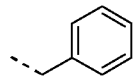
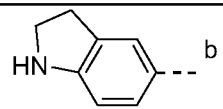
Table 5 : Other compounds prepared according to the Examples wherein A is a *N*-containing heterocycle

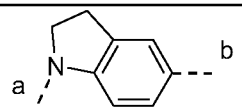
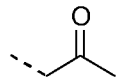
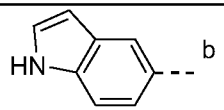
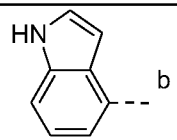
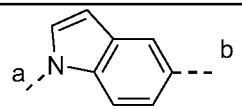
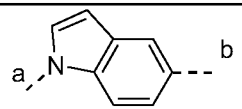
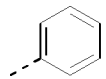
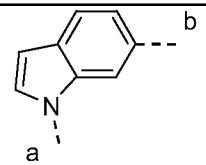
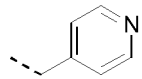
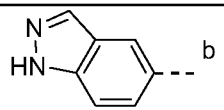


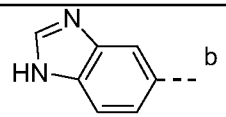
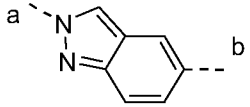
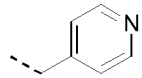
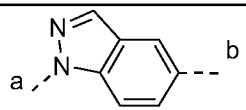
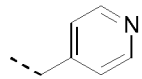
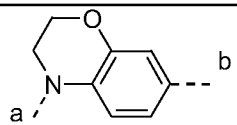
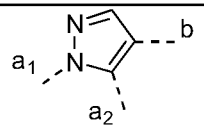
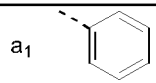
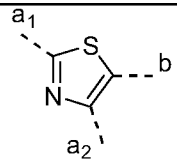
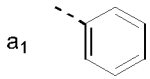
a--**A**--b : a is the side with the R^4 moiety; b is the side with the L moiety

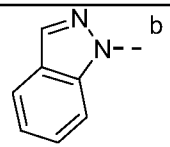
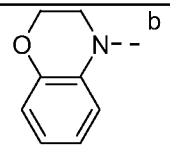
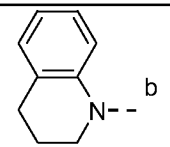
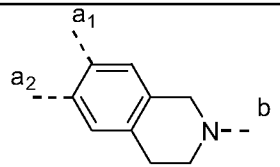
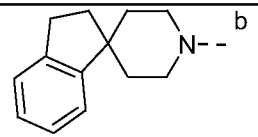
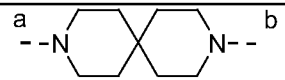
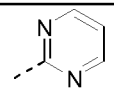
Co. nr.	**Exp nr.**	**--V^1-M^1**	**--L--**	a--**A**--b	**--R^4**
5-054	B47*	--CH_2 CH_2 CH_2CH_3	cb		
5-023	B1	--CH_2 CH_2 CH_2CH_3	cb		
5-001	B11	--CH_2 CH_2 CH_2CH_3	cb		

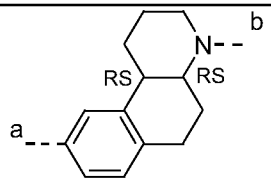
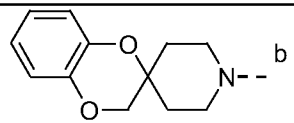
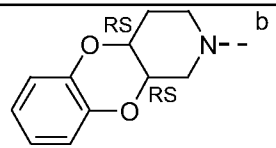
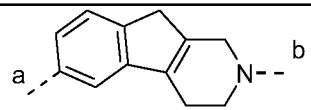
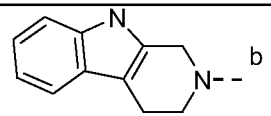
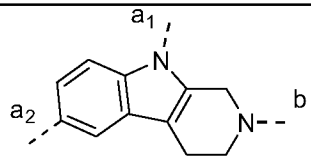
Co. nr.	**Exp nr.**	**--V^1-M^1**	**--L--**	a--A--b	**--R^4**
5-002	B1	--CH_2 CH_2 CH_2CH_3	cb		
5-003	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-004	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-005	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-006	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-007*	B30	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-008	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb		

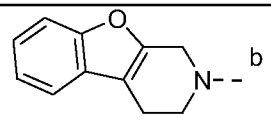
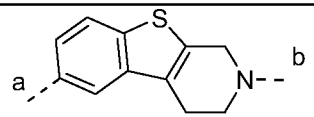
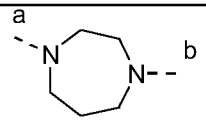
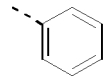
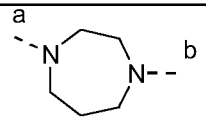
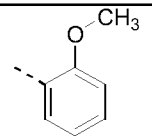
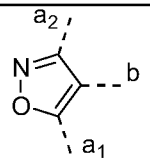
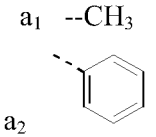
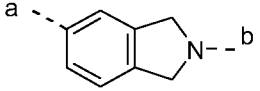
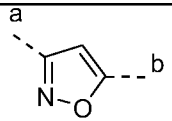
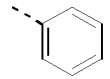
Co. nr.	Exp nr.	--V^1-M^1	--L--	a--A--b	--R^4
5-009	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-053	B44*	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-052	B40*	--CH_2-CH_2-$CH(CH_3)_2$	cb		– trifluoromethylsulfonic acid (salt form)
5-010	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		--O-CH_3
5-011	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		--$(CH_2)_3$OH
5-012	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-013	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-014	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		–

Co. nr.	Exp nr.	--V^1-M^1	--L--	a--A--b	--R^4
5-015	B36*	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-016	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-017	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-018	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		--CH_3
5-019	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-020	B32	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-021	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		–

Co. nr.	Exp nr.	--V^1-M^1	--L--	a--A--b	--R^4
5-022	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-024	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-025	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-026	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		--CH_3
5-027	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		 a_2 --CH_3
5-028	B1	--CH_2-CH_2-$CH(CH_3)_2$	cb		 a_2 --CH_3

Co. nr.	Exp nr.	--V^1-M^1	--L--	a--A--b	--R^4
5-029	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-030	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-031	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-032	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb		a_1 --OCH_3 a_2 --OCH_3
5-033	B23	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-034	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		

Co. nr.	Exp nr.	--V^1-M^1	--L--	a--A--b	--R^4
5-035	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		--OCH_3
5-036	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-037	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-038	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		--F
5-039	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-040	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		a_1 --CH_3 a_2 --F

Co. nr.	Exp nr.	--V^1-M^1	--L--	a--A--b	--R^4
5-041	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		–
5-042	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		--Cl
5-043	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-044	B33	--CH_2-CH_2-$CH(CH_3)_2$	cb		
5-045	B1	--CH_2-CH_2-$CH(CH_3)_2$	--OCH_2--		
5-046	B29	--CH_2-CH_2-$CH(CH_3)_2$	--$O(CH_2)_2$--		--F
5-047	B1	--CH_2-CH_2-$CH(CH_3)_2$	--NH--		

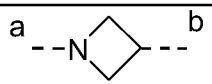
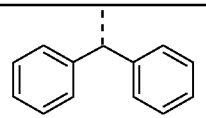
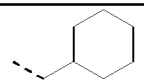
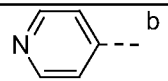
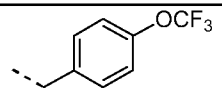
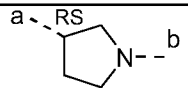
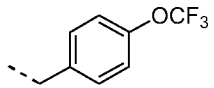
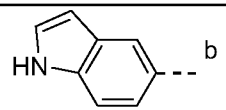
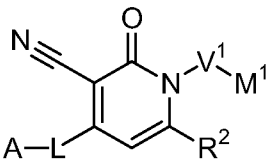
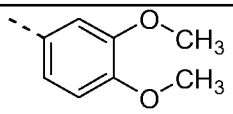
Co. nr.	Exp nr.	--V^1-M^1	--L--	a--A--b	--R^4
5-048	B33	--CH_2-CH_2-$CH(CH_3)_2$	--$N(CH_3)$--		
5-049	B10				–
5-050	B33		cb		--$N(CH_3)_2$
5-051	B1		cb		–

Table 6 : Compounds prepared according to the Examples wherein R^2 is not hydrogen.



Co.nr.	Exp. nr.	V^1	M^1	R^2	--L-A
6-001	B1	--CH_2-CH_2-$CH(CH_3)$-CH_2--	--H	--CH_3	

C. Physico-Chemical Data

LCMS-methods:

LCMS – general procedure A

The HPLC gradient was supplied by a Alliance 2795XE comprising a quaternary pump with degasser, an autosampler, a column oven, a photo diode-array detector (PDA 2996) and a column as specified in the respective methods below. Flow from the column was split to a MS detector. MS detectors were configured with electrospray ionization source. Nitrogen was used as the nebulizer gas. Mass spectra were acquired from 50 to 600 in 0.5 seconds. The capillary needle voltage was 3.5 kV and the source temperature was maintained at 140 °C. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

LCMS – general procedure B

The HPLC gradient was supplied by a HP 1100 from Agilent Technologies comprising a pump (quaternary or binary) with degasser, an autosampler, a column oven, a diode-array detector (DAD) and a column as specified in the respective methods below. Flow from the column was split to a MS detector. The MS detector was configured with an electrospray ionization source. Nitrogen was used as the nebulizer gas. The source temperature was maintained at 140 °C. Data acquisition was performed with MassLynx-Openlynx software.

LCMS – general procedure C

The LC gradient was supplied by an Acquity UPLC (Waters) system comprising a binary pump, a sample organizer, a column heater (set at 55 °C) and diode-array detector (DAD). Flow from the column was split to a MS detector. The MS detector was configured with an electrospray ionization source. Mass spectra were acquired by scanning from 100 to 1000 in 0.18 seconds using a dwell time of 0.02 seconds. The capillary needle voltage was 3.5 kV and the source temperature was maintained at 140 °C. Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

Method 1

In addition to general procedure A: Reversed phase HPLC was carried out on an Zorbax-C18 cartridge (3.5 μm, 4.6 x 50 mm) from Agilent Technologies, with a flow rate of 1 ml/min. The column oven was set at 25 °C. Two mobile phases (mobile phase A: water + 0.5% of formic acid; mobile phase B: acetonitrile + 0.5 % of formic acid) were used. First, 95 % A and 5 % B was hold for 0.1 minutes. Then a gradient was applied to 100 % B at 5 minutes, kept till 6.0 minutes and equilibrated to initial conditions at 6.5 minutes until 7.0 minutes. Typical injection volumes of 5-20 μL were used. ES MS detector was used, acquiring both in positive and negative ionization modes. Cone voltage was 30 V for positive and 63 V for negative ionization mode.

Method 2

In addition to general procedure A: Reversed phase HPLC was carried out on an Zorbax-C18 cartridge (1.8 μm, 4.6 x 30 mm) from Agilent Technologies, with a flow rate of 1.5 ml/min. The column oven was set at 30 °C. Two mobile phases (mobile phase A: water + 0.05% of formic acid; mobile phase B: acetonitrile + 0.05 % of formic acid) were used. The gradient conditions used are: 90 % A and 10 % B to 100 % B at 3.5 minutes, kept till 3.7 minutes and equilibrated to initial conditions at 3.8 minutes until 4.5 minutes. Typical injection volumes of 5-20 μL were used. ES MS detector was used, acquiring both in positive and negative ionization modes. Cone voltage was 30 V for positive and 63 V for negative ionization mode.

Method 3

In addition to general procedure B: Reversed phase HPLC was carried out on an ACE-C18 column (3.0 µm, 4.6 x 30 mm) from Advanced Chromatography Technologies, with a flow rate of 1.5 ml/min, at 40 ºC. The gradient conditions used are: 80 % A (0.5 g/l ammonium acetate solution), 10 % B (acetonitrile), 10 % C (methanol) to 50 % B and 50 % C in 6.5 minutes, to 100 % B at 7 minutes and equilibrated to initial conditions at 7.5 minutes until 9.0 minutes. Injection volume 5 µl. High-resolution mass spectra (Time of Flight, TOF) were acquired only in positive ionization mode by scanning from 100 to 750 in 0.5 seconds using a dwell time of 0.1 seconds. The capillary needle voltage was 2.5 kV for positive ionization mode and the cone voltage was 20 V. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

Method 4

In addition to general procedure B: Same as Method 3, but using 10 µL of injection volume.

Method 5

In addition to general procedure B: Reversed phase HPLC was carried out on an ACE-C18 column (3.0 µm, 4.6 x 30 mm) from Advanced Chromatography Technologies, with a flow rate of 1.5 ml/min, at 40 ºC. The gradient conditions used are: 80 % A (0.5 g/l ammonium acetate solution), 10 % B (acetonitrile), 10 % C (methanol) to 50 % B and 50 % C in 6.5 minutes, to 100 % B at 7 minutes and equilibrated to initial conditions at 7.5 minutes until 9.0 minutes. Injection volume 5 µl. Low-resolution mass spectra (ZQ detector; quadrupole) were acquired by scanning from 100 to 1000 in 1.0 second using a dwell time of 0.3 seconds. The capillary needle voltage was 3 kV. The cone voltage was 20 V and 50 V for positive ionization mode and 20 V for negative ionization mode.

Method 6

In addition to general procedure C: Reversed phase UPLC was carried out on a bridged ethylsiloxane/silica (BEH) C18 column (1.7 µm, 2.1 x 50 mm) with a flow rate of 0.8 ml/min. Two mobile phases (mobile phase A: 0.1 % formic acid in H_2O/methanol

95/5; mobile phase B: methanol) were used to run a gradient condition from 95 % A to 5 % A, 95 % B in 1.3 minutes and hold for 0.2 minutes. An injection volume of 0.5 µl was used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

Method 7

In addition to general procedure B: Reversed phase HPLC was carried out on an XDB-C18 cartridge (1.8 µm, 2.1 x 30 mm) from Agilent, at 60ºC with a flow rate of 1 ml/min, at 60 ºC. The gradient conditions used are: 90 % A (0.5 g/l ammonium acetate solution), 5 % B (acetonitrile), 5 % C (methanol) to 50 % B and 50 % C in 6.5 minutes, to 100 % B at 7 minutes and equilibrated to initial conditions at 7.5 minutes until 9.0 minutes. Injection volume 2 µl. High-resolution mass spectra (Time of Flight, TOF) were acquired only in positive ionization mode by scanning from 100 to 750 in 0.5 seconds using a dwell time of 0.1 seconds. The capillary needle voltage was 2.5 kV and the cone voltage was 20 V. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

Method 8

In addition to general procedure B: Reversed phase HPLC was carried out on a XDB-C18 cartridge (1.8 µm, 4.6 x 30 mm) from Agilent, with a flow rate of 1.5 ml/min, at 60 ºC. The gradient conditions used are: 80 % A (0.5 g/l ammonium acetate solution), 20 % B (mixture of Acetonitrile/Methanol, 1/1) to 100 % B in 6.5 minutes, kept till 7 minutes and equilibrated to initial conditions at 7.5 minutes until 9.0 minutes. Injection volume 5 µl. Low-resolution mass spectra (ZQ detector; quadrupole) were acquired by scanning from 100 to 1000 in 1.0 second using a dwell time of 0.3 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V and 50 V for positive ionization mode and 20 V for negative ionization mode.

Method 9

In addition to general procedure B: Reversed phase HPLC was carried out on an ACE-C18 column (3.0 µm, 4.6 x 30 mm) from Advanced Chromatography Technologies, with a flow rate of 1.5 ml/min, at 40 ºC. The gradient conditions used are: 80 % A (0.5 g/l ammonium acetate solution), 10 % B (acetonitrile), 10 % C (metha-

nol) to 50 % B and 50 % C in 6.5 minutes, to 100 % B at 7 minutes and equilibrated to initial conditions at 7.5 minutes until 9.0 minutes. Injection volume 5 µl. High-resolution mass spectra (Time of Flight, TOF) were acquired by scanning from 100 to 750 in 0.5 seconds using a dwell time of 0.3 seconds. The capillary needle voltage was 2.5 kV for positive ionization mode and 2.9 kV for negative ionization mode. The cone voltage was 20 V for both positive and negative ionization modes. Leucine-Enkephaline was the standard substance used for the lock mass calibration. .

Melting point determination was performed in open capillary tubes either on a Buchi B-540 or Mettler FP62.

Table 7 : Physico-chemical data for the compounds. For salt forms, the [MH+] of the free base was reported.

Co.Nr	Melting point (°C)	$[MH^+]$	RT (min)	LCMS Method	Physical form
1-003		339	4.38	Method 3	White solid
1-004		378	4.00	Method 3	White solid
1-005		413	4.54	Method 3	Pale yellow solid
1-006		427	4.43	Method 8	Pale yellow solid
1-007	159	363	2.92	Method 2	Light yellow solid
1-008	148	299	4.59	Method 1	White solid
1-009	149	293	4.43	Method 3	Yellow solid
1-010	decomposes	336	5.00	Method 5	Yellow solid
1-011	60	323	4.43	Method 3	Yellow solid
1-012	decomposes	323	4.55	Method 3	Yellow solid
1-013	128	337	2.95	Method 2	White solid
1-014	143	391	3.22	Method 2	Yellow solid
1-015		307		Method 1	Solid
1-016		331	2.56	Method 2	Light yellow solid
1-017		331	2.60	Method 2	Light brown solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
1-018	155	291	4.19	Method 1	Yellow solid
1-019	118	307	4.45	Method 1	White solid
1-021		331	2.59	Method 2	Light yellow solid
1-022		335	3.92	Method 3	Light brown solid
1-023		295	1.15	Method 6	Beige solid
1-024	181	385	2.70	Method 2	Light yellow solid
1-025		397	4.92	Method 3	Light brown solid
1-026		351	2.62	Method 2	White solid
1-027		351	2.63	Method 2	Light yellow solid
1-028	180	327	4.54	Method 1	Pink solid
1-030	153	371	2.76	Method 2	White solid
1-031	167	468	4.62	Method 3	White solid
1-032	190	456	2.70	Method 2	Yellow solid
1-033	97	470	4.47	Method 3	White solid
1-034		498	4.53	Method 8	White solid
1-035	136	498	4.52	Method 8	White solid
1-036		498	5.19	Method 3	White solid
1-037	184	500	4.47	Method 3	White solid
1-038	140	514	4.64	Method 3	White solid
1-039	169	401	2.78	Method 2	White solid
1-040	180	429	2.47	Method 2	White solid
1-041	155	463	3.17	Method 2	Beige solid
1-042	185	363	2.90	Method 2	White solid
1-043	185	288	2.71	Method 1	Beige solid
1-044	141	288	3.34	Method 1	White solid
1-045	160	288	2.81	Method 1	Solid
1-046	185	362	3.96	Method 1	White solid
1-047		317	4.09	Method 3	Pale yellow solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
1-048	188	347	4.20	Method 4	White solid
1-049	decomposes	409	5.13	Method 3	White solid
1-050	135	245	3.85	Method 1	Yellow solid
1-051		305	4.29	Method 1	Yellow solid
1-052	118	321	4.40	Method 1	Yellow solid
1-053	decomposes	315	4.25	Method 3	White solid
1-055	123	337	2.73	Method 2	White solid
1-056	195	352	3.64	Method 7	Bright yellow solid
1-057	136	371	4.04	Method 3	White solid
1-058	122	336	4.72	Method 7	Yellow solid
1-059	103	259	4.18	Method 1	Yellow solid
1-060		347	3.00	Method 3	Pale brown solid
1-061		346	3.93	Method 3	Pale yellow solid
1-062		346	3.61	Method 7	White solid
1-063	102	374	4.16	Method 3	White solid
1-064	121	360	3.97	Method 7	White solid
1-065		360	4.22	Method 7	White solid
1-066		364	3.79	Method 3	White solid
1-067		414	4.68	Method 7	White solid
1-068	decomposes	414	4.67	Method 7	Off white solid
1-069		414	4.40	Method 7	Off white solid
1-070		380	4.10	Method 7	Off white solid
1-071		371	3.86	Method 7	White solid
1-072		371	3.90	Method 7	White solid
1-073		431	4.32	Method 3	Off white solid
1-074		347	3.32	Method 7	White solid
1-075		347	3.36	Method 7	White solid
1-076		347	3.55	Method 7	White solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
1-077	108	259	3.92	Method 1	Beige solid
1-078	170	346	3.06	Method 8	White solid
1-079	103	273	4.22	Method 1	White solid
1-080	149	267	4.45	Method 1	White solid
1-081		257	4.13	Method 1	Yellow solid
1-082	123	273	4.29	Method 1	Yellow solid
1-083		307	4.66	Method 4	Yellow solid
1-084	142	267	4.25	Method 1	White solid
1-085	102	281	2.72	Method 2	White solid
1-086	168	323	3.16	Method 2	Orange solid
1-087	125	285	3.97	Method 3	Pale yellow solid
1-088	161	285	4.09	Method 4	White solid
1-089	decomposes	285	4.07	Method 3	White solid
1-090	123	301	2.74	Method 2	White solid
1-091	137	301	2.76	Method 2	Yellow solid
1-092		423	5.01	Method 3	White solid
1-093	172	343	3.05	Method 2	Off white solid
1-094	131	343	3.03	Method 2	Light yellow solid
1-095	85	325	3.76	Method 1	White solid
1-096	201	283	3.72	Method 1	Light brown solid
1-097	210	283	3.66	Method 1	White solid
1-098	145	297	2.04	Method 2	White solid
1-099		327	3.35	Method 3	Beige solid
1-100		297	4.11	Method 5	Yellow oil
1-101	96	297	4.31	Method 1	White solid
1-102	99	270	4.07	Method 1	Light yellow solid
1-103	91	311	4.22	Method 1	White solid
1-104		311	4.52	Method 3	Cream solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
1-105	107	325	2.96	Method 2	Light orange solid
1-106		339	4.54	Method 3	Pale yellow solid
1-107	67	311	2.51	Method 2	Light yellow solid
1-108		313	3.51	Method 3	Cream solid
1-109		357	3.35	Method 3	White solid
1-110	52	327	4.03	Method 3	Yellow solid
1-111	129	325	2.89	Method 2	Light yellow solid
1-112	149	331	4.33	Method 7	White solid
1-113	65	315	4.35	Method 1	White solid
1-114	133	315	4.30	Method 1	Yellow solid
1-115	154	357	3.06	Method 2	White solid
1-116		333	2.69	Method 2	White oil
1-117	166	359	5.21	Method 5	White solid
1-118	decomposes	339	3.68	Method 3	White solid
1-119	decomposes	333	4.39	Method 5	Cream solid
1-120	122	351	4.74	Method 3	Yellow solid
1-121		363	4.67	Method 3	White solid
1-122	131	381	4.61	Method 3	White solid
1-123	189	399	4.92	Method 3	White solid
1-124		385	5.88	Method 3	Pale yellow solid
1-125		355	4.00	Method 3	White solid
1-126	decomposes	353	4.08	Method 5	Cream solid
1-127	156	354	3.52	Method 1	White solid
1-128	107	368	2.05	Method 1	White solid
1-129		384	3.23	Method 3	Cream solid
1-130	159	340	3.06	Method 3	White Solid
1-131	132	322	2.42	Method 2	Pink solid
1-132		336	3.98	Method 3	White solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
1-133		337	4.72	Method 7	White solid
1-134	294	371	5.40	Method 3	Cream solid
1-135		351	5.33	Method 4	White solid
1-136		397	4.64	Method 5	Cream solid
1-137		411	4.78	Method 3	White solid
1-138		441	4.70	Method 3	Cream solid
1-139		396	3.95	Method 3	Pale brown solid
1-140		359	5.13	Method 3	White solid
1-141		373	5.38	Method 3	White solid
1-142		403	5.01	Method 3	White solid
1-143	118	389	3.07	Method 2	White solid
1-144	100	403	3.03	Method 2	White solid
1-145	212	403	3.02	Method 2	White solid
1-146	139	391	3.07	Method 2	White solid
1-147	146	391	3.07	Method 2	White solid
1-148	173	391	3.06	Method 2	Yellow solid
1-149	120	407	3.23	Method 2	White solid
1-150	177	407	3.18	Method 2	White solid
1-151	154	398	2.89	Method 2	White solid
1-152	193	384	2.86	Method 2	White solid
1-153	171	398	2.89	Method 2	Yellow solid
1-154		360	4.23	Method 3	White solid
1-155	132	360	4.07	Method 7	Off white solid
1-156	139	360	4.09	Method 3	Off white solid
1-157	162	374	4.36	Method 5	White solid
1-158	142	374	4.23	Method 5	Cream solid
1-159	171	374	4.25	Method 5	White solid
1-160		374	4.18	Method 3	Cream solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
1-161		378	4.17	Method 3	White solid
1-162	156	392	4.21	Method 3	Pale brown solid
1-163	202	442	2.94	Method 2	White solid
1-164	165	408	2.82	Method 2	White solid
1-165		408	2.15	Method 2	White solid
1-166		404	4.05	Method 3	Cream solid
1-167		404	4.05	Method 3	White solid
1-168	decomposes	364	3.27	Method 5	Freeze-dried
1-169	144	3.94	2.62	Method 2	Beige solid
1-170		282	3.10	Method 3	Yellow solid
1-171	189	296	3.97	Method 3	Bright yellow solid
1-172	137	310	4.51	Method 1	Green solid
1-173	130	324	1.81	Method 2	Grey solid
1-174		340	4.02	Method 9	Yellow solid
1-175	75	324	3.54	Method 1	Brown solid
1-176	198	324	3.55	Method 1	White solid
1-177	112	352	2.13	Method 2	White solid
1-178	157	338	3.39	Method 1	Beige solid
1-179	144	338	3.39	Method 1	White solid
1-180					Yellow solid
1-181	decomposes	353	2.79	Method 3	Pale yellow solid
1-182		367	3.31	Method 3	Bright yellow solid
1-183		354	5.04	Method 3	Pale yellow solid
1-184		368	3.30	Method 3	White solid
1-185		384	4.45	Method 4	Yellow solid
1-186	269	321	3.47	Method 3	Pale brown solid
1-187		322	4.52	Method 3	Yellow

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
1-188		364	5.66	Method 3	Bright yellow solid
1-189		384	4.22	Method 3	Yellow solid
1-190		384	4.21	Method 7	Yellow solid
1-191	decomposes	400	4.48	Method 7	Pale yellow solid
1-192	119				Bright yellow solid
1-193		358	5.21	Method 3	Brown solid
1-194		372	5.17	Method 3	Yellow solid
1-195		372	5.35	Method 3	Bright yellow oil
1-196		386	5.33	Method 3	Yellow solid
1-197		418	5.47	Method 3	White solid
1-198		404	4.71	Method 3	White solid
1-199	136	390	2.93	Method 2	Yellow solid
1-200	162	390	2.94	Method 2	Yellow solid
1-201		342	3.35	Method 3	Cream solid
1-202	146	406	3.07	Method 2	Yellow solid
1-203	173	402	2.90	Method 2	Yellow solid
1-204	157	397	2.75	Method 2	Yellow solid
1-205		456	5.69	Method 3	Yellow solid
1-206	209	397	2.74	Method 2	Yellow solid
1-207		379	2.68	Method 3	Yellow solid
1-208		359	3.35	Method 7	Pale yellow solid
1-209		373	4.08	Method 3	Yellow solid
1-210	73	373	4.01	Method 3	Yellow solid
1-211	142	401	4.53	Method 3	Pale yellow solid
1-212	294	401	4.44	Method 3	Pale yellow solid
1-213	96	401	1.61	Method 2	White solid
1-214		326	4.26	Method 3	Brown solid
1-215	70	360	3.70	Method 1	White solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
1-216	191	360	3.67	Method 1	White solid
1-217		414	3.49	Method 7	Bright yellow solid
1-218		336	5.10	Method 3	Yellow solid
1-219		350	5.32	Method 5	Bright yellow solid
1-220	213	366	3.79	Method 3	Yellow solid
1-221		380	4.60	Method 4	Yellow solid
1-222		352	4.17	Method 5	Yellow solid
1-223	171	352	4.09	Method 3	Yellow solid
1-224	decomposes	368	3.67	Method 4	Yellow solid
1-225	151	382	4.08	Method 3	Yellow solid
1-226	118	430	4.80	Method 3	Yellow solid
1-227	162	380	4.79	Method 3	Yellow solid
1-228	148	400	5.19	Method 3	Bright yellow solid
1-229	148	366	3.94	Method 3	White solid
1-230	143	393	3.98	Method 3	Yellow solid
1-231	decomposes	393	3.68	Method 3	Yellow solid
1-232		391	4.77	Method 3	Yellow solid
1-233		427	5.45	Method 4	Orange solid
1-234		428	3.94	Method 3	Orange solid
1-235	151	333	3.57	Method 5	White solid
1-236	decomposes	334	3.50	Method 5	Pale yellow solid
1-237					Yellow solid
1-238	130	309	4.02	Method 1	Beige Solid
1-239	120	353	4.34	Method 1	Yellow solid
1-240	169	339	3.73	Method 1	White solid
1-241	172	338	1.94	Method 2	White solid
1-242	(oil)	325	2.54	Method 2	Black oil
1-243	166	338	2.05	Method 2	Off white solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
1-244	122	352	2.10	Method 2	White solid
1-245	135-140	414	2.62	Method 2	White solid
1-246		350	3.50	Method 3	Cream solid
1-247	217	587	5.02	Method 8	White solid
1-248		347	3.44	Method 3	White solid
1-249		350	3.68	Method 7	Yellow solid
1-250		334	3.89	Method 3	White solid
1-251	117	309	4.09	Method 3	Off white solid
1-252	120-121	311	4.24	Method 1	Beige solid
1-253		325	4.14	Method 3	White solid
1-254	122	306	2.37	Method 2	White solid
1-255	233	494	2.78	Method 2	Yellow solid
1-256	128	313	4.55	Method 1	Yellow solid
1-257	181	345	3.69	Method 1	White solid
1-258		390	4.35	Method 4	Colourless oil
1-259		323	4.62	Method 3	Pale grey solid
1-260		295	4.46	Method 4	White solid
1-261		293	4.70	Method 3	Yellow solid
1-262		338	4.75	Method 3	White solid
1-263	decomposes	338	4.83	Method 5	Creamy green solid
1-264		325	4.46	Method 3	White solid
1-265	88	325	4.52	Method 5	White solid
1-266		323	4.51	Method 3	Yellow solid
1-267		291	4.78	Method 3	Brown solid
1-268		321	4.85	Method 3	Cream solid
1-269		334	5.24	Method 3	White solid
1-270	166	334	5.24	Method 5	Orange solid
1-271		500	4.41	Method 3	White solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
1-272		401	4.78	Method 3	White solid
1-273		347	4.15	Method 7	White solid
1-274	decomposes	283	4.05	Method 3	White solid
1-275	174	297	4.10	Method 5	White solid
1-276		311	4.33	Method 5	White
1-277		365	4.65	Method 3	White solid
1-278		375	4.54	Method 3	White solid
1-279	116	381	4.69	Method 3	White solid
1-280		327	4.18	Method 5	White solid
1-281	83	341	4.21	Method 5	White solid
1-282	153	313	4.12	Method 3	White solid
1-283		345	4.08	Method 3	Pale pink solid
1-284	190	363	4.32	Method 5	White solid
1-285	200	381	4.83	Method 5	White solid
1-286		322	3.73	Method 3	Pale yellow solid
1-287		397	4.99	Method 3	Pale yellow solid
1-288	169	323	4.30	Method 3	White solid
1-289		403	5.02	Method 3	Pale yellow
1-290	148	445	5.24	Method 3	White solid
1-291		352	5.16	Method 3	Pale yellow solid
1-292	154	396	3.82	Method 3	White solid
1-293	209	372	4.43	Method 3	White solid
1-294		306	3.97	Method 3	White solid
1-295		359	3.31	Method 3	Yellow solid
1-296	151	361	3.57	Method 7	Off white solid
1-297		350	4.78	Method 7	Pale yellow solid
1-298	decomposes	282	3.97	Method 3	Cream solid
1-299		296	4.00	Method 3	Pale brown oil

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
1-300	decomposes	367	3.91	Method 3	White solid
1-301	decomposes	374	5.13	Method 3	Yellow solid
1-302		375	4.01	Method 3	Yellow solid
1-303		310	4.14	Method 3	White solid
1-304		322	4.51	Method 7	White solid
1-306		374	4.22	Method 7	
2-001	183	437	4.95	Method 3	Pale yellow solid
2-002	127	469	5.26	Method 3	White solid
2-003	134	455	5.13	Method 3	Pale yellow solid
2-004		338	3.36	Method 3	Pale yellow solid
2-005		367	4.07	Method 3	White solid
2-006		379	4.08	Method 3	Pale yellow solid
2-007		369	3.76	Method 3	Off white solid
2-008		382	3.45	Method 3	Pale yellow solid
2-009		424	3.34	Method 3	Pale yellow solid
2-010	112	469	5.21	Method 3	White solid
2-011		351	4.40	Method 3	Yellow solid
2-012		365	4.44	Method 3	White solid
2-013		381	4.32	Method 3	Pale yellow solid
2-014		433	5.04	Method 3	White solid
2-015	decomposes	401	4.66	Method 3	Beige solid
2-016		409	4.33	Method 3	White solid
2-017		379	4.55	Method 3	Pale brown solid
2-018		391	4.75	Method 3	Pale yellow oil
2-019		413	4.49	Method 3	Yellow gum
2-020		463	5.05	Method 3	Pale yellow solid
2-021		379	4.99	Method 3	Pale yellow solid
2-022	256	483	5.49	Method 3	White solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
2-023		366	3.32	Method 3	Yellow gum
2-024		352	3.83	Method 3	Yellow solid
2-025		366	4.17	Method 3	Yellow solid
2-026	135	420	4.69	Method 3	White solid
2-027		377	3.72	Method 3	Off white solid
2-028		353	3.56	Method 3	Pale creamy solid
2-029	155	421	4.71	Method 3	Pale brown solid
2-030		353	2.80	Method 3	Yellow solid
2-031	245	387	3.38	Method 3	Yellow solid
2-032		383	3.40	Method 3	Yellow solid
2-033		429	4.23	Method 3	Yellow gum
2-034	decomposes	417	3.89	Method 3	Pale yellow solid
2-035	288	392	4.15	Method 3	White solid
2-036	159	396	3.67	Method 3	Off white solid
2-037	223				White solid
2-038	140	435	4.73	Method 3	White solid
2-039	125	467	5.05	Method 3	White solid
2-040	157				Pale yellow solid
2-041	decomposes	365	3.38	Method 3	Pale brown solid
2-042	decomposes	469	4.91	Method 3	White solid
2-043	110	483	4.97	Method 3	Pale yellow solid
2-044	156	487	4.93	Method 4	White solid
2-045	decomposes	519	5.47	Method 3	Pale yellow solid
2-046	92	497	3.96	Method 8	Yellow solid
2-047		470	3.94	Method 3	Yellow solid
2-048	258	524	5.04	Method 3	White solid
2-049		403	4.27	Method 4	Light brown solid
2-050		421	4.39	Method 3	White solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
2-051	239	439	4.49	Method 3	White solid
2-052		439	4.59	Method 3	White solid
2-053		415	4.48	Method 3	White solid
2-054		429	4.42	Method 3	Yellow oil
2-055		390	3.59	Method 3	White solid
3-001	124	338	3.57	Method 7	Pale yellow solid
3-002					White solid
3-003	125	379	4.41	Method 3	White solid
3-004	188	434	4.90	Method 3	Off white solid
3-005		393	4.47	Method 3	White solid
3-006	131	461	5.22	Method 3	White solid
3-007	208	380	4.35	Method 3	White solid
3-008		448	5.10	Method 3	Pale brown solid
3-009	117	462	5.20	Method 3	Off white solid
3-010	187				White solid
3-011	decomposes	351	2.55	Method 3	White solid
3-012		432	4.60	Method 3	Cream solid
3-013	211	497	4.95	Method 3	White solid
3-014		432	5.35	Method 3	White solid
4-001		337	3.28	Method 3	White solid
4-002		337	3.22	Method 7	White solid
4-003	132	351	3.33	Method 7	
4-004	188	353	3.20	Method 3	Cream solid
4-005		353	3.87	Method 3	Cream solid
4-006		367	3.94	Method 7	White solid
4-007		367	3.51	Method 7	Pale yellow solid
4-008		381	3.79	Method 7	White solid
4-009		377	3.91	Method 7	White solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
4-010		342	4.19	Method 3	White solid
4-012	296	378	4.48	Method 3	White solid
4-013		350	5.06	Method 3	White solid
4-014	decomposes	350	4.76	Method 3	White solid
4-015		364	5.33	Method 3	Yellow oil
4-016	112	418	5.09	Method 7	White solid
4-017		380	5.18	Method 3	White solid
4-018		384	4.94	Method 3	White solid
4-019	100	412	5.18	Method 3	White solid
4-020		448	5.43	Method 3	White gummy solid
4-021	decomposes	410	4.82	Method 3	White solid
4-022		464	5.30	Method 3	White solid
4-023		365	4.43	Method 3	Beige solid
4-025	283	447	4.63	Method 3	White solid
4-026		393	4.41	Method 3	Brown solid
4-027	113	411	4.57	Method 3	White solid
4-028		461	5.25	Method 3	White solid
4-029	91	461	5.28	Method 3	White solid
4-030		425	5.09	Method 3	White foam
4-031	141	447	5.31	Method 3	White solid
4-032		475	5.02	Method 3	
4-033		475	5.03	Method 3	Yellow solid
4-034	253	405	4.4	Method 3	Pale brown solid
4-035		389	4.93	Method 3	Pale yellow solid
4-036		405	5.29	Method 3	Browm gummy oil
4-037	78	407	4.86	Method 3	Yellow solid
4-038	214	391	4.35	Method 3	Beige solid
4-039	123	408	5.09	Method 3	White solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
4-040	113	412	4.91	Method 3	Pale cream solid
4-041		418	4.82	Method 3	Pale brown solid
4-042	decomposes	433	4.13	Method 7	Yellow solid
4-043	138	379	4.64	Method 3	White solid
4-044		435	4.53	Method 3	Pale yellow solid
4-045		380	4.93	Method 3	White solid
4-046	282	414	3.73	Method 3	White solid
4-047	128	334	4.05	Method 7	White solid
4-048		378	4.38	Method 7	Off white solid
4-049	138	497	4.89	Method 3	White solid
4-050	decomposes	491	4.20	Method 3	White solid
4-051	decomposes	509	4.88	Method 3	Pale brown solid
4-052		499	4.39	Method 7	Pale brown solid
4-053		485	3.85	Method 7	Yellow solid
4-054					Cream solid
4-055	155	435	3.85	Method 3	Cream solid
4-056		431	4.16	Method 3	Cream solid
4-057	242	449	4.54	Method 3	Cream solid
4-058		499	5.05	Method 3	White solid
4-059	157	475	5.27	Method 3	White solid
4-060	96				Off white solid
4-061	175	447	4.20	Method 3	Cream solid
4-062	139	454	5.06	Method 3	White solid
4-063		471	3.56	Method 7	Off white solid
4-064	159	443	4.43	Method 3	White solid
4-065		511	5.24	Method 3	White solid
4-066		400	4.83	Method 3	White solid
5-001	decomposes	384	3.31	Method 3	Off white solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
5-002	164.7	398	3.24	Method 3	White solid
5-003	decomposes	322	4.33	Method 3	White solid
5-004		377	4.2	Method 3	Pale cream gum
5-005	96	447	5.16	Method 3	White solid
5-006	100	397	4.71	Method 3	White solid
5-007		350	4.75	Method 3	Colourless oil
5-008	102	436	5.11	Method 3	White solid
5-009		473	4.97	Method 3	White solid
5-010	118	298	2.37	Method 2	White solid
5-011		326	2.96	Method 3	Pale brown solid
5-012		257	2.72	Method 3	White solid
5-013		347	4.26	Method 3	White solid
5-014		308	3.92	Method 5	Orange solid
5-015		350	3.75	Method 5	Pale yellow solid
5-016	decomposes	306	3.93	Method 3	Pale brown solid
5-017	decomposes	306	3.84	Method 3	Pale green solid
5-018	281	320	4.37	Method 3	Pale yellow solid
5-019		382	5.31	Method 3	Pale yellow solid
5-020	232	397	4.21	Method 3	Cream solid
5-021	decomposes	307	3.31	Method 3	Syrup
5-022		307	2.93	Method 3	Beige solid
5-023	decomposes	384	3.51	Method 3	Cream solid
5-024	284	398	3.53	Method 3	Cream solid
5-025		398	3.72	Method 3	Cream solid
5-026	decomposes	338	4.43	Method 5	Bright yellow solid
5-027	decomposes	347	4.08	Method 7	White solid
5-028		364	4.87	Method 3	White solid
5-029	234	307	3.89	Method 3	Pale yellow solid

Co.Nr	Melting point (°C)	[MH$^+$]	RT (min)	LCMS Method	Physical form
5-030		324	4.4	Method 3	Cream solid
5-031	134	322	4.72	Method 3	Yellow solid
5-032		382	4.04	Method 3	White solid
5-033		376	5.35	Method 3	White solid
5-034		421	4.44	Method 3	Pale cream solid
5-035	169	406	5.04	Method 3	White solid
5-036		394	4.96	Method 3	White solid
5-037	217	380	4.57	Method 3	Cream solid
5-038	141				Cream solid
5-039	276	361	4.52	Method 3	White solid
5-040	111	393	4.87	Method 3	Cream solid
5-041	130	362	4.85	Method 3	White solid
5-042		412	5.73	Method 3	Pale yellow
5-043	decomposes	365	4.57	Method 3	Pale yellow solid
5-044		395	4.51	Method 3	Brown gummy solid
5-045		378	4.06	Method 3	White solid
5-046		370	4.08	Method 4	White solid
5-047		349	4.37	Method 3	White solid
5-048		441	5.22	Method 3	Colourless oil
5-049		318	4.39	Method 3	Pale grey solid
5-050		407	3.66	Method 3	White solid
5-051	166	410	2.63	Method 2	Grey solid
6-001	175	341	5.54	Method 2	Beige solid

decomposes = product decomposes in the course of the determination.

D. Pharmacological examples

The compounds provided in the present invention are positive allosteric modulators of mGluR2. These compounds appear to potentiate glutamate responses by binding to an allosteric site other than the glutamate binding site. The response of mGluR2 to a concentration of glutamate is increased when compounds of Formula (I) are present. Compounds of Formula (I) are expected to have their effect substantially at mGluR2 by virtue of their ability to enhance the function of the receptor. The behaviour of positive allosteric modulators tested at mGluR2 using the [^{35}S]GTPγS binding assay method described below and which is suitable for the identification of such compounds, and more particularly the compounds according to Formula (I), are shown in Table 4.

[^{35}S]GTPγS binding assay

The [^{35}S]GTPγS binding is a functional membrane-based assay used to study G-protein coupled receptor (GPCR) function whereby incorporation of a non-hydrolysable form of GTP, [^{35}S]GTPγS (guanosine 5'-triphosphate, labelled with gamma-emitting ^{35}S), is measured. The G-protein α subunit catalyzes the exchange of guanosine 5'-diphosphate (GDP) by guanosine triphosphate (GTP) and on activation of the GPCR by an agonist, [^{35}S]GTPγS, becomes incorporated and cannot be cleaved to continue the exchange cycle (Harper (1998) Current Protocols in Pharmacology 2.6.1-10, John Wiley & Sons, Inc.). The amount of radioactive [^{35}S]GTPγS incorporation is a direct measure of the activity of the G-protein and hence the activity of the agonist can be determined. mGluR2 receptors are shown to be preferentially coupled to Gαi-protein, a preferential coupling for this method, and hence it is widely used to study receptor activation of mGluR2 receptors both in recombinant cell lines and in tissues (Schaffhauser et al 2003, Pinkerton et al, 2004, Mutel et al (1998) Journal of Neurochemistry. 71:2558-64; Schaffhauser et al (1998) Molecular Pharmacology 53:228-33). Here we describe the use of the [^{35}S]GTPγS binding assay using membranes from cells transfected with the human mGluR2 receptor and adapted from Schaffhauser et al ((2003) Molecular Pharmacology 4:798-810) for the detection of the positive allosteric modulation (PAM) properties of the compounds of this invention.

Membrane preparation

CHO-cells were cultured to pre-confluence and stimulated with 5 mM butyrate for 24 hours, prior to washing in PBS, and then collection by scraping in homogenisation buffer (50 mM Tris-HCl buffer, pH 7.4, 4°C). Cell lysates were homogenized briefly (15s) using an ultra-turrax homogenizer. The homogenate was centrifuged at 23 500 x g for 10 minutes and the supernatant discarded. The pellet was resuspended in 5 mM Tris-HCl, pH 7.4 and centrifuged again (30 000 x g, 20 min, 4°C). The final pellet was resuspended in 50 mM HEPES, pH 7.4 and stored at -80°C in appropriate aliquots before use. Protein concentration was determined by the Bradford method (Bio-Rad, USA) with bovine serum albumin as standard.

[^{35}S]GTPγS binding assay

Measurement of mGluR2 positive allosteric modulators in membranes containing human mGluR2 was performed using frozen membranes that were thawed and briefly homogenised prior to pre-incubation in 96-well microplates (15 µg/assay well, 30 minutes, 30°C) in assay buffer (50 mM HEPES pH 7.4, 100 mM NaCl, 3 mM $MgCl_2$, 50 µM GDP, 10 µg/ml saponin,) with increasing concentrations of positive allosteric modulator (from 0.3 nM to 50 µM) and either a minimal pre-determined concentration of glutamate (PAM assay), or no added glutamate. For the PAM assay, membranes were pre-incubated with glutamate at EC_{25} concentration, i.e. a concentration that gives 25 % of the maximal response glutamate, and is in accordance to published data (Pin et al. (1999) Eur. J. Pharmacol. 375:277-294). After addition of [^{35}S]GTPγS (0.1 nM, f.c.) to achieve a total reaction volume of 200 µl, microplates were shaken briefly and further incubated to allow [^{35}S]GTPγS incorporation on activation (30 minutes, 30 °C). The reaction was stopped by rapid vacuum filtration over glass-fibre filter plates (Unifilter 96-well GF/B filter plates, Perkin-Elmer, Downers Grove, USA) microplate using a 96-well plate cell harvester (Filtermate, Perkin-Elmer, USA), and then by washing three times with 300 µl of ice-cold wash buffer ($Na_2PO_4.2H_20$ 10 mM, $NaH_2PO_4.H_20$ 10 mM, pH = 7.4). Filters were then air-dried, and 40 µl of liquid scintillation cocktail (Microscint-O) was added to each well, and membrane-bound [^{35}S]GTPγS was measured in a 96-well scintillation plate reader

(Top-Count, Perkin-Elmer, USA). Non-specific [^{35}S]GTPγS binding is determined in the presence of cold 10 μM GTP. Each curve was performed at least once using duplicate sample per data point and at 11 concentrations.

Data analysis

The concentration-response curves of representative compounds of the present invention in the presence of added EC_{25} of mGluR2 agonist glutamate to determine positive allosteric modulation (PAM), were generated using the Prism GraphPad software (Graph Pad Inc, San Diego, USA). The curves were fitted to a four-parameter logistic equation (Y=Bottom + (Top-Bottom)/(1+10^((LogEC_{50}-X)*Hill Slope) allowing determination of EC_{50} values.

Table 8. Pharmacological data for compounds according to the invention.

All compounds were tested in presence of mGluR2 agonist, glutamate at a predetermined EC_{25} concentration, to determine positive allosteric modulation (GTPγS-PAM). Values shown are averages of duplicate values of 11-concentration response curves, from at least one experiment. All compounds showed a pEC_{50} value of more than 5.0, from 5.1 (weak activity) to 7.6 (very high activity). The error of determination of a pEC_{50} value for a single experiment is estimated to be about 0.3 log-units.

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
1-093	7.6
5-020	7.6
1-204	7.6
1-202	7.5
4-065	7.5
4-066	7.5
1-140	7.4
1-196	7.4
5-033	7.4
4-062	7.4
4-039	7.4
1-151	7.4
1-145	7.4
1-268	7.3
4-016	7.3
1-188	7.3
1-124	7.3
5-041	7.3
1-153	7.3
1-149	7.3
5-019	7.3
4-022	7.3
1-148	7.3
1-206	7.3
4-060	7.3
1-194	7.2
1-141	7.2
1-117	7.2
4-014	7.2
1-287	7.2

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
1-086	7.2
1-092	7.2
1-144	7.2
1-146	7.2
1-199	7.2
4-031	7.2
1-267	7.1
1-289	7.1
5-039	7.1
1-134	7.1
2-048	7.1
4-019	7.1
1-147	7.1
1-228	7.1
1-143	7.1
1-200	7.1
1-165	7.1
1-163	7.1
1-150	7.1
1-010	7.0
1-270	7.0
1-014	7.0
1-115	7.0
4-015	7.0
4-035	7.0
4-028	7.0
1-152	7.0
1-025	7.0
1-172	6.9
1-285	6.9

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
1-187	6.9
1-024	6.9
1-013	6.9
1-195	6.9
1-272	6.9
4-020	6.9
4-045	6.9
4-017	6.9
4-037	6.9
5-018	6.9
4-041	6.9
1-226	6.9
1-049	6.9
4-064	6.9
4-029	6.9
1-256	6.8
1-290	6.8
1-269	6.8
1-042	6.8
1-039	6.8
1-123	6.8
1-164	6.8
3-009	6.8
2-022	6.8
1-271	6.8
2-003	6.8
1-004	6.8
2-006	6.8
1-067	6.8
1-083	6.7

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
1-218	6.7
5-026	6.7
1-219	6.7
1-133	6.7
3-014	6.7
2-026	6.7
1-301	6.7
1-259	6.7
1-040	6.7
5-042	6.7
1-261	6.7
5-038	6.7
4-021	6.7
4-049	6.7
5-048	6.7
2-017	6.7
1-297	6.7
1-008	6.6
5-016	6.6
5-003	6.6
1-277	6.6
5-051	6.6
1-041	6.6
1-205	6.6
5-036	6.6
5-008	6.6
4-036	6.6
2-029	6.6
1-183	6.6
2-043	6.6

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
4-058	6.6
1-197	6.6
4-059	6.6
3-004	6.6
1-068	6.6
1-258	6.5
1-112	6.5
1-180	6.5
1-266	6.5
5-028	6.5
1-142	6.5
1-030	6.5
1-278	6.5
5-027	6.5
1-111	6.5
5-040	6.5
1-203	6.5
1-022	6.5
3-008	6.5
2-002	6.5
4-047	6.5
1-006	6.5
1-058	6.5
1-191	6.5
4-032	6.4
1-012	6.4
1-157	6.4
1-007	6.4
1-279	6.4
1-105	6.4

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
4-012	6.4
4-038	6.4
5-037	6.4
1-237	6.4
4-040	6.4
1-221	6.4
1-162	6.4
4-033	6.4
5-025	6.4
5-034	6.4
1-190	6.4
1-247	6.4
1-005	6.4
1-073	6.4
1-064	6.4
1-120	6.3
2-011	6.3
1-026	6.3
1-027	6.3
1-158	6.3
1-159	6.3
1-192	6.3
1-253	6.3
1-167	6.3
5-013	6.3
1-171	6.3
1-291	6.3
1-094	6.3
1-230	6.3
4-018	6.3

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
1-121	6.3
1-156	6.3
1-154	6.3
4-043	6.3
5-047	6.3
1-227	6.3
4-051	6.3
1-169	6.3
2-040	6.3
1-066	6.3
2-045	6.3
4-005	6.3
4-006	6.3
4-009	6.3
1-155	6.3
1-095	6.2
1-113	6.2
1-021	6.2
1-136	6.2
1-284	6.2
1-126	6.2
1-119	6.2
1-106	6.2
1-160	6.2
1-233	6.2
2-042	6.2
1-116	6.2
2-053	6.2
1-211	6.2
2-016	6.2

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
1-161	6.2
1-003	6.2
1-036	6.2
2-005	6.2
1-057	6.2
1-273	6.2
1-071	6.2
4-052	6.2
1-070	6.2
1-019	6.1
1-239	6.1
1-214	6.1
1-085	6.1
1-170	6.1
5-017	6.1
1-282	6.1
1-283	6.1
2-028	6.1
2-013	6.1
1-138	6.1
2-025	6.1
1-255	6.1
1-032	6.1
1-245	6.1
1-090	6.1
1-186	6.1
1-038	6.1
2-020	6.1
2-014	6.1
1-035	6.1

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
2-039	6.1
5-023	6.1
1-114	6.0
1-210	6.0
1-017	6.0
1-263	6.0
1-135	6.0
1-137	6.0
1-099	6.0
2-035	6.0
5-043	6.0
1-122	6.0
1-288	6.0
5-044	6.0
4-042	6.0
1-185	6.0
1-212	6.0
4-057	6.0
1-048	6.0
2-037	6.0
2-010	6.0
1-060	6.0
2-007	6.0
1-063	6.0
5-001	6.0
1-065	6.0
1-046	5.9
1-260	5.9
1-251	5.9
1-275	5.9

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
1-265	5.9
5-032	5.9
1-208	5.9
1-209	5.9
1-055	5.9
1-234	5.9
1-220	5.9
1-224	5.9
2-015	5.9
2-021	5.9
1-198	5.9
5-007	5.9
4-027	5.9
4-030	5.9
1-292	5.9
1-302	5.9
3-002	5.9
3-012	5.9
1-034	5.9
1-102	5.8
1-097	5.8
1-096	5.8
1-009	5.8
1-274	5.8
1-174	5.8
1-280	5.8
5-015	5.8
1-250	5.8
1-166	5.8
1-264	5.8

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
1-262	5.8
5-049	5.8
1-091	5.8
5-035	5.8
4-026	5.8
5-021	5.8
2-049	5.8
2-044	5.8
4-061	5.8
1-189	5.8
3-010	5.8
1-231	5.8
2-008	5.8
4-007	5.8
1-072	5.8
4-008	5.8
1-296	5.8
1-082	5.7
1-052	5.7
1-103	5.7
1-223	5.7
1-011	5.7
1-118	5.7
1-104	5.7
5-014	5.7
1-016	5.7
1-236	5.7
2-024	5.7
4-010	5.7
2-033	5.7

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
1-300	5.7
1-304	5.7
4-013	5.7
1-132	5.7
1-225	5.7
1-037	5.7
5-005	5.7
5-009	5.7
2-004	5.7
4-001	5.7
4-048	5.7
1-018	5.6
1-110	5.6
1-047	5.6
1-088	5.6
1-276	5.6
1-254	5.6
2-018	5.6
1-031	5.6
1-033	5.6
1-131	5.6
4-044	5.6
3-006	5.6
2-050	5.6
5-024	5.6
1-293	5.6
1-056	5.6
1-069	5.6
1-217	5.6
1-179	5.5

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
1-101	5.5
1-215	5.5
1-238	5.5
1-128	5.5
1-182	5.5
1-089	5.5
1-303	5.5
1-248	5.5
1-107	5.5
4-034	5.5
2-051	5.5
2-001	5.5
2-046	5.5
1-294	5.5
2-041	5.5
4-004	5.5
4-053	5.5
1-077	5.4
1-015	5.4
1-087	5.4
1-298	5.4
1-201	5.4
1-246	5.4
1-184	5.4
1-286	5.4
2-034	5.4
1-249	5.4
1-139	5.4
1-177	5.4
1-242	5.4

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
2-055	5.4
1-306	5.4
5-045	5.4
5-006	5.4
3-013	5.4
2-052	5.4
1-295	5.4
1-078	5.4
4-002	5.4
1-076	5.4
4-003	5.4
1-079	5.3
1-059	5.3
1-176	5.3
1-053	5.3
5-004	5.3
1-125	5.3
1-109	5.3
1-193	5.3
4-023	5.3
2-047	5.3
2-054	5.3
4-056	5.3
2-038	5.3
1-074	5.3
1-075	5.3
4-063	5.3
1-081	5.2
1-252	5.2
1-168	5.2

Co. Nr.	GTPgS - hR2 PAM pEC_{50}
1-108	5.2
5-011	5.2
2-019	5.2
1-173	5.2
5-030	5.2
5-031	5.2
1-244	5.2
4-024	5.2
3-007	5.2
2-027	5.2
1-061	5.2
2-009	5.2
5-002	5.2
1-062	5.2
1-084	5.1
1-050	5.1
5-010	5.1
1-127	5.1
1-098	5.1
1-181	5.1
1-281	5.1
1-222	5.1
1-235	5.1
5-029	5.1
1-129	5.1
1-229	5.1
1-213	5.1
3-011	5.1

E. Composition examples

"Active ingredient" (a.i.) as used throughout these examples relates to a final compound of formula (i), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof, a quaternary ammonium salt thereof and prodrugs thereof.

Typical examples of recipes for the formulation of the invention are as follows:

1. Tablets

Active ingredient	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg
Magnesium stearate	5 mg
Potato starch	ad 200 mg

In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

2. Suspension

An aqueous suspension is prepared for oral administration so that each 1 milliliter contains 1 to 5 mg of one of the active compounds , 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

3. Injectable

A parenteral composition is prepared by stirring 1.5 % by weight of active ingredient of the invention in 10% by volume propylene glycol and water.

4. Ointment

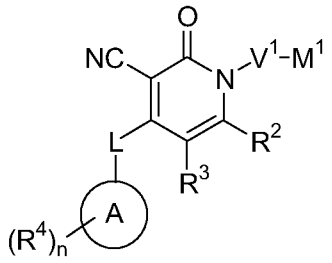
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

Reasonable variations are not to be regarded as a departure from the scope of the invention. It will be obvious that the thus described invention may be varied in many ways by those skilled in the art.

CLAIMS

1. Compound according to the general Formula (I),



(I)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, an *N*-oxide form thereof or a quaternary ammonium salt thereof, wherein

V^1 is selected from the group of a covalent bond and a bivalent saturated or unsaturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms ;

M^1 is selected from the group of hydrogen ; cycloC_{3-7}alkyl ; aryl ; alkylcarbonyl ; alkyloxy ; aryloxy ; arylalkyloxy ; arylcarbonyl ; hexahydrothiopyranyl ; and Het^1 ;

L is selected from the group of a covalent bond ; -O- ; -OCH_2- ; -OCH_2CH_2- ; -OCH_2CH_2O- ; -$OCH_2CH_2OCH_2$- ; -S- ; -NR^7- ; -NR^7CH_2- ; -NR^7cycloC_{3-7} ; -$NR^7CH_2CH_2$- ; -$OCH_2CH_2N(R^7)CH_2$- ; -CH_2- ; -CH_2CH_2-; -$CH_2CH_2CH_2$; -C≡C- ; -C=O- ; and -$C(R^8)$=$C(R^9)$- ; wherein each of R^7, independently of each other, is selected from the group of hydrogen and C_{1-3}alkyl ; and wherein R^8 and R^9, independently of each other, are selected from the group of hydrogen, halo and C_{1-3}alkyl ;

R^2 and R^3 are each independently of each other hydrogen, halo or alkyl ;

A is Het^2 or phenyl, wherein each radical is optionally substituted with n radicals R^4, wherein n is an integer equal to zero, 1, 2 or 3 ;

R^4 is selected from the group of halo ; cyano ; hydroxy ; oxo ; formyl ; ethanoyl ; carboxyl ; nitro ; thio ; alkyl ; alkyloxy ; alkyloxyalkyl ; alkyloxycarbonyl ; alkyloxycarbonylalkyl ; alkylcarbonyl ; alkylcarbonyloxy ; alkylcarbonylalkyloxy ; polyhaloC_{1-3}alkyl ; polyhaloC_{1-3}alkyloxy ; polyhaloC_{1-3}alkylthio ; alkylthio ; alkylsulfonyl ; Het^3 ; Het^3-alkyl ; Het^3-oxy ; Het^3-oxyalkyl ; Het^3-alkyloxy ; Het^3-oxyalkyloxy ; Het^3-carbonyl ; Het^3-carbonylalkyl ; Het^3-thio ; Het^3-thioalkyl ; Het^3-sulfonyl ; aryl ; arylalkyl ; aryloxy ; aryloxyalkyl ; arylalkyloxy ; arylalkenyl ; arylcarbonylalkyl ; arylthioalkyl ; arylsulfonyl ; -NR^aR^b ; alkyl-NR^aR^b ; O-alkyl-NR^aR^b ; -C(=O)-NR^aR^b ; -C(=O)-alkyl-NR^aR^b ; and O-alkyl-C(=O)-NR^aR^b ; wherein R^a and R^b are selected from the group of hydrogen, alkyl, alkylcarbonyl, arylalkyl, alkyloxyalkyl, Het^3, Het^3alkyl, alkylsulfonyl, alkyl-NR^cR^d, and C(=O)alkyl-NR^cR^d, wherein R^c and R^d are selected from the group of hydrogen, alkyl and alkylcarbonyl ;

or two radicals R^4 may be combined to form a bivalent radical -X^1-C_{1-6}-X^2- wherein C_{1-6} is a saturated or unsaturated, straight or branched hydrocarbon radical having 1 to 6 carbon atoms and X^1 and X^2 are each independently C, O or NH ; wherein the bivalent radical is optionally substituted with one or more radicals selected from the group of halo, polyhaloC_{1-3}alkyl, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl and ethanoyl ;

Het^1 is selected from the group of tetrahydropyranyl ; and pyridinyl ; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, C_{1-3}alkyl, polyhaloC_{1-3}alkyl, polyhaloC_{1-3}alkyloxy, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl, ethanoyl, and C_{1-3}alkyloxy ;

Het^2 is selected from the group of piperazinyl ; piperidinyl ; thienyl ; furanyl ; 1*H*-indazolyl ; 1*H*-benzimidazolyl ; 1,2,3,4-tetrahydro -isoquinolinyl ; 2,5-diaza-bicyclo[2.2.1]heptyl ; pyrrolidinyl ; azetidinyl ; 2,7-diaza- spiro-[3.5]nonyl ; pyridinyl ; pyrazolyl ; indolinyl ; 1*H*-indolyl ; 1*H*-indazolyl ; benzomorpholinyl ; thiazolyl ; 1,2,3,4- tetrahydroquinolinyl ; 3,9-diaza-

spiro[5.5]undecyl ; 1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolinyl ; 1,2,3,4,4a,10a-hexahydro-benzo[5,6][1,4]dioxino[2,3-c]pyridinyl ; 2,3,4,9-tetrahydro-1*H*-indeno[2,1-c]pyridinyl ; 2,3,4,9-tetrahydro-1*H*-β-carbolinyl; 1,2,3,4-tetrahydro- benzo[4,5]furo[2,3-c]pyridinyl ; 1,2,3,4-tetrahydro-benzo[4,5]thieno[2,3-c]pyridinyl ; [1,4]diazepyl ; isoxazolyl ; indanyl ; and indolyl ;

Het^3 is selected from the group of pyridinyl ; pyrimidinyl ; pyridazilyl ; pyrazinyl ; piperidinyl ; pyrrolyl ; pyrrolidinyl ; piperazinyl ; triazolyl ; tetrazolyl ; indolyl ; thienyl ; furanyl ; tetrahydropyranyl ; tetrahydro-thiopyran-1,1-dioxide ; thiazolyl ; thiadiazolyl ; isothiazolyl ; oxazolyl ; morpholinyl ; oxadiazolyl ; isoxazolyl ; imidazolyl ; pyrazolyl ; benzoimidazolyl ; benzoxazolyl; benzothienyl ; benzothiazolyl ; benzofuranyl ; benzomorpholinyl ; 1,2,3,4-tetrahydro-isoquinolinyl ; thionaphtyl ; indolyl ; indolinyl ; quinolyl ; isoquinolyl ; quinoxalyl ; phthalazyl ; benzo[1,3]dioxyl ; and quinazolyl ; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, C_{1-6}alkyl, polyhaloC_{1-3}alkyl, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl, ethanoyl, phenyl, pyrrolidinyl, piperidinyl, pyridinyl, morpholinyl, mono- and di(alkyl)amino, and C_{1-3}alkyloxy ;

aryl is naphthyl, phenyl, or biphenyl ; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other selected from the group of halo, C_{1-3}alkyl, polyhaloC_{1-3}alkyl, polyhaloC_{1-3}-alkyloxy, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl, ethanoyl, ethyloxycarbonyl, and C_{1-3}alkyloxy ;

alkyl is a saturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms ; or is a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms ; or is saturated hydrocarbon radical from 4 to 12 carbonatoms, comprising at least one saturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and at least one saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms ; wherein each

carbon atom may optionally be substituted with one or more radicals selected from the group of halo, polyhaloC_{1-3}alkyl, cyano, hydroxy, amino, oxo, carboxyl, nitro, thio, formyl, ethanoyl, carbamoyl ; phenyl ; and a bivalent radical $-OCH_2CH_2O-$; and

alkenyl is alkyl, additionally containing one or more double bonds.

2. Compound according to claim 1, characterized in that V^1 is selected from the group of a covalent bond ; $-CH_2-$; $-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-$; $-CH_2-CH=CH-$; $-CH_2-CH_2-CH_2-CH_2-$; $-CH_2-CH(CH_3)-CH_2-$; $-CH(CH_3)-CH_2-CH_2-CH_2-$; $-CH_2-CH(CH_3)-CH_2-CH_2-$; and $-CH_2-CH_2-CH(CH_3)-CH_2-$.

3. Compound according to any one of claims 1 to 2, characterized in that M^1 is selected from the group of hydrogen ; cycloC_{3-7}alkyl ; phenyl ; biphenyl ; phenyloxy ; benzyloxy ; furanyl ; and pyridinyl ; wherein any one of said radicals is optionally substituted with one or more radicals selected from the group of halo ; C_{1-3}alkyl ; polyhaloC_{1-3}alkyl ; polyhaloC_{1-3}alkyloxy ; and C_{1-3}alkyloxy.

4. Compound according to any one of claims 1 to 3, characterized in that V^1-M^1 is selected from the group of $-CH_2-CH_2-CH_2-CH_3$; $-CH_2-CH(CH_3)-CH_3$; $-CH(CH_3)-CH_2-CH_2-CH_3$; $-CH_2-CH(CH_3-)CH_2-CH_3$; $-CH_2-CH_2-CH(CH_3)-CH_3$; or V^1 is selected from the group of covalent bond ; $-CH_2-$; $-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-$; and $-CH_2-CH=CH-$; and M^1 is selected from the group of cyclopropyl ; cyclopentyl ; cyclohexyl ; phenyl ; biphenyl ; phenyloxy ; benzyloxy ; furanyl ; and pyridinyl ; wherein each radical M^1 is optionally substituted with one or more radicals selected from the group of halo ; C_{1-3}alkyl ; polyhaloC_{1-3}alkyl ; polyhaloC_{1-3}alkyloxy ; and C_{1-3}alkyloxy.

5. Compound according to any one of claims 1 to 4, wherein R^2 and R^3 are each independently hydrogen or methyl.

6. Compound according to any one of claims 1 to 5, characterized in that L is selected from the group of a covalent bond ; -O- ; $-OCH_2-$; $-OCH_2CH_2-$; $-OCH_2CH_2O-$; $-OCH_2CH_2OCH_2-$; $-NR^7-$; $-NR^7CH_2-$; $-NR^7cycloC_{3-7}$; $-OCH_2CH_2N(R^7)CH_2-$; $-CH_2CH_2-$; -C≡C- ; -C=O- and -CH=CH- ; wherein each of R^7, independently of each other, is selected from the group of hydrogen and C_{1-3}alkyl.

7. Compound according to any one of claims 1 to 6, characterized in that A is selected from the group of phenyl, piperazinyl, and piperidinyl.

8. Compound according to any one of claims 1 to 7, characterized in that R^4 is selected from the group of halo ; cyano ; hydroxy ; ethanoyl ; alkyl ; alkyloxy ; alkyloxyalkyl ; alkyloxycarbonyl ; alkyloxycarbonylalkyl ; alkylcarbonyl ; alkylcarbonyloxy ; alkylcarbonylalkyloxy ; polyhaloC_{1-3}alkyl ; polyhaloC_{1-3}alkyloxy ; polyhaloC_{1-3}alkylthio ; alkylthio ; alkylsulfonyl ; Het^3 ; Het^3-alkyl ; Het^3-oxy ; Het^3-oxyalkyl ; Het^3-alkyloxy ; Het^3-oxyalkyloxy ; Het^3-carbonyl ; Het^3-thioalkyl ; aryl ; arylalkyl ; aryloxy ; aryloxyalkyl ; arylalkyloxy ; arylalkenyl ; arylcarbonylalkyl ; arylsulfonyl ; $-NR^aR^b$; alkyl-NR^aR^b ; O-alkyl-NR^aR^b ; $-C(=O)-NR^aR^b$; $-C(=O)$-alkyl-NR^aR^b ; and O-alkyl-$C(=O)-NR^aR^b$; wherein R^a and R^b are selected from the group of hydrogen, alkyl, alkylcarbonyl, arylalkyl, alkyloxyalkyl, Het^3, Het^3alkyl, alkylsulfonyl, alkyl-NR^cR^d and C(=O)alkyl-NR^cR^d, wherein R^c and R^d are selected from the group of hydrogen, alkyl and alkylcarbonyl ;
or two radicals R^4 may be combined to form a bivalent radical $-X^1-C_{1-6}-X^2-$ wherein C_{1-6} is a saturated or unsaturated, straight or branched hydrocarbon radical having 1 to 6 carbon atoms and X^1 and X^2 are each independently C or O.

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9. Compound according to any one of claims 1 to 8, characterized in that two radicals R^4 may be combined to form a bivalent radical selected from the group of $-CH_2CH_2-O-$; $-O-CH_2-O-$; and $-O-CH_2CH_2-O-$.

10. Compound according to any one of claims 1 to 9, characterized in that Het^1 is selected from the group of tetrahydropyranyl and pyridinyl ; wherein each radical Het^1 is optionally substituted with 1, 2 or 3 polyhaloC_{1-3}alkyl substituents.

11. Compound according to any one of claims 1 to 10, characterized in that Het^3 is selected from the group of pyridinyl ; pyrimidinyl ; pyridazilyl ; pyrazinyl ; piperidinyl ; pyrrolidinyl ; piperazinyl ; triazolyl ; tetrahydropyranyl ; tetrahydro-thiopyran-1,1-dioxide ; thiazolyl ; oxazolyl ; morpholinyl, oxadiazolyl ; imidazolyl ; benzoxazolyl; benzothienyl ; benzofuranyl ; 1,2,3,4-tetrahydro-isoquinolinyl ; indolyl ; indolinyl ; phthalazyl ; and benzo[1,3]dioxyl ; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, C_{1-6}alkyl, polyhaloC_{1-3}alkyl, cyano, hydroxy, oxo, ethanoyl, phenyl, pyrrolidinyl, piperidinyl, pyridinyl, morpholinyl, mono- and di(alkyl)amino, and C_{1-3}alkyloxy.

12. Compound according to claim 1, characterized in that :

V^1 is selected from the group of a covalent bond, $-CH_2-$; $-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-$; $-CH_2-CH=CH-$; $-CH_2-CH_2-CH_2-CH_2-$; $-CH_2-CH(CH_3)CH_2-$; $-CH(CH_3)-CH_2-CH_2-CH_2-$; $-CH_2-CH(CH_3-)CH_2-CH_2-$; and $-CH_2-CH_2-CH(CH_3)-CH_2-$;

M^1 is selected from the group of hydrogen ; cycloC_{3-7}alkyl ; phenyl ; biphenyl ; phenyloxy ; benzyloxy ; furanyl, and pyridinyl ; wherein M^1 is optionally substituted with one or more radicals selected from the group of halo ; C_{1-3}alkyl ; polyhaloC_{1-3}alkyl ; polyhaloC_{1-3}alkyloxy ; and C_{1-3}alkyloxy ;

L is selected from the group of covalent bond ; -O- ; $-OCH_2-$; $-OCH_2CH_2-$; $-OCH_2CH_2O-$; $-OCH_2CH_2OCH_2-$; $-NR^7-$; $-NR^7CH_2-$; $-NR^7$cycloC_{3-7} ; $-OCH_2CH_2N(R^7)CH_2-$; $-CH_2CH_2-$; $-C\equiv C-$; -C=O- and -CH=CH- ; wherein each of R^7, independently of each other, is selected from the group of hydrogen and C_{1-3}alkyl ;

R^2 and R^3 are each independently of each other hydrogen, halo or alkyl ;

A is selected from the group of phenyl, piperazinyl, and piperidinyl, wherein each radical is optionally substituted with n radicals R^4, wherein n is an integer equal to zero or 1 ;

R^4 is selected from the group of halo ; cyano ; hydroxy ; ethanoyl ; alkyl ; alkyloxy ; alkyloxyalkyl ; alkyloxycarbonyl ; alkyloxycarbonylalkyl ; alkylcarbonyl ; alkylcarbonyloxy ; alkylcarbonylalkyloxy ; polyhaloC_{1-3}alkyl ; polyhaloC_{1-3}alkyloxy ; polyhaloC_{1-3}alkylthio ; alkylthio ; alkylsulfonyl ; Het^3 ; Het^3-alkyl ; Het^3-oxy ; Het^3-oxyalkyl ; Het^3-alkyloxy ; Het^3-oxyalkyloxy ; Het^3-carbonyl ; Het^3-thioalkyl ; aryl ; arylalkyl ; aryloxy ; aryloxyalkyl ; arylalkyloxy ; arylalkenyl ; arylcarbonylalkyl ; arylsulfonyl ; -NR^aR^b ; alkyl-NR^aR^b ; O-alkyl-NR^aR^b ; -C(=O)-NR^aR^b ; -C(=O)-alkyl-NR^aR^b ; and O-alkyl-C(=O)-NR^aR^b ; wherein R^a and R^b are selected from the group of hydrogen, alkyl, alkylcarbonyl, arylalkyl, alkyloxyalkyl, Het^3, Het^3alkyl, alkylsulfonyl, alkyl-NR^cR^d and C(=O)alkyl-NR^cR^d, wherein R^c and R^d are selected from the group of hydrogen, alkyl and alkylcarbonyl ; or two radicals R^4 may be combined to form a bivalent radical selected from the group of -CH_2CH_2-O- ; -O-CH_2-O- ; and -O-CH_2CH_2-O- ;

Het^1 is selected from the group of tetrahydropyranyl ; and pyridinyl ; wherein each radical Het^1 is optionally substituted with 1, 2 or 3 polyhaloC_{1-3}alkyl substituents ;

Het^2 is selected from the group of piperazinyl ; piperidinyl ; thienyl ; furanyl ; 1*H*-indazolyl ; 1*H*-benzimidazolyl ; 1,2,3,4-tetrahydro-isoquinolinyl ; 2,5-diaza-bicyclo[2.2.1]heptyl ; pyrrolidinyl ; azetidinyl ; 2,7-diaza-spiro[3.5]nonyl ; pyridinyl ; pyrazolyl ; indolinyl ; 1*H*-indolyl ; 1*H*-indazolyl ; benzomorpholinyl ; thiazolyl ; 1,2,3,4-tetrahydroquinolinyl ; 3,9-diazaspiro[5.5]undecyl ; 1,2,3,4,4a,5,6,10b-octahydro-benzo-[f]quinolinyl ; 1,2,3,4,4a,10a-hexahydro-benzo[5,6][1,4] dioxino[2,3-c]-pyridinyl ; 2,3,4,9-tetrahydro-1*H*-indeno[2,1-c]pyridinyl ; 2,3,4,9--tetrahydro-1*H*-β-carbolinyl;

1,2,3,4-tetrahydro-benzo[4,5]furo[2,3-c]pyridinyl ; 1,2,3,4-tetrahydro-benzo[4,5]thieno[2,3-c]pyridinyl ; [1,4]diazepyl ; isoxazolyl ; indanyl ; and indolyl ;

Het^3 is selected from the group of pyridinyl ; pyrimidinyl ; pyridazilyl ; pyrazinyl ; piperidinyl ; pyrrolidinyl ; piperazinyl ; triazolyl ; tetrahydropyranyl ; tetrahydro-thiopyran-1,1-dioxide ; thiazolyl ; oxazolyl ; morpholinyl ; oxadiazolyl ; imidazolyl ; benzoxazolyl; benzothienyl ; benzofuranyl ; 1,2,3,4-tetrahydro-isoquinolinyl ; indolyl ; indolinyl ; phthalazyl ; and benzo[1,3]dioxyl ; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, C_{1-6}alkyl, polyhaloC_{1-3}alkyl, cyano, hydroxy, oxo, ethanoyl, phenyl, pyrrolidinyl, piperidinyl, pyridinyl, morpholinyl, mono- and di(alkyl)amino, and C_{1-3}alkyloxy ;

aryl is phenyl or biphenyl ; wherein each radical is optionally substituted with 1, 2 or 3 substituents, each independently from each other selected from the group of halo, C_{1-3}alkyl, polyhaloC_{1-3}alkyl, polyhaloC_{1-3}-alkyloxy, cyano, nitro, ethyloxycarbonyl, and C_{1-3}alkyloxy ; and

alkyl is a saturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms ; or is a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms ; or is saturated hydrocarbon radical from 4 to 12 carbonatoms, comprising at least one saturated, straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and at least one saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms ; wherein each carbon atom may optionally be substituted with one or more radicals selected from the group of cyano, hydroxy, carboxyl, carbamoyl, phenyl, and a bivalent radical $-OCH_2CH_2O-$.

13. A compound according to any one of claims 1 to 12 wherein said compound is selected from the group of :

- 4-(4-(*N*-acetylmethyl)phenyl)-3-cyano-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-179);

- 4-(3,4-dimethoxyphenyl)-3-cyano-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-110);
- 3-cyano-4-(3-fluoro-4-methoxyphenyl)-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-114);
- 3-cyano-4-(4-hydroxypropylphenyl)-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-095);
- 3-cyano-4-(4-methoxymethylphenyl)-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-103);
- 3-cyano-4-(2-fluoro-4-methoxyphenyl)-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-113);
- 3-cyano-4-(4-(*N*-morpholyl)phenyl)-1-(3-methylbutyl)pyridine-2(1*H*)-one (compound 1-223);
- 3-cyano-1-(3-methylbutyl)-4-(phenylethynyl)pyridine-2(1*H*)-one (compound 1-267);
- 3-cyano-1-butyl-4-[4-(2-methyl-pyridin-4-yloxy)-phenyl]-pyridine-2(1*H*)-one (compound 1-064); and
- 3-cyano-1-cyclopropylmethyl-4-(4-phenyl-piperidin-1-yl)-pyridine-2(1*H*)-one (compound 4-047).

14. A compound according to any one of claims 1 to 13 which exist as optical isomers, wherein said compound is either the racemic mixture or the individual optical isomer.

15. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 14 and a pharmaceutically acceptable carrier and/or excipient.

16. A compound according to any one of claims 1 to 14 for use as a medicament.

17. Use of a compound according to any one of claims 1 to 14 or a pharmaceutical composition according to claim 15 for the manufacture of a medicament for treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 positive allosteric modulators.

18. Use of a compound according to any one of claims 1 to 14 or a pharmaceutical composition according to claim 15 for the manufacture of a medicament for treating, or preventing, ameliorating, controlling or reducing the risk of various neurological and psychiatric disorders associated with glutamate dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 positive allosteric modulators.

19. Use according to any one of claims 17 and 18, wherein the condition or disorder is a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.

20. Use according to claim 19, wherein the central nervous system disorder is an anxiety disorder, selected from the group of agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), social phobia and other phobias.

21. Use according to claim 19, wherein the central nervous system disorder is a psychotic disorder selected from the group of schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform disorder and substance-induced psychotic disorder.

22. Use according to claim 19, wherein the central nervous system disorder is a personality disorder selected from the group of obsessive-compulsive personality disorder and schizoid, schizotypal disorder.

23. Use according to claim 19, wherein the central nervous system disorder is a substance-related disorder selected from the group of alcohol abuse, alcohol dependence, alcohol withdrawal, alcohol withdrawal delirium, alcohol-induced psychotic disorder, amphetamine dependence, amphetamine withdrawal, cocaine dependence, cocaine withdrawal, nicotine dependence, nicotine withdrawal, opioid dependence and opioid withdrawal.

24. Use according to claim 19, wherein the central nervous system disorder is an eating disorder selected from the group of anorexia nervosa and bulimia nervosa.

25. Use according to claim 19, wherein the central nervous system disorder is a mood disorder selected from the group of bipolar disorders (I & II), cyclothymic disorder, depression, dysthymic disorder, major depressive disorder and substance-induced mood disorder.

26. Use according to claim 19, wherein the central nervous system disorder is migraine.

27. Use according to claim 19, wherein the central nervous system disorder is epilepsy or a convulsive disorder selected from the group of generalized nonconvulsive epilepsy, generalized convulsive epilepsy, petit mal status epilepticus, grand mal status epilepticus, partial epilepsy with or without impairment of consciousness, infantile spasms, epilepsy partialis continua, and other forms of epilepsy.

28. Use according to claim 19, wherein the childhood disorder is attention-deficit/hyperactivity disorder.

29. Use according to claim 19, wherein the central nervous system disorder is a cognitive disorder selected from the group of delirium, substance-induced persisting delirium, dementia, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, dementia of the Alzheimer's type, substance-induced persisting dementia and mild cognitive impairment.

30. Use according to claim 19, wherein the central nervous system disorder is selected from the group of anxiety, schizophrenia, migraine, depression, and epilepsy.

31. Use according to any one of claims 17 to 30, wherein the mGluR2 positive allosteric modulator has an EC_{50} of about 1 μM or less.

32. Use of a compound according to claims 1 to 14 for the preparation of a tracer for imaging an mGluR2 receptor.

33. Use of a compound according to any one of claims 1 to 14 in combination with an orthosteric agonist of mGluR2 for the manufacture of a medicament for treating or preventing a condition as cited in any one of claims 17 to 30, in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 allosteric modulators.