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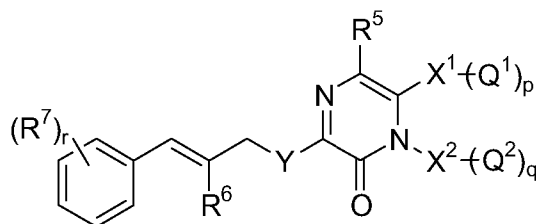
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(54) Title: SUBSTITUTED PYRAZINONE DERIVATIVES FOR USE AS A MEDICINE



(I)

(57) Abstract: The present invention concerns substituted pyrazinone derivatives 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, wherein the variables are defined in Claim 1, having selective α_{2C} -adrenoceptor antagonist activity. It further relates to their preparation, compositions comprising them

and their use as a medicine. The compounds according to the invention are useful for the prevention and/or treatment of central nervous system disorders, mood disorders, anxiety disorders, stress-related disorders associated with depression and/or anxiety, cognitive disorders, personality disorders, schizoaffective disorders, Parkinson's disease, dementia of the Alzheimer's type, chronic pain conditions, neurodegenerative diseases, addiction disorders, mood disorders and sexual dysfunction.



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SUBSTITUTED PYRAZINONE DERIVATIVES FOR USE AS A MEDICINE

Field of the Invention

The present invention concerns substituted pyrazinone derivatives having selective α_{2C} -adrenoceptor antagonist activity. Some compounds also show moderate 5-HTT activity. It further relates to their preparation, pharmaceutical compositions comprising them and their use as a medicine, especially for the treatment of central nervous system disorders.

10 Background of the Invention

Adrenergic receptors form the interface between the endogenous catecholamines epinephrine and norepinephrine and a wide array of target cells in the body to mediate the biological effects of the sympathetic nervous system. They are divided into three major subcategories, α_1 , α_2 and β . To date, nine distinct adrenergic receptor subtypes have been cloned from several species: α_{1A} , α_{1B} , α_{1D} , α_{2A} , α_{2B} , α_{2C} , β_1 , β_2 and β_3 (Hieble, J. P.; et al. *J. Med. Chem.* **1995**, 38, 3415-3444). Available α_2 ligands have only marginal subtype selectivity. A complicating factor is that α_2 -adrenoceptor ligands, which are imidazoles or imidazolines, also bind with moderate-to-high affinity to non-adrenoceptor imidazoline binding sites.

20 The three α_2 -adrenoceptor subtypes share many common properties. They are G-protein-coupled receptors with seven transmembrane domains of the aminebinding subfamily. All three subtypes are coupled to the Gi/o signalling system, inhibiting the activity of adenylate cyclase, the opening of voltage-gated Ca^{2+} channels and the opening of K^+ channels. The three receptors are encoded by distinct genes (Bylund, D. B.; et al. *Pharmacol. Rev.* **1994**, 46, 121-136 and Hieble, J. P. et al. *Pharmacol. Commun.* **1995**, 6, 91-97), localized to different chromosomes; in humans the gene for α_{2A} is found on chromosome 10, the α_{2B} -gene on chromosome 2 and the α_{2C} -gene on chromosome 4. The subtypes are well conserved across mammalian species. In rats and mice, however, there is a single amino acid substitution which decreases the affinity of the rodent α_{2A} -adrenoceptor for the classical α_2 -antagonists, yohimbine and rauwolscine. The general consensus is that this so-called α_{2D} -adrenoceptor subtype represents the rodent homologue of the human α_{2A} -subtype.

The α_2 -adrenoceptor subtypes are differentially distributed in cells and tissues, clearly endowing the receptors with different physiological functions and pharmacological activity profiles. Different regulatory regions in the receptor genes and different protein structures also confer different regulatory properties on the three receptors, both
5 with regard to receptor synthesis and post-translational events.

α_2 -Adrenergic receptors were initially characterized as presynaptic receptors that serve as parts of a negative feedback loop to regulate the release of norepinephrine. Soon it was shown that α_2 -adrenoceptors are not restricted to presynaptic locations but also have postsynaptic functions. The α_{2A} -adrenoceptor is the major inhibitory pre-
10 synaptic receptor (autoreceptor) regulating release of norepinephrine from sympathetic neurons as part of a feedback loop. The α_{2C} -adrenoceptor turned out to function as an additional presynaptic regulator in all central and peripheral nervous tissues investigated. However, the relative contributions of α_{2A} and α_{2C} -receptors differed between central and peripheral nerves, with the α_{2C} -subtype being more prominent in sym-
15 pathetic nerve endings than in central adrenergic neurons (Philipp, M. et al. *Am. J. Physiol. Regul. Integr. Comput. Physiol.* **2002**, 283, R287-R295 and Kable, J. W. et al. *J. Pharmacol. Exp. Ther.* **2000**, 293, 1-7). The α_{2C} -adrenoceptor is particularly suited to control neurotransmitter release at low action potential frequencies. In contrast, the α_{2A} -adrenoceptor seems to operate primarily at high stimulation frequencies in sympathetic
20 nerves and may thus be responsible for controlling norepinephrine release during maximal sympathetic activation (Bucheler, M. M. et al. *Neuroscience* **2002**, 109, 819-826). α_{2B} -Adrenoceptors are located on postsynaptic cells to mediate the effects of catecholamines released from sympathetic nerves, e.g., vasoconstriction. α_2 -Adrenergic receptors not only inhibit release of their own neurotransmitters but can
25 also regulate the exocytosis of a number of other neurotransmitters in the central and peripheral nervous system. In the brain, α_{2A} - and α_{2C} -adrenoceptors can inhibit dopamine release in basal ganglia as well as serotonin secretion in mouse hippocampal or brain cortex slices. In contrast, the inhibitory effect of α_2 -adrenoceptor agonists on gastrointestinal motility was mediated solely by the α_{2A} -subtype. Part of the functional dif-
30 ferences between α_{2A} - and α_{2C} -receptors may be explained by their distinct subcellular localization patterns. When expressed in rat fibroblasts, α_{2A} - and α_{2B} -adrenoceptors are targeted to the plasma membrane. On stimulation with agonist, only α_{2B} -adrenoceptors are reversibly internalized into endosomes. α_{2C} -Adrenoceptors are primarily localized in an intracellular membrane compartment, from where they can be translocated to the

cell surface after exposure to cold temperature (see a.o. Docherty J.R. et. al. *Eur. J. Pharmacol.* **1998**, 361, 1-15).

The establishment of genetically engineered mice lacking or overexpressing α_2 -adrenoceptor subtypes has yielded important information for understanding the subtype specific functions (MacDonald, E. et al. *Trends Pharmacol. Sci.* **1997**, 18, 211-219). The examination of the phenotype of these strains of mice demonstrated that the α_{2A} -subtype is responsible for inhibition of neurotransmitter release from central and peripheral sympathetic nerves and for most of the centrally mediated effects of α_2 -agonists. The α_{2B} subtype is primarily responsible for the initial peripheral hypertensive responses evoked by the α_2 -agonists and takes part in the hypertension induced by salt (Link et al. *Science* **1996**, 273, 803-805 and Makaritsis, K. P. et al. *Hypertension* **1999**, 33, 14-17).

Clarification of the physiological role of the α_{2C} subtype proved more difficult. Despite a rather wide distribution in the CNS, its role did not appear critical in the mediation of the cardiovascular effects of nonselective α_2 -agonists. Its participation has been suggested in the hypothermia induced by dexmedetomidine and in the hyperlocomotion induced by D-amphetamine (Rohrer, D. K. et al. *Annu. Rev. Pharmacol Toxicol.* **1998**, 38, 351-373). Another potentially important response mediated by the α_{2C} -adrenoceptor is constriction of cutaneous arteries, leading to a reduction in cutaneous blood flow (Chotani, M. A. et al. *Am. J. Physiol. Heart Circ. Physiol.* **2004**, 286, 59-67). Recent studies carried out on double knockout mice have suggested that α_{2C} -adrenoceptor is also expressed at the presynaptic level where, together with α_{2A} , it actively participates in the control of neurotransmitter release. While α_{2A} -adrenoceptor is particularly efficient at high stimulation frequencies, α_{2C} -adrenoceptor acts rather at low stimulation frequencies. Moreover, it has been suggested that α_{2C} subtype participates in the modulation of motor behavior and the memory processes (Bjorklund, M. et al. *Neuroscience* **1999**, 88, 1187-1198 and Tanila, H. et al. *Eur. J. Neurosci.* **1999**, 11, 599-603). Other central effects triggered by this subtype include also the startle reflex and aggression response to stress and locomotion (Sallinen, J. et al. *J. Neurosci.* **1998**, 18, 3035-3042 and Sallinen, J. et al. *Neuroscience* **1998**, 86, 959-965). Last, it was recently pointed out that the α_{2C} -adrenoceptor might contribute to α_2 -agonist-mediated spinal analgesia and adrenergic-opioid synergy (Fairbanks, C. A. et al. *J. Pharm.Exp. Ther.* **2002**, 300, 282-290).

Because of their widespread distribution in the central nervous system, α_2 -receptors affect a number of behavioral functions. The effect of altered α_{2C} -adrenergic receptor expression has been evaluated in several different behavioral paradigms (Kable J.W. et al., *Journal of Pharmacology and Experimental Therapeutics*, **2000**, 293 (1): 1-7), proving that α_{2C} -adrenergic antagonists may have therapeutic value in the treatment of stress-related psychiatric disorders. In each of the behavioral paradigms, it is unclear whether the α_{2C} -subtype plays some direct role in mediating behavior or whether altered α_{2C} -receptor expression produces effects because of altered metabolism or downstream modulation of other neurotransmitter systems. Interestingly, α_{2C} -receptor-deficient mice had enhanced startle responses, diminished prepulse inhibition, and shortened attack latency in the isolation aggression test. Thus drugs acting via the α_{2C} -adrenoceptor may have therapeutic value in disorders associated with enhanced startle responses and sensorimotor gating deficits, such as schizophrenia, attention deficit disorder, posttraumatic stress disorder, and drug withdrawal. In addition to the α_{2C} -subtype, the α_{2A} -adrenoceptor has an important .

With more and more studies of the α_2 -adrenoceptor physiology in gene-targeted mice being published, the situation becomes more complicated than initially anticipated. Indeed, only a few biological functions of α_2 -receptors were found to be mediated by one single α_2 -adrenergic receptor subtype. For other α_2 -receptor-mediated functions, two different strategies seem to have emerged to regulate adrenergic signal transduction: some biological functions are controlled by two counteracting α_2 -receptor subtypes, and some require two receptor subtypes with similar but complementary effects. Because the α_{2A} -subtype mediates most of the classical effects of α_2 -adrenergic agonists, it is doubtful that an α_{2A} -selective agonist would have a substantially better clinical profile than the currently available agents. Drugs acting at α_{2B} - or α_{2C} -adrenergic receptors are likely to have fewer of the classical α_2 -adrenergic side effects than α_{2A} -specific agents. It would appear likely that α_{2C} -selective agents may be useful in at least some nervous system disorders, in particular central nervous system disorders.

Background prior art

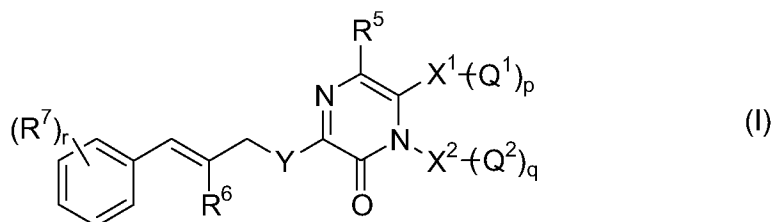
Analysis of the pipeline databases to date indicate that there are several adrenergic α_2 -antagonists in the market, by companies including Akzo Nobel (Organon), Novartis, Pfizer, and Schering AG. None of those compounds are selective for any of the three α_2 -adrenoceptors. These compounds are indicated mainly for depression, hypertensive disorders and dyskinesias associated with Parkinson's disease. Companies with α_2 -adrenoceptor antagonists in clinical development include Britannia Pharmaceuticals, IVAX, Juvantia Pharmaceuticals, MAP Pharmaceuticals, Novartis, Novo Nordisk, Organon, Pierre Fabre, and Sanofi-Aventis.

Regarding the development of selective α_{2C} -adrenoceptor antagonists to date, OPC-28326 is the only compound in clinical development (in Phase 2 by Otsuka Pharmaceuticals for hypertensive disorders and peripheral vascular disease). The rest of the α_{2C} antagonists are in preclinical development by Oy Juvantia Pharma Ltd (JP 1514 and JP 1302, published in WO 01/64645 and WO 04/067513) and by Novartis AG (NVP-ABE651 and NVP-ABE697, published in WO 01/55132 and *J. Label Compd. Radiopharm* **2002**, 45, 1180), indicated mainly for depression and schizophrenia. In addition, several compounds are listed at the very early stages of development (biological testing) by Juvantia and Kyowa Hakko, for depression and Parkinson's disease.

Description of the Invention

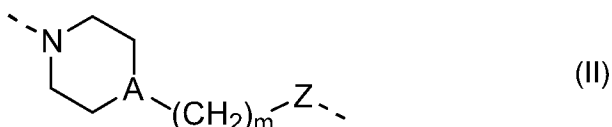
It is the object of the present invention to provide a compound with a binding affinity towards α_2 -adrenoceptor receptors, in particular towards α_{2C} -adrenoceptor receptors, in particular as an antagonist.

This goal was achieved by a compound according to the general Formula (I)



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

Y is a bivalent radical of Formula (II)



wherein

A is a nitrogen or a carbon-atom ;

m is an integer equal to zero, 1 or 2 ; and

Z is a covalent bond or N-R⁴ ; wherein R⁴ is selected from the group of hydrogen ; (C₁₋₃)alkyl and phenylcarboxyl(C₁₋₃)alkyl ;

R⁵ is selected from the group of hydrogen and halo ;

R⁶ is selected from the group of hydrogen and (C₁₋₃)alkyl ;

R⁷ is selected from the group of hydrogen, (C₁₋₃)alkyl; (C₁₋₃)alkyloxy ; halo; cyano ; nitro ; formyl ; ethanoyl ; hydroxy ; amino ; trifluoromethyl ; mono- and di((C₁₋₃)alkyl)amino ; mono- and di((C₁₋₃)alkylcarbonyl)amino ; carboxyl; morpholinyl ; and thio ; and r is an integer equal to zero, 1, 2, 3, 4, or 5.;

X¹, X² are each, independently from each other, a bond, a saturated or an unsaturated bivalent (C₁₋₈)-hydrocarbon radical, wherein one or more bivalent -CH₂-units may optionally be replaced by a respective bivalent phenyl-unit ; and wherein one or more hydrogen atoms may be replaced by a radical selected from the group of oxo ; (C₁₋₃)alkyloxy ; halo ; cyano ; nitro ; formyl ; hydroxy ; amino ; trifluoromethyl ; mono- and di((C₁₋₃)alkyl)amino ; carboxyl ; and thio ;

Q¹, Q² are each, independently from each other, a radical selected from the group of hydrogen ; -NR¹R² ; Pir ; -OR^{3a} ; SR^{3b} ; SO₂R^{3c} ; aryl ; and Het; wherein two radicals -OR^{3a} may be taken together to form a bivalent radical -O-(CH₂)_r-O- wherein r is an integer equal to 1, 2 or 3 ;

p, q are each, independently from each other, an integer equal to 1 or 2;

R¹ and R² are each, independently from each other, a radical selected from the group of hydrogen ; alkyl ; alkenyl ; alkynyl ; aryl ; arylalkyl ; diarylalkyl ; alkylcarbonyl ; alkylcarbonylalkyl ; alkenylcarbonyl ; alkyloxy ; alkyloxyalkyl ; alkyloxycarbonyl ; alkyloxyalkylcarbonyl ; alkyloxycarbonylalkyl ; alkyloxycarbonylalkylcarbonyl; alkylsulfonyl ; arylsulfonyl ; arylalkylsulfonyl ; arylalkenylsulfonyl ; Het-sulfonyl ; arylcarbonyl ; aryloxyalkyl ; arylalkylcarbonyl ; Het ; Het-alkyl ; Het-alkylcarbonyl ; Het-carbonyl ; Het-carbonylalkyl ; alkyl-NR^aR^b; carbonyl-NR^aR^b ; carbonylalkyl-NR^aR^b ; alkylcarbonyl-NR^aR^b ; and alkylcarbonylalkyl-NR^aR^b ; wherein R^a and R^b are each independently selected

- from the group of hydrogen, alkyl, alkylcarbonyl, alkyloxyalkyl, alkyloxycarbonylalkyl, aryl, arylalkyl, Het and alkyl-NR^cR^d, wherein R^c and R^d are each independently from each other hydrogen or alkyl ;
- 5 Pir is a radical containing at least one N, by which it is attached to the X-radical, selected from the group of pyrrolidinyl ; imidazolidinyl ; pyrazolidinyl ; piperidinyl ; piperazinyl ; pyrrolyl ; pyrrolinyl ; imidazolyl ; pyrrazolinyl ; pyrrolyl ; imidazolyl ; pyrazolyl ; triazolyl ; azepyl ; diazepyl ; morpholinyl ; thiomorpholinyl ; indolyl ; isoindolyl ; indolinyl ; indazolyl ; benzimidazolyl ; and 1,2,3,4-tetrahydro-isoquinolinyl ; wherein each Pir-radical is optionally substituted by 1, 2 or 3 radicals selected from the group of hydroxy ; halo ;
- 10 oxo ; (C₁₋₃)alkyl ; (C₁₋₃)alkenyl (C₁₋₃)alkyloxycarbonyl ; Het-carbonyl ; (C₁₋₃)alkylamino ; trifluoromethyl ; (C₀₋₃)alkylphenyl ; pyrimidinyl ; pyrrolidinyl ; and pyridinyloxy ;
- 15 R^{3a}, R^{3b}, R^{3c} are each, independently from each other, a radical selected from the group of hydrogen ; alkyl ; trihaloalkyl ; aryl ; arylalkyl ; alkyloxyalkyl ; Het ; and Het-alkyl ;
- Het is a heterocyclic radical selected from the group of pyrrolidinyl ; imidazolidinyl ; pyrazolidinyl ; piperidinyl ; piperazinyl ; pyrrolyl ; pyrrolinyl ; imidazolyl ; pyrrazolinyl ; pyrrolyl ; imidazolyl ; pyrazolyl ; triazolyl ; pyridinyl ;
- 20 pyridazinyl ; pyrimidinyl ; pyrazinyl ; triazinyl ; azepyl ; diazepyl ; morpholinyl ; thiomorpholinyl ; indolyl ; isoindolyl ; indolinyl ; indazolyl ; benzimidazolyl ; 1,2,3,4-tetrahydro-isoquinolinyl ; furyl ; thienyl ; oxazolyl ; isoxazolyl ; thiazolyl ; thiadiazolyl ; isothiazolyl ; dioxolyl ; dithianyl ; tetrahydrofuryl ; tetrahydropyranyl ; quinolinyl ; isoquinolinyl ; quinoxalinyl ; benzoxazolyl ; benzisoxazolyl ; benzothiazolyl ; benzisothiazolyl ; benzofuranyl ; benzothienyl ; benzopiperidinyl ; benzomorpholinyl ; chromenyl ; and imidazo[1,2-*a*]pyridinyl ; wherein each Het-radical is optionally substituted by one or more radicals selected from the group of halo ; oxo ; (C₁₋₃)alkyl ; (C₁₋₃)alkylcarbonyl ; (C₁₋₃)alkenylthio ; imidazolyl-(C₁₋₃)alkyl ; aryl(C₁₋₃)alkyl and (C₁₋₃)alkyloxycarbonyl ;
- 30 aryl is naphthyl or phenyl, each optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of oxo ; (C₁₋₃)alkyl ; (C₁₋₃)alkyloxy ; halo ; cyano ; nitro ; formyl ; ethanoyl ; hydroxy ; amino ; trifluoromethyl ; mono- and di((C₁₋₃)alkyl)amino ; mono- and di((C₁₋₃)alkylcarbonyl)amino ; carboxyl ; morpholinyl ; and thio ;
- 35

- alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 8 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 8 carbon atoms ; wherein each radical is optionally substituted on one or more carbon atoms with one or more radicals selected from the group of oxo ; (C₁₋₃)alkyloxy, halo ; cyano ; nitro ; formyl ; hydroxy ; amino ; carboxyl ; and thio ;
- alkenyl is an alkyl radical as defined above, further having one or more double bonds ;
- alkynyl is an alkyl radical as defined above, further having one or more triple bonds; and
- arylalkyl is an alkyl radical as defined above, further having one or more CH₃-groups replaced by phenyl.

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, 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 for the preparation of a medicament for the prevention and/or treatment of a disorder or disease responsive to antagonism of the α_2 -adrenergic receptor, in particular to antagonism of the α_{2C} -adrenergic receptor.

In particular, the invention relates to the use of a compound according to the invention for the preparation of a medicament for the prevention and/or treatment of central nervous system disorders, mood disorders, anxiety disorders, stress-related disorders associated with depression and/or anxiety, cognitive disorders, personality disorders, schizoaffective disorders, Parkinson's disease, dementia of the Alzheimer's type, chronic pain conditions, neurodegenerative diseases, addiction disorders, mood disorders and sexual dysfunction.

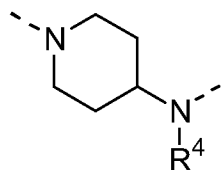
A compound according to the invention may also be suitable as add-on treatment and/or prophylaxis in the above listed diseases in combination with antidepressants, anxiolytics and/or antipsychotics which are currently available or in development or which will become available in the future, to improve efficacy and/or onset of action.

This is evaluated in rodent models in which antidepressants, anxiolytics and/or antipsychotics are shown to be active. For example, compounds are evaluated in combination with antidepressants, anxiolytics and/or antipsychotics for attenuation of stress-induced hyperthermia.

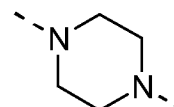
- 5 The invention therefore also relates to the use of a compound according to the invention for use as an add-on treatment with one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics, to a pharmaceutical composition comprising a compound according to the invention and one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics,
10 as well as to a process for the preparation of such pharmaceutical compositions and to the use of such a composition for the manufacture of a medicament, in particular to improve efficacy and/or onset of action in the treatment of depression and/or anxiety.

Detailed description of the invention

- 15 In a preferred embodiment, the invention relates to a compound according to the invention, wherein Y is a bivalent radical of formula (II-a) or (II-b).



(II-a)



(II-b)

In a preferred embodiment, the invention relates to a compound according to the invention, wherein R⁴ is hydrogen ; methyl ; ethyl ; *n*-propyl ; isopropyl ; and cyclopropyl. More preferably, R⁴ is hydrogen or methyl. Most preferably, R⁴ is hydrogen.

- 20 In a preferred embodiment, the invention relates to a compound according to the invention, wherein R⁵ is hydrogen or chloro. More preferred, R⁵ is hydrogen.

In a preferred embodiment, the invention relates to a compound according to the invention, wherein R⁶ is hydrogen ; methyl ; ethyl ; *n*-propyl ; isopropyl ; and cyclopropyl. More preferably, R⁶ is hydrogen or methyl. Most preferably, R⁶ is methyl.

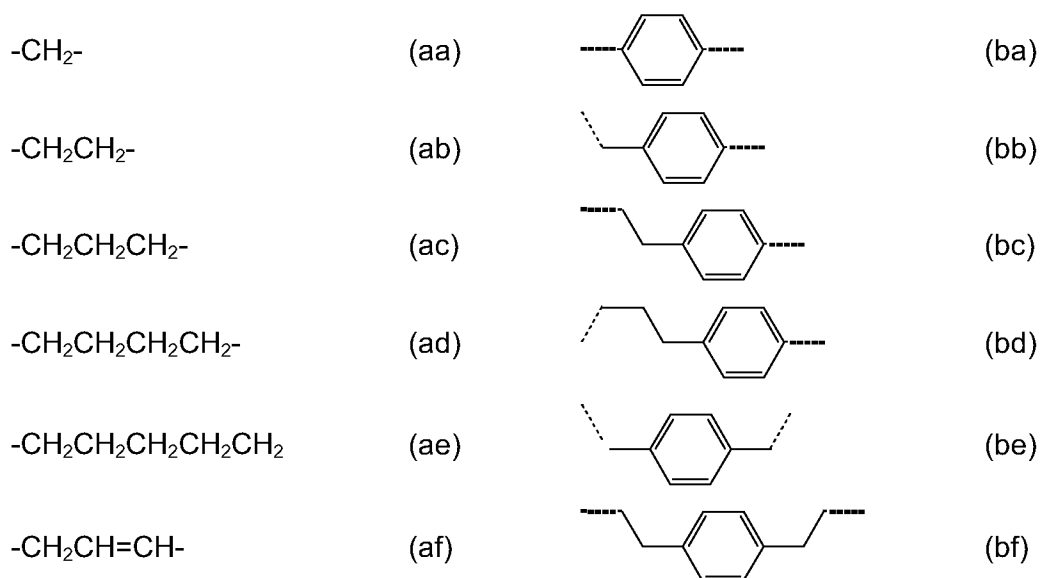
- 25 In a preferred embodiment, the invention relates to a compound according to the invention, wherein R⁷ is hydrogen.

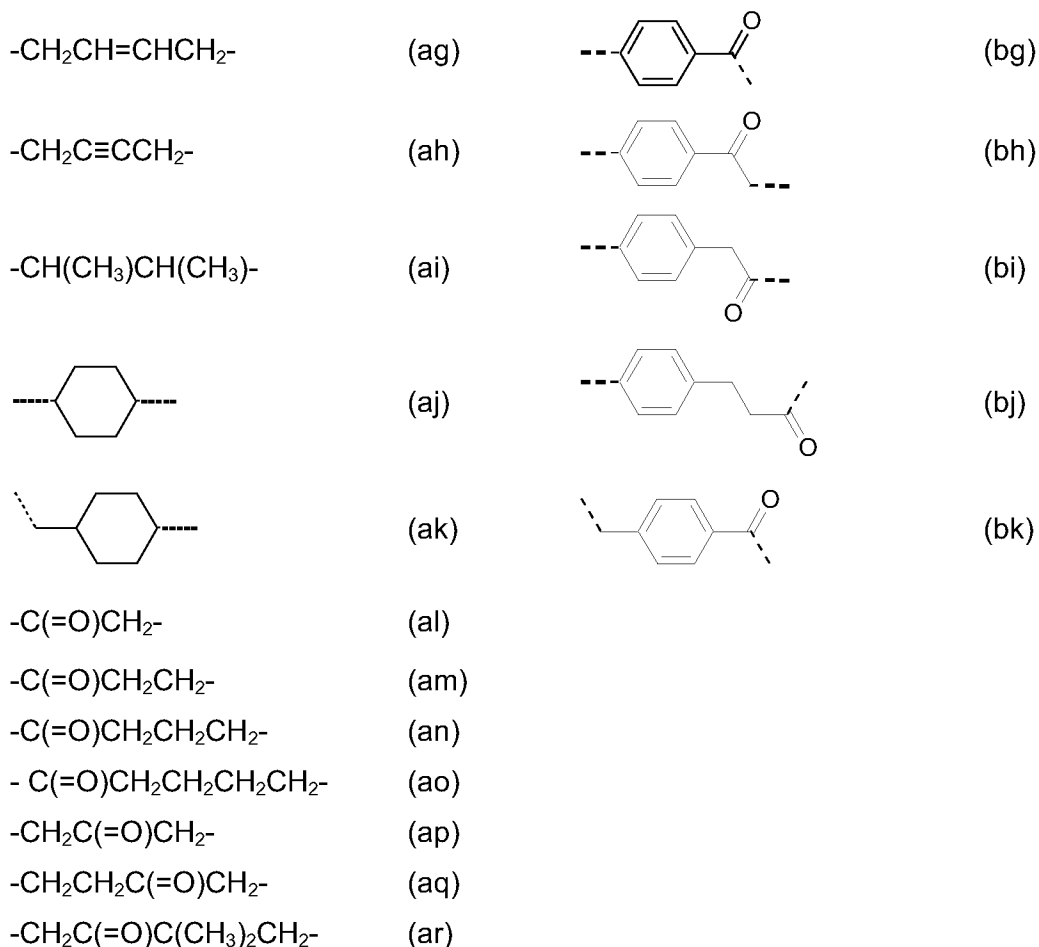
In a preferred embodiment, the invention relates to a compound according to the invention, wherein each of X^1 and X^2 , independently from each other, are a bond or a (C₁₋₈)-hydrocarbon radical, more preferably a (C₁₋₆)-hydrocarbon radical, even more preferably a (C₁₋₅)-hydrocarbon radical, most preferably a (C₁₋₄)-hydrocarbon radical. In one preferred embodiment, one bivalent -CH₂-unit in said hydrocarbon radical is replaced by a bivalent phenyl-unit. In another preferred embodiment, two hydrogen atoms in said hydrocarbon radical are replaced by an oxo-radical. In still another preferred embodiment, both one bivalent -CH₂-unit in said hydrocarbon radical is replaced by a bivalent phenyl-unit and two hydrogen atoms in said hydrocarbon radical are replaced by an oxo-radical.

In a further preferred embodiment, the invention relates to a compound according to the invention, wherein X^1 is a bond and Q¹ is hydrogen and X^2 is a bond or a (C₁₋₈)-hydrocarbon radical, more preferably a (C₁₋₆)-hydrocarbon radical, even more preferably a (C₁₋₅)-hydrocarbon radical, most preferably a (C₁₋₄)-hydrocarbon radical.

In one preferred embodiment of X^2 , one bivalent -CH₂-unit of the hydrocarbon radical X^2 is replaced by a bivalent phenyl-unit. In another preferred embodiment of X^2 , two hydrogen atoms of the hydrocarbon radical X^2 are replaced by an oxo-radical.

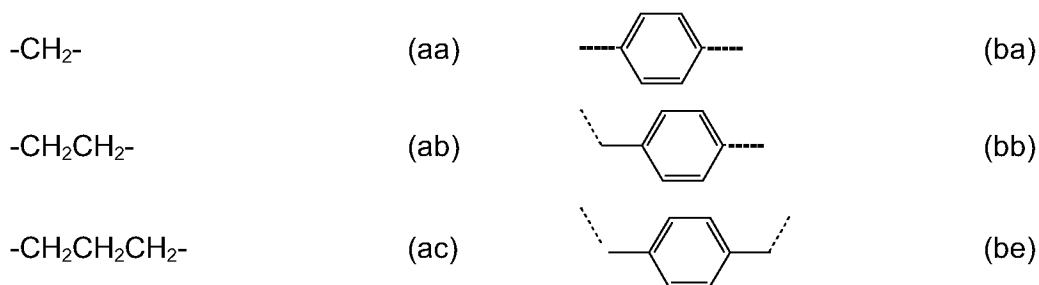
In a further preferred embodiment, the invention relates to a compound according to the invention, wherein each of X^1 and X^2 , and preferably X^2 , independently from each other, are selected from the group of a bond and any one of the radicals defined below :

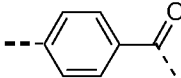
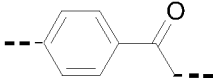
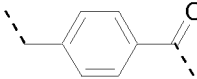




It is within the ambit of the invention that each of the radicals can be used as a linker in which either the left side (left bond) of the linker or the right side (right bond) of the linker is connected to the central pyrazinone-moiety. This is particularly relevant for non-symmetrical linkers that can thus be used in two configurations.

- 5 In a further preferred embodiment, the invention relates to a compound according to the invention, wherein each of X^1 and X^2 , and preferably X^2 , independently from each other, are selected from the group of a bond and any one of the radicals as defined below:



$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$	(ad)		(bg)
$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$	(ae)		(bh)
$-\text{CH}_2\text{CH}=\text{CH}-$	(af)		(bk)
$-\text{CH}_2\text{CH}=\text{CHCH}_2-$	(ag)		
$-\text{CH}_2\text{C}\equiv\text{CCH}_2-$	(ah)		
	(aj)		
$-\text{C}(=\text{O})\text{CH}_2-$	(al)		
$-\text{C}(=\text{O})\text{CH}_2\text{CH}_2-$	(am)		
$-\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$	(ao)		
$-\text{CH}_2\text{C}(=\text{O})\text{CH}_2-$	(ap)		
$-\text{CH}_2\text{C}(=\text{O})\text{C}(\text{CH}_3)_2\text{CH}_2-$	(ar)		

In every embodiment of this invention, when each of X^1 and X^2 , and preferably X^2 , is or contains a phenyl-unit, the attachments to the phenyl-unit can be in ortho, meta or para-position ; preferably the attachments to the phenyl-unit are in meta or para-position, most preferably in para-position.

In a preferred embodiment, the invention relates to a compound according to the invention, wherein

X^1 is a bond, $p=1$ and Q^1 is hydrogen ; and

$q=1$ and Q^2 is selected from the group of hydrogen ; $-\text{NR}^1\text{R}^2$; Pir ; $-\text{OR}^{3a}$; SR^{3b} ; SO_2R^{3c} ; aryl ; and Het.

In a preferred embodiment, the invention relates to a compound wherein Q^1 and Q^2 , and preferably Q^2 is $-\text{NR}^1\text{R}^2$, and wherein R^1 and R^2 are each, independently from each other, a radical selected from the group of hydrogen ; alkyl ; alkynyl ; aryl ; arylalkyl ; diarylalkyl ; alkylcarbonyl ; alkylcarbonylalkyl ; alkyloxycarbonyl ; alkyloxyalkylcarbonyl ; alkyloxycarbonylalkyl ; alkyloxycarbonylalkylcarbonyl ; alkylsulfonyl ; arylsulfonyl ; arylalkylsulfonyl ; arylalkenylsulfonyl ; Het-sulfonyl ; arylcarbonyl ; arylalkylcarbonyl ; Het ; Het-alkyl ; Het-carbonyl ; alkyl- NR^aR^b ; and carbonyl- NR^aR^b ; wherein R^a and R^b are each independently selected from the group of hydrogen, alkyl, alkylcarbonyl, aryl, and arylalkyl.

Preferably, when R¹ or R² comprises an alkyl moiety, the alkyl moiety is methyl ; ethyl ; propyl, including *n*-propyl and isopropyl ; butyl, including *n*-butyl and *t*-butyl ; cyclopropyl ; cyclohexyl ; or a bivalent moiety derived therefrom in the sense that one hydrogen is replaced by a bond to form a bivalent radical, such as for instance is the case in the moiety phenylalkyl.

In a further preferred embodiment, the invention relates to a compound according to the invention, wherein Pir is a radical containing at least one N, by which it is attached to the radical X¹ or X², selected from the group of pyrrolidinyl ; piperidinyl ; piperazinyl ; pyrrolyl ; morpholinyl ; and isoindolyl ; wherein each Pir-radical is optionally substituted by 1, 2 or 3 radicals selected from the group of hydroxy ; (C₁₋₃)alkyl ; (C₁₋₃)alkenyl ; (C₁₋₃)alkyloxycarbonyl ; Het-carbonyl ; (C₁₋₃)alkylamino ; trifluoromethyl ; (C₀₋₃)alkylphenyl ; and pyrrolidinyl.

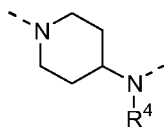
In a further preferred embodiment, the invention relates to a compound according to the invention, wherein R^{3a}, R^{3b}, R^{3c} are each, independently from each other, a radical selected from the group of hydrogen ; alkyl ; trihaloalkyl ; aryl ; arylalkyl ; and alkyloxyalkyl.

In a further embodiment, the invention relates to a compound according to the invention, wherein Het is a heterocyclic radical selected from the group of is a heterocyclic radical selected from the group of pyrrolidinyl ; piperidinyl ; imidazolyl ; pyridinyl ; morpholinyl ; furyl ; thienyl ; isoxazolyl ; thiazolyl ; tetrahydrofuryl ; tetrahydropyranyl ; quinolinyl ; benzomorpholinyl ; wherein each Het-radical is optionally substituted by one or more radicals selected from the group of halo ; oxo ; (C₁₋₃)alkyl ; aryl(C₁₋₃)alkyl and (C₁₋₃)alkyloxycarbonyl.

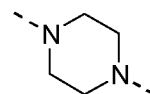
Most preferably, the invention relates to a compound according to the invention, wherein aryl is phenyl, optionally substituted with 1 or 2 substituents, each independently from each other, selected from the group of (C₁₋₃)alkyloxy ; halo ; cyano ; ethanoyl ; trifluoromethyl ; mono- and di((C₁₋₃)alkylcarbonyl)amino ; and morpholinyl.

In a further preferred embodiment, the invention relates to a compound according to the invention, wherein

Y is a bivalent radical of Formula (II-a) or (II-b)



(II-a)



(II-b)

wherein R^4 is hydrogen or methyl ;

R^5 is hydrogen or chloro ;

R^6 is hydrogen or methyl ;

R^7 is hydrogen ;

5 X^1, X^2 are each, independently from each other, a bond, a saturated or an unsaturated bivalent (C_{1-8})-hydrocarbon radical, wherein one or more bivalent $-CH_2$ -units may optionally be replaced by a respective bivalent phenyl-unit ; and wherein one or more hydrogen atoms may be replaced by an oxo-radical ;

10 Q^1, Q^2 are each, independently from each other, a radical selected from the group of hydrogen ; $-NR^1R^2$; Pir ; $-OR^{3a}$; SR^{3b} ; SO_2R^{3c} ; aryl ; and Het ;

p, q are each, independently from each other, an integer equal to 1 ;

15 R^1 and R^2 are each, independently from each other, a radical selected from the group of hydrogen ; alkyl ; alkynyl ; aryl ; arylalkyl ; diarylalkyl ; alkylcarbonyl ; alkylcarbonylalkyl ; alkyloxycarbonyl ; alkyloxyalkylcarbonyl ; alkyloxycarbonylalkyl ; alkyloxycarbonylalkylcarbonyl ; alkylsulfonyl ; arylsulfonyl ; arylalkylsulfonyl ; arylalkenylsulfonyl ; Het-sulfonyl ; arylcarbonyl ; arylalkylcarbonyl ; Het ; Het-alkyl ; Het-carbonyl ; alkyl- NR^aR^b ; and carbonyl- NR^aR^b ; wherein R^a and R^b are each independently selected from the group of hydrogen, alkyl, alkylcarbonyl, aryl, and arylalkyl ;

20 Pir is a radical containing at least one N, by which it is attached to the radical X^1 or X^2 , selected from the group of pyrrolidinyl ; piperidinyl ; piperazinyl ; pyrrolyl ; morpholinyl ; and isoindolyl ; wherein each Pir-radical is optionally substituted by 1, 2 or 3 radicals selected from the group of hydroxy ; (C_{1-3}) alkyl ; (C_{1-3}) alkenyl ; (C_{1-3}) alkyloxycarbonyl ; Het-carbonyl ; (C_{1-3}) alkylamino ; trifluoromethyl ; (C_{0-3}) alkylphenyl ; and pyrrolidinyl ;

25 R^{3a}, R^{3b}, R^{3c} are each, independently from each other, a radical selected from the group of a radical selected from the group of hydrogen ; alkyl ; trihaloalkyl ; aryl ; arylalkyl ; and alkyloxyalkyl.

30 Het is a heterocyclic radical selected from the group of pyrrolidinyl ; piperidinyl ; imidazolyl ; pyridinyl ; morpholinyl ; furyl ; thienyl ; isoxazolyl ; thiazolyl ; tetrahydro-

furyl ; tetrahydropyranyl ; quinolinyl; benzomorpholinyl ; wherein each Het-radical is optionally substituted by one or more radicals selected from the group of halo ; oxo ; (C₁₋₃)alkyl ; aryl(C₁₋₃)alkyl and (C₁₋₃)alkyloxycarbonyl.

- 5 aryl is phenyl, optionally substituted with 1 or 2 substituents, each independently from each other, selected from the group of (C₁₋₃)alkyloxy ; halo ; cyano ; ethanoyl ; trifluoromethyl ; mono- and di((C₁₋₃)alkylcarbonyl)amino ; and morpholinyl ;
- 10 alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 8 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 8 carbon atoms ; wherein each radical is optionally substituted on one or more carbon atoms with one or more radicals selected from the group of (C₁₋₃)alkyloxy ; hydroxy ; and thio ;
- 15 alkenyl is an alkyl radical as defined above, further having one or more double bonds ;
- alkynyl is an alkyl radical as defined above, further having one or more triple bonds ; and
- 20 arylalkyl is an alkyl radical as defined above, further having one or more CH₃-groups replaced by phenyl.

The cinnamyl-moiety in Formula (I) can have an E or Z configuration. Preferably, the cinnamyl-moiety has the E-configuration. Compositions comprising compounds according to the invention having both configurations (mixtures) are also within the scope of the invention. Preferably, a composition contains essentially only a compound according to the invention having a cinnamyl-moiety with an E-configuration. However, small amounts (about up to 5 %) of the other configuration, preferably Z-configuration may also be present in the composition.

In the framework of this application, and unless the number of carbon atoms is indicated differently, alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 8 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms being part of a straight or branched saturated hydrocarbon radical having from 1 to 8 carbon atoms ; wherein each radical is optionally substituted on one or more carbon atoms with one or more radicals selected from the group of oxo ;

(C₁₋₃)alkyloxy ; halo ; cyano ; nitro ; formyl ; hydroxy ; amino ; carboxyl ; and thio. Preferably, alkyl is methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclohexylmethyl and cyclohexylethyl.

In the framework of this application, alkenyl is an alkyl radical as defined above
5 having one or more double bonds. Preferably, alkenyl is ethenyl, propenyl and butynyl.

In the framework of this application, alkynyl is an alkyl radical as defined above having one or more triple bonds. Preferably, alkynyl is ethynyl and propynyl.

In the framework of this application, arylalkyl is an alkyl radical as defined above, having one or more -CH₂-radicals replaced by phenyl-radical. Examples of
10 such radicals are benzyl, diphenylmethyl and 1,1-diphenylethyl.

In the framework of this application, halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms, wherein one or more carbon atoms is
15 substituted with one or more halo atoms. Preferably, halo is bromo, fluoro or chloro ; more preferably, halo is fluoro. Preferably, haloalkyl is trifluoroalkyl ; more preferably haloalkyl is trifluoromethyl.

In the framework of this application, unless otherwise indicated, a bond can be any bond, including a covalent bond, a single bond, a double bond, a triple bond, a coordination bond and a hydrogen bond.
20

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

25 A pharmaceutically acceptable acid addition salt is defined to comprise a therapeutically active non-toxic acid addition salt form that a compound according to Formula (I) is able to form. Said salt can be obtained by treating the base form of a compound according to Formula (I) with an appropriate acid, for example an inorganic acid, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulphuric
30 acid, nitric acid and phosphoric acid ; an organic acid, 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, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cy-

clamic acid, salicylic acid, p-aminosalicylic acid and pamoic acid.

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

The compound according to Formula (I) containing an acidic proton may also
5 be converted into a therapeutically active non-toxic metal or amine addition salt form (base addition salt) by treatment with an appropriate organic and inorganic base. Appropriate base salt 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, hy-
10 bramine salts, and salts with amino acids, for example arginine and lysine.

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

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

The *N*-oxide form of the compound according to Formula (I) is meant to comprise a compound of Formula (I) wherein one or several nitrogen atoms are oxidized to so-called *N*-oxides, particularly those *N*-oxides wherein one or more tertiary nitrogens (e.g. of the piperazinyll or piperidinyll radical) are *N*-oxidized. Such *N*-oxides can easily
20 be obtained by a skilled person without any inventive skills and they are obvious alternatives for a compound 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
25 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.

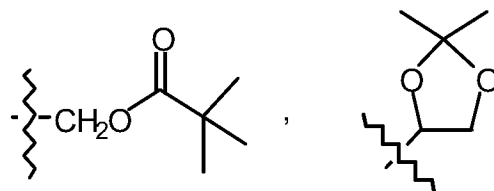
A compound of Formula (I) may be converted to the corresponding *N*-oxide form following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the compound
30 of Formula (I) with an appropriate organic or 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, benzenecarboxoperoxy acid or

halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic 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.

A quaternary ammonium salt of compound according to Formula (I) defines said compound which is 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 methylodide and benzylodide. 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 at least one positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate ions.

The invention also comprises a derivative compound (usually called "pro-drug") of a pharmacologically-active compound according to the invention, in particular according to Formula (I), which is degraded *in vivo* to yield a compound 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.

A pro-drug form of a pharmacologically-active compound according to the invention will generally be a compound according to Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, an *N*-oxide form thereof, or a quaternary ammonium salt 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 $-\text{CONR}^y\text{R}^z$, wherein R^y is H, C_{1-6} alkyl, phenyl or benzyl and R^z is $-\text{OH}$, H, C_{1-6} alkyl, phenyl or benzyl. A compound according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze
 5 with first order kinetics in aqueous solution.

In the framework of this application, a compound according to the invention is inherently intended to comprise all stereochemically isomeric forms thereof. The term “stereochemically isomeric form” as used herein defines all the possible isomeric forms that a compound of Formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound 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
 10 bonds can have an E or Z-stereochemistry at said double bond. Hence, all stereochemically isomeric forms of a compound of Formula (I) are 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
 20 center, the reference center. The configuration of the second stereogenic center is indicated using relative descriptors $[\text{R}^*, \text{R}^*]$ or $[\text{R}^*, \text{S}^*]$, where R^* is always specified as the reference center and $[\text{R}^*, \text{R}^*]$ indicates centers with the same chirality and $[\text{R}^*, \text{S}^*]$ 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- $[\text{R}^*, \text{S}^*]$. 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
 25

carbon atom in the ring system (hydrogen atom in a compound 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.

5 In the framework of this application, a compound according to the invention is inherently intended to comprise all isotopic combinations of its chemical elements. In the framework of this application, a chemical 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
10 natural abundance or in an isotopically enriched form. In particular, when hydrogen is mentioned, it is understood to refer to ^1H , ^2H , ^3H 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 mix-
15 tures thereof ; and when fluor is mentioned, it is understood to refer to ^{18}F , ^{19}F and mix- tures thereof.

A compound according to the invention therefore inherently comprises a com-
pound with one or more isotopes of one or more element, and mixtures thereof, includ-
ing a radioactive compound, also called radiolabelled compound, wherein one or more
20 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), a pharmaceutically acceptable acid or base addition salt thereof, an *N*-oxide form thereof, or a quaternary ammonium salt thereof, which contains at least one radioactive atom. For example, a compound can be labelled with positron or with gamma emitting
25 radioactive isotopes. For radioligand-binding techniques (membrane receptor assay), the ^3H -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 min-
utes respectively. Since the half-lives of these radioactive isotopes are so short, it is
30 only feasible to use them at institutions which have an accelerator on site for their pro-
duction, thus limiting their use. The most widely used of these are ^{18}F , $^{99\text{m}}\text{Tc}$, ^{201}Tl and ^{123}I . The handling of these radioactive isotopes, their production, isolation and incorpo-
ration in a molecule are known to the skilled person.

In particular, the radioactive atom is selected from the group of hydrogen, car-

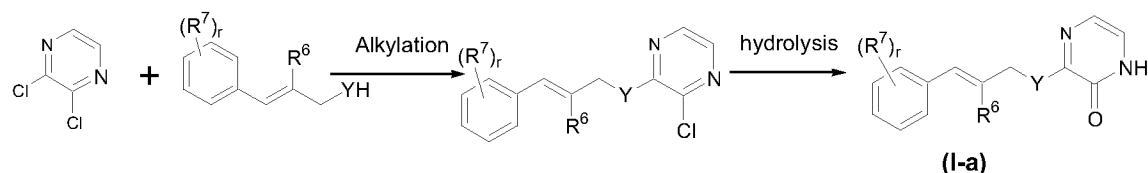
bon, nitrogen, sulfur, oxygen and halogen. Preferably, the radioactive atom is selected from the group of hydrogen, carbon and halogen.

In particular, the radioactive isotope is selected from the group of ^3H , ^{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 ^3H , ^{11}C and ^{18}F .

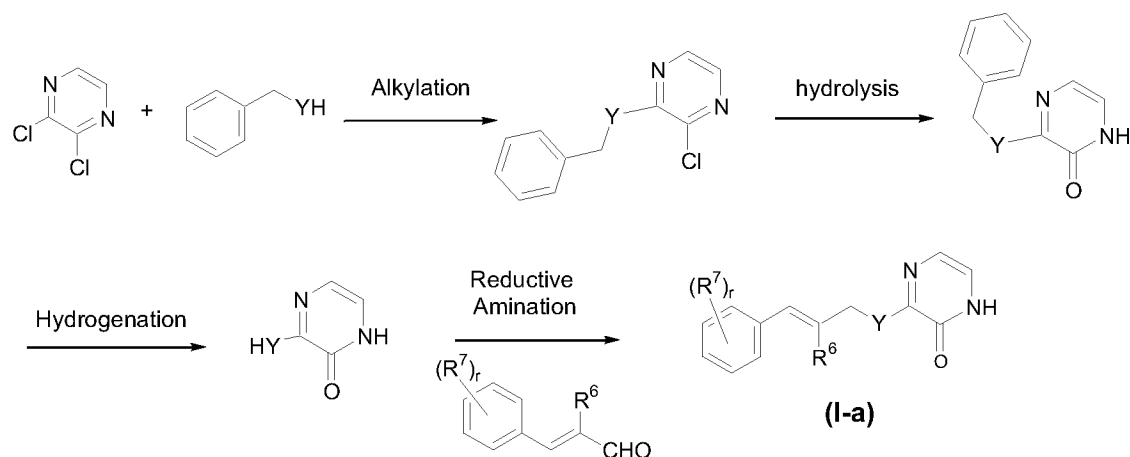
Preparation

A compound according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person. In particular, a pyrazinone derivative can be prepared according to one or more of the following preparation methods.

Preparation of the final compound (I-a).



Scheme 1A



Scheme 1B

Alkylation reactions of the starting material 2,3-dichloropyrazine with aminoderivatives (Scheme 1A) or (Scheme 1B) may be performed in an aprotic solvent, such as, for in-

stance DMF or DMSO, in the presence of an inorganic base, such as K_2CO_3 , Na_2CO_3 , NaOH or KOH, at a convenient temperature, either by conventional heating or under microwave irradiation, for a period of time to ensure the completion of the reaction, which may typically be about 16 hours under conventional heating.

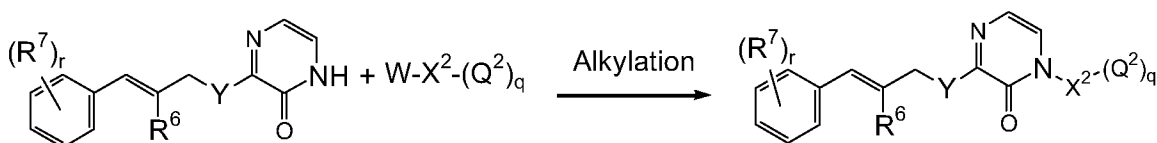
- 5 Hydrolysis reactions may be performed either in acidic inorganic solvents, such as 10% HCl_{aq} , using a co-solvent such as THF, by conventional heating or under microwave heating, for a period of time to ensure the completion of the reaction, which may typically be about 16 hours under conventional heating, or under basic conditions, such as in $NaOH_{aq}$ or in a DMSO solvent, for a period of time to ensure the completion of the reaction, which may typically be about 0.5 hours under microwave irradiation.

Hydrogenation may be performed in an alcoholic solvent, such as MeOH, in the presence of AcOH and Pd/C, under conventional heating, for a period of time to ensure the completion of the reaction, which may typically be about 16 hours at about 50 °C.

- 15 The reductive amination reaction may be performed in an aprotic solvent such as 1,2-dichloroethane, in the presence of the reducing agent such as triacetoxyborohydride, for a period of time to ensure the completion of the reaction, which may typically be about 16 hours at room temperature.

- 20 The final compound (I-a) is the starting compound for the compounds of the reaction schemes below. Variables Y, R^6 , R^7 and rare defined as in Formula (I), unless otherwise specified.

Preparation of a final compound in which X^2 is a saturated or an unsaturated hydrocarbon radical.



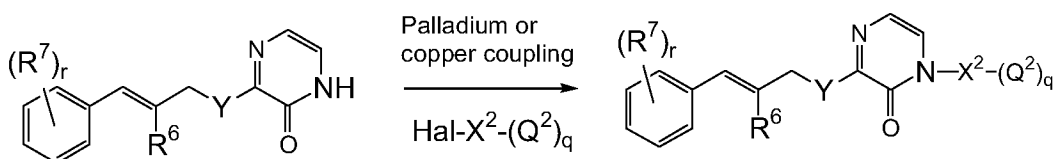
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Scheme 2A

The W-radical in the compound $W-X^2-(Q^2)_q$ is a leaving group, such as for instance Cl-, Br-, $MeSO_2O^-$ and $p-MePhSO_2O^-$; X^2 is a (C_{1-8}) -hydrocarbon radical, more preferably a (C_{1-6}) -hydrocarbon radical, even more preferably a (C_{1-5}) -hydrocarbon radical, most

preferably a (C₁₋₄)-hydrocarbon radical. and Y, Q², R⁶, R⁷, r and q are defined as in Formula (I). The alkylation reaction may be performed in an aprotic solvent, such as CH₃CN, DMF or THF in the presence of an inorganic base, such as K₂CO₃, Na₂CO₃, Cs₂CO₃, or an organic base such as TBD, PS-TBD, at a convenient temperature, either
 5 under conventional heating or microwave irradiation, for a period of time to ensure the completion of the reaction, which may typically be about 20 minutes at about 120° C under microwave irradiation.

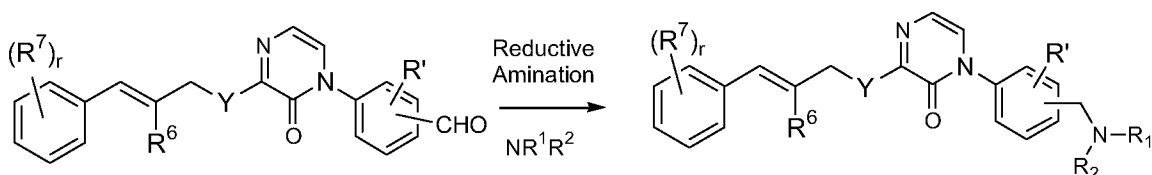
Preparation of a final compound in which X² is an phenyl-radical, or X² is a covalent bond and Q² is a heteroaryl-radical.
 10



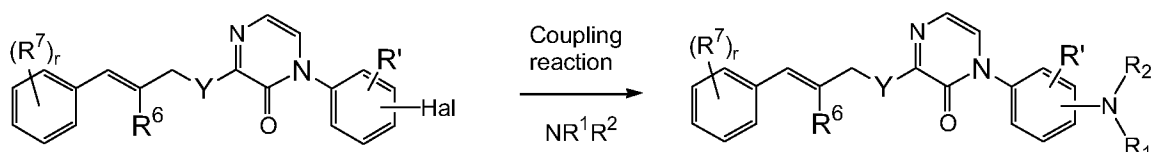
Scheme 2B

The Hal-radical in Hal-X²-(Q²)_p preferably represents a Br- or I-radical or a suitable equivalent radical such as B(OH)₂. X² is an optionally substituted phenyl ; or X² is a covalent bond and Q² is an optionally substituted heteroaryl. Variables Y, R⁶, R⁷, Q², r and q are defined as in Formula (I). The palladium coupling reaction is performed in an aprotic solvent such as toluene or dioxane, in the presence of a palladium catalyst such as Pd(AcO)₂ or Pd(dba)₃, in the presence of a suitable base such as Cs₂CO₃ or *t*-BuONa and of a ligand, such as BINAP or Xantphos, at a convenient temperature, either by conventional heating or under microwave irradiation, for a period of time to ensure the completion of the reaction. As an alternative, a copper coupling reaction may also be used to prepare the (hetero)aryl derivatives. The reaction is performed using an aprotic solvent, such as dioxane or DMF, in the presence of CuI, an inorganic base such K₃PO₄ and MeNH(CH₂)₂NHMe as a ligand, heating at a convenient temperature under traditional heating or microwave irradiation, for a period of time to ensure the
 25 completion of the reaction, which is typically about 25 minutes at about 175 °C under microwave irradiation.

Preparation of a final compound in which X^2 = phenyl and Q^2 is NR_1R_2



Scheme 3A



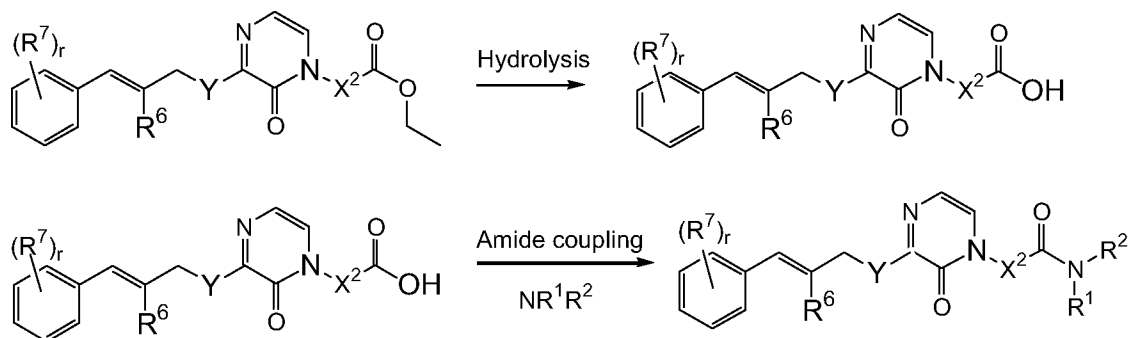
Scheme 3B

5

The transformations of different functional groups Q^2 , present in the final compound prepared by scheme 2B, into different functional groups present in other final compounds according to Formula (I), can be performed by synthesis methods well known by the person skilled in the art, such as reductive amination (Scheme 3A) or coupling reactions (Scheme 3B). Variables Y , R^1 , R^2 , R^6 , R^7 , r and Q^2 are defined as in Formula (I). R' is an optional substitution of the phenyl-moiety as defined in Formula (I), such as for example oxo ; (C_{1-3}) alkyloxy ; halo ; cyano ; nitro ; formyl ; hydroxy ; amino ; trifluoromethyl ; mono- and di $((C_{1-3})$ alkyl)amino ; carboxyl ; and thio. Hal is a halogen, such as F, Cl, Br and I.

15

Preparation of a final compound : amides

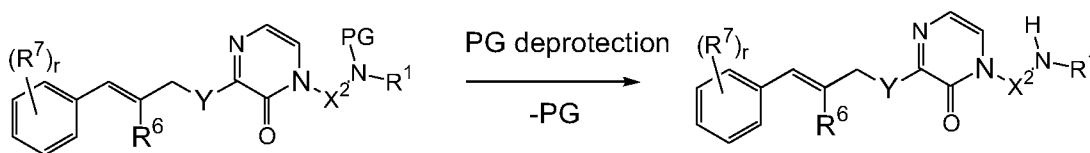


Scheme 4

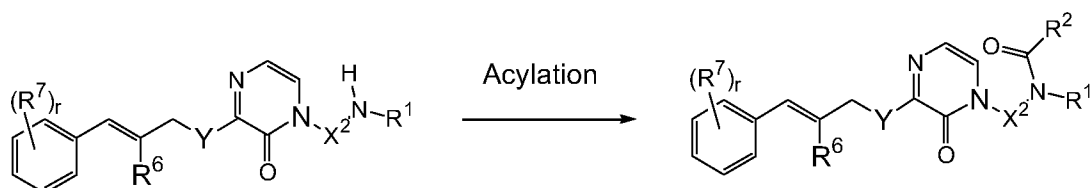
When the $-X^2-Q^2$ -moiety (or part of it) is an amide derivative, preparation may be per-

formed starting from the ester derivative, which was synthesized by either methods shown in Schemes 2A or 2B. Thus, basic hydrolysis of the ester group by standard and well known reaction techniques, in an aprotic solvent such as THF or dioxane, in the presence of an inorganic base, such as LiOH, KOH, or NaOH, at room temperature, for a period of time to ensure the completion of the reaction, yields the corresponding carboxylic acid derivative. Amide coupling of this carboxylic acid with different amines is performed using standard reaction conditions, for example, using HATU as coupling agent, in an aprotic solvent such as THF, DMF, CH₂Cl₂ (DCM), at room temperature, for a period of time to ensure the completion of the reaction. Variables Y, R¹, R², R⁶, R⁷, X², r and Q² are defined as in Formula (I).

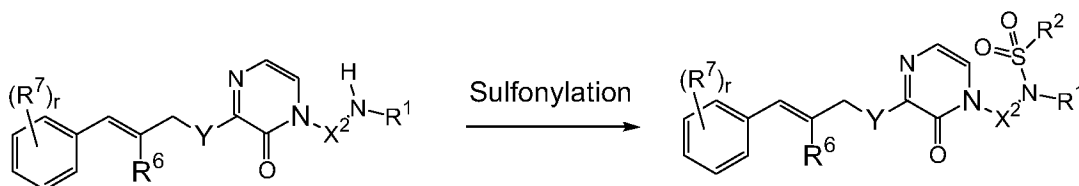
Preparation of a final compound : modified amines



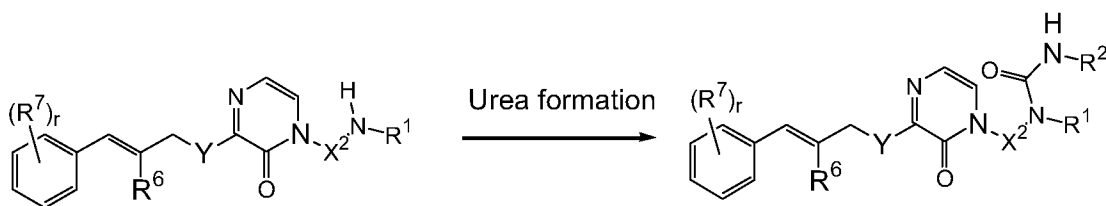
Scheme 5A



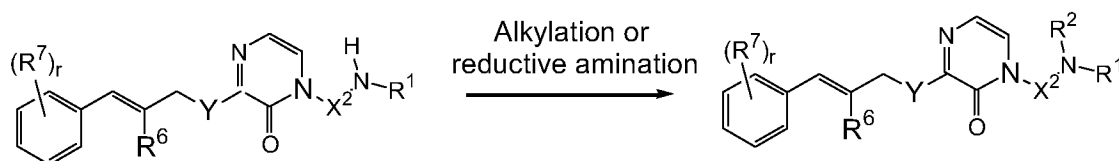
Scheme 5B



Scheme 5C



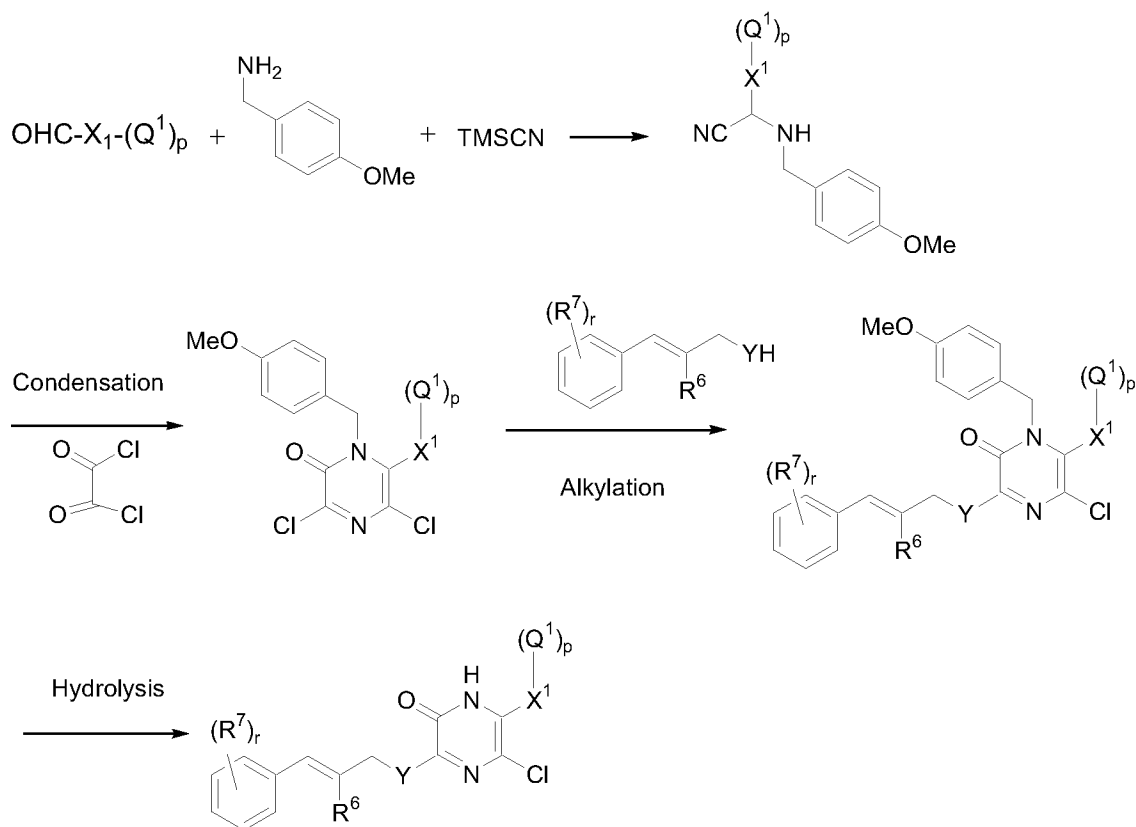
Scheme 5D



Scheme 5E

When amino group is protected with a protecting group, deprotection reaction may be carried out by synthetic methods well known to the person skilled in the art. Transformations of the amino group of Q², present in the intermediate and final compounds, into different amino derivatives of Q², present in other final compounds according to Formula (I) may be performed by synthetic methods well known by the person skilled in the art, such as acylation, sulfonylation, urea formation, alkylation or reductive amination reactions. Schemes 5A-E show a general overview of such chemical transformations. Variables Y, X², R¹, R², R⁶, R⁷ and r are defined as in Formula (I).

Preparation of final a compound : Compound substituted on carbon-6 of the pyrazine-core.



Scheme 6

- 5 Reductive amination of the required starting material shown in the scheme was performed in the presence of trimethylsilyl cyanide (TMSCN), in an aprotic solvent, such as dichloromethane, and in the presence of a reducing agent such as $\text{Ti}(\text{iPrO})_4$, at a convenient temperature, for a period of time to ensure the completion of the reaction, typically 16 hours at room temperature.
 - 10 Cyclization of the intermediates was achieved by reaction with oxalyl chloride in an aprotic solvent such as dichloroethane, at a convenient temperature, for a period of time to ensure the completion of the reaction, typically 60 hours at room temperature.
- The alkylation reaction with intermediate $\text{Ph-CH=C(R}^6\text{)CH}_2\text{YH}$ was performed in an aprotic solvent such as 1,2-dichloroethane, acetonitrile or DMF, in the presence of an inorganic base, such as K_2CO_3 , Na_2CO_3 , NaOH , KOH , at a convenient temperature, either by conventional heating or under microwave irradiation, for a period of time to ensure the completion of the reaction, typically 30 minutes at 130 °C under microwave

irradiation.

Hydrolysis was performed in acidic media, such as trifluoroacetic acid, at a convenient temperature, either by conventional heating or under microwave irradiation, for a period of time to ensure the completion of the reaction, typically 15 minutes at 140 °C under
5 microwave irradiation. Variables Y, X¹, Q¹, R⁶ and p are defined as in Formula (I).

The transformations of different functional groups Q¹, present in the final compound prepared by scheme 6, into different functional groups present in other final compounds according to Formula (I), can be performed by synthesis methods well known by the person skilled in the art.

10

Pharmacology

A compound according to the invention, in particular compound according to Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, an *N*-oxide form thereof, or a quaternary ammonium salt thereof, has surprisingly been
15 shown to have a binding affinity towards α_2 -adrenergic receptor, in particular towards α_{2C} -adrenergic receptor, in particular as an antagonist.

In view of their above mentioned potency, a compound according to the invention is suitable for the prevention and/or treatment of diseases where antagonism of the α_2 -adrenergic receptor, in particular antagonism of the α_{2C} -adrenergic receptor is of
20 therapeutic use. In particular, a compound according to the invention may be suitable for treatment and/or prophylaxis in the following diseases :

- Central nervous system disorders, including :
- Mood disorders, including particularly major depressive disorder, depression with or without psychotic features, catatonic features, melancholic features, atypical features of postpartum onset and, in the case of recurrent episodes, with or without
25 seasonal pattern, dysthymic disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, recurrent brief depressive disorder, mixed affective disorder, bipolar disorder not otherwise specified, mood disorder due to a general medical condition, substance-induced mood disorder, mood disorder not otherwise specified,
30 seasonal affective disorder and premenstrual dysphoric disorders.
- Anxiety disorders, including panic attack, agoraphobia, panic disorder without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social

phobia, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder and anxiety disorder not otherwise specified.

- 5 • Stress-related disorders associated with depression and/or anxiety, including acute stress reaction, adjustment disorders (brief depressive reaction, prolonged depressive reaction, mixed anxiety and depressive reaction, adjustment disorder with predominant disturbance of other emotions, adjustment disorder with predominant disturbance of conduct, adjustment disorder with mixed disturbance of emotions and
10 conduct, adjustment disorders with other specified predominant symptoms) and other reactions to severe stress.
- Dementia, amnesic disorders and cognitive disorders not otherwise specified, especially dementia caused by degenerative disorders, lesions, trauma, infections, vascular disorders, toxins, anoxia, vitamin deficiency or endocrinic disorders, or
15 amnesic disorders caused by alcohol or other causes of thiamine deficiency, bilateral temporal lobe damage due to Herpes simplex encephalitis and other limbic encephalitis, neuronal loss secondary to anoxia / hypoglycaemia / severe convulsions and surgery, degenerative disorders, vascular disorders or pathology around ventricle III.
- 20 • Cognitive disorders, in particular due to cognitive impairment resulting from other medical conditions.
- Personality disorders, including paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder, antisocial personality disorder, borderline personality disorder, histrionic personality disorder, narcissistic personality disorder, avoidant personality disorder, dependent personality disorder, obsessive-
25 compulsive personality disorder and personality disorder not otherwise specified.
- Schizoaffective disorders resulting from various causes, including schizoaffective disorders of the manic type, of the depressive type, of mixed type, paranoid, disorganized, catatonic, undifferentiated and residual schizophrenia, schizophreniform
30 disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, substance-induced psychotic disorder and psychotic disorder not otherwise specified.

- Akinesia, akinetic-rigid syndromes, dyskinesia and medication-induced parkinsonism, Gilles de la Tourette syndrome and its symptoms, tremor, chorea, myoclonus, tics and dystonia.
- Attention-deficit / hyperactivity disorder (ADHD).
- 5 • Parkinson's disease, drug-induced Parkinsonism, post-encephalitic Parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification.
- Dementia of the Alzheimer's type, with early or late onset, with depressed mood.
- Behavioural disturbances and conduct disorders in dementia and the mentally re-
10 tardated, including restlessness and agitation.
- Extra-pyramidal movement disorders.
- Down's syndrome.
- Akathisia.
- Eating Disorders, including anorexia nervosa, atypical anorexia nervosa, bulimia
15 nervosa, atypical bulimia nervosa, overeating associated with other psychological disturbances, vomiting associated with other psychological disturbances and non-specified eating disorders.
- AIDS-associated dementia.
- Chronic pain conditions, including neuropathic pain, inflammatory pain, cancer pain
20 and post-operative pain following surgery, including dental surgery. These indications might also include acute pain, skeletal muscle pain, low back pain, upper extremity pain, fibromyalgia and myofascial pain syndromes, orofacial pain, abdominal pain, phantom pain, tic douloureux and atypical face pain, nerve root damage and arachnoiditis, geriatric pain, central pain and inflammatory pain.
- 25 • Neurodegenerative diseases, including Alzheimer's disease, Huntington's chorea, Creutzfeld-Jacob disease, Pick's disease, demyelinating disorders, such as multiple sclerosis and ALS, other neuropathies and neuralgia, multiple sclerosis, amyotropical lateral sclerosis, stroke and head trauma.
- Addiction disorders, including :
- 30 • Substance dependence or abuse with or without physiological dependence, particularly where the substance is alcohol, amphetamines, amphetamine-like sub-

stances, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, phencyclidine-like compounds, sedative-hypnotics, benzodiazepines and/or other substances, particularly useful for treating withdrawal from the above substances and alcohol withdrawal delirium.

- 5 • Mood disorders induced particularly by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances.
- Anxiety disorders induced particularly by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives,
10 hypnotics, anxiolytics and other substances and adjustment disorders with anxiety.
- Smoking cessation.
- Body weight control, including obesity.
- Sleep disorders and disturbances, including :
 - Dyssomnias and/or parasomnias as primary sleep disorders, sleep disorders re-
15 lated to another mental disorder, sleep disorder due to a general medical condition and substance-induced sleep disorder.
 - Circadian rhythms disorders.
 - Improving the quality of sleep.
- Sexual dysfunction, including sexual desire disorders, sexual arousal disorders,
20 orgasmic disorders, sexual pain disorders, sexual dysfunction due to a general medical condition, substance-induced sexual dysfunction and sexual dysfunction not otherwise specified.

The invention therefore relates to a compound according to the invention for use as a medicine.

- 25 The invention also relates to the use of a compound according to the invention for the preparation of a medicament for the prevention and/or treatment of central nervous system disorders, mood disorders, anxiety disorders, stress-related disorders associated with depression and/or anxiety, cognitive disorders, personality disorders, schizoaffective disorders, Parkinson's disease, dementia of the Alzheimer's type,
30 chronic pain conditions, neurodegenerative diseases, addiction disorders, mood disorders and sexual dysfunction.

A compound according to the invention may be co-administered as add-on treatment and/or prophylaxis in the above listed diseases in combination with antidepressants, anxiolytics and/or antipsychotics which are currently available or in development or which will become available in the future, in particular to improve efficacy and/or onset of action. It will be appreciated that a compound of the present invention and the other agents may be present as a combined preparation for simultaneous, separate or sequential use for the prevention and/or treatment of depression and/or anxiety. Such combined preparations may be, for example, in the form of a twin pack. It will also be appreciated that a compound of the present invention and the other agents may be administered as separate pharmaceutical compositions, either simultaneously or sequentially.

The invention therefore relates to the use of a compound according to the invention as an add-on treatment in combination with one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics.

Suitable classes of antidepressant agents include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRI's), monoamine oxidase inhibitors (MAOI's), reversible inhibitors of monoamine oxidase (RIMA's), serotonin and noradrenaline reuptake inhibitors (SNRI's), noradrenergic and specific serotonergic antidepressants (NaSSA's), corticotropin releasing factor (CRF) antagonists, α -adrenoreceptor antagonists and atypical antidepressants.

Suitable examples of norepinephrine reuptake inhibitors include amitriptyline, clomipramine, doxepin, imipramine, trimipramine, amoxapine, desipramine, maprotiline, nortriptyline, protriptyline, reboxetine and pharmaceutically acceptable salts thereof.

Suitable examples of selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine, paroxetine, sertraline and pharmaceutically acceptable salts thereof.

Suitable examples of monoamine oxidase inhibitors include isocarboxazid, phenelzine, tranylcypromine, selegiline and pharmaceutically acceptable salts thereof.

Suitable examples of reversible inhibitors of monoamine oxidase include moclobemide and pharmaceutically acceptable salts thereof.

Suitable examples of serotonin and noradrenaline reuptake inhibitors include venlafaxine and pharmaceutically acceptable salts thereof.

Suitable atypical antidepressants include bupropion, lithium, nefazodone, trazodone, viloxazine, sibutramine and pharmaceutically acceptable salts thereof.

Other suitable antidepressants include adinazolam, alaproclate, amineptine, amitriptyline/chlordiazepoxide combination, atipamezole, azamianserin, bazinaprine, 5 befuraline, bifemelane, binodaline, bipenamol, brofaromine, bupropion, caroxazone, cericlamine, cianopramine, cimoxatone, citalopram, clemeprol, clovoxamine, dazepinil, deanol, demexiptiline, dibenzepin, dothiepin, droxidopa, enefexine, estazolam, etoperidone, femoxetine, fengabine, fezolamine, fluotracen, idazoxan, indalpine, indeloxazine, iprindole, levoprotiline, litoxetine, lofepramine, medifoxamine, metapramine, metralindole, mianserin, milnacipran, minaprine, mirtazapine, monirelin, nebracetam, nefopam, 10 nialamide, nomifensine, norfluoxetine, orotirelin, oxaflorane, pinazepam, pirlindone, pizotyline, ritanserin, rolipram, sercloremine, setiptiline, sibutramine, sulbutiamine, sulpiride, teniloxazine, thozalinone, thymoliberin, tianeptine, tiflucarbine, tofenacin, tofisopam, toloxatone, tomoxetine, veralipride, viqualine, zimelidine and zometapine and 15 pharmaceutically acceptable salts thereof, and St. John's wort herb, or *Hypericum perforatum*, or extracts thereof.

Suitable classes of anti-anxiety agents include benzodiazepines and 5-HT_{1A} receptor agonists or antagonists, especially 5-HT_{1A} partial agonists, corticotropin releasing factor (CRF) antagonists, compounds having muscarinic cholinergic activity and 20 compounds acting on ion channels. In addition to benzodiazepines, other suitable classes of anti-anxiety agents are nonbenzodiazepine sedative-hypnotic drugs such as zolpidem; mood-stabilizing drugs such as clobazam, gabapentin, lamotrigine, loreclezole, oxcarbamazepine, stiripentol and vigabatrin; and barbiturates.

Suitable antipsychotic agents are selected from the group consisting of acetophenazine, in particular the maleate salt; alentemol, in particular the hydrobromide salt; 25 alpertine; azaperone; batelapine, in particular the maleate salt; benperidol; benzinodopyrine, in particular the hydrochloride salt; brofoxine; bromperidol; butaclamol, in particular the hydrochloride salt; butaperazine; carphenazine, in particular the maleate salt; carvotroline, in particular the hydrochloride salt; chlorpromazine; chlorprothixene; 30 cinperene; cintriamide; clomacran, in particular the phosphate salt; clopenthixol; clopimozide; clopipazan, in particular the mesylate salt; cloroperone, in particular the hydrochloride salt; clothiapine; clothixamide, in particular the maleate salt; clozapine; cyclophenazine, in particular the hydrochloride salt; droperidol; etazolate, in particular the hydrochloride salt; fenimide; flucindole; flumezapine; fluphenazine, in particular the de-

canoate, enanthate and/or hydrochloride salts; fluspiroperone; fluspirilene; flutroline; gevotroline, in particular the hydrochloride salt; halopemide; haloperidol; iloperidone; imidoline, in particular the hydrochloride salt; lenperone; loxapine; mazapertine, in particular the succinate salt; mesoridazine; metiapine; milenperone; milipertine; molindone, in particular the hydrochloride salt; naranol, in particular the hydrochloride salt; 5 neflumozide, in particular the hydrochloride salt; ocaperidone; olanzapine; oxiperomide; penfluridol; pentiapine, in particular the maleate salt; perphenazine; pimozide; pinoxepin, in particular the hydrochloride salt; pipamperone; piperacetazine; pipotiazine, in particular the palmitate salt; piquindone, in particular the hydrochloride salt; prochlorperazine, in particular the edisylate salt; prochlorperazine, in particular the 10 maleate salt; promazine, in particular the hydrochloride salt; quetiapine; remoxipride; risperidone; rimcazol, in particular the hydrochloride salt; seiperidol, in particular the hydrochloride salt; sertindole; setoperone; spiperone; sulpiride; thioridazine; thiothixene; thorazine; tioperidone, in particular the hydrochloride salt; tiospirone, in particular the 15 hydrochloride salt; trifluoperazine, in particular the hydrochloride salt; trifluoperidol; trifluopromazine; ziprasidone, in particular the hydrochloride salt; and mixtures thereof.

Some compound according to the invention surprisingly also shows a moderate 5-HT-reuptake inhibition activity and may therefore very well be suited for use in the treatment and/or prophylaxis of depression. It is thought that a 5-HT reuptake inhibitor 20 with associated α_2 -adrenoceptor antagonistic activity might be a new type of antidepressant, with a dual action on the central noradrenergic and serotonergic neuronal systems. The immediate effect on monoamine release of autoreceptor blockade may accelerate the onset of action of such a compound, compared to currently available drugs that require desensitization of the autoreceptors involved in the feedback 25 mechanism in order to become fully effective. In addition, α_{2C} -adrenoceptor antagonism improves sexual function as shown by treatment with the α_{2C} -adrenoceptor antagonist yohimbine, thereby potentially reducing one of the side effects related to 5-HT uptake inhibition and enhancement of NEergic neurotransmission improves social function more effectively than SSRIs (J. Ignacio Andrés et al., J. Med. Chem. (2005), Vol. 48, 30 2054-2071)).

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 compound according to Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, an *N*-oxide form thereof, or a quaternary ammonium salt thereof.

A compound according to the invention 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 composition 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. This pharmaceutical composition is 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 suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as 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 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 deleteri-

ous 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.

5 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
10 tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof. Since a compound according to the invention is a potent orally administrable dopamine antagonist, a pharmaceutical composition comprising said compound for administration orally is especially advantageous.
15

The invention also relates to a pharmaceutical composition comprising a compound according to the invention and one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics as well as to the use of such a composition for the manufacture of a medicament, in particular to improve efficacy
20 and/or onset of action in the treatment of depression and/or anxiety.

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

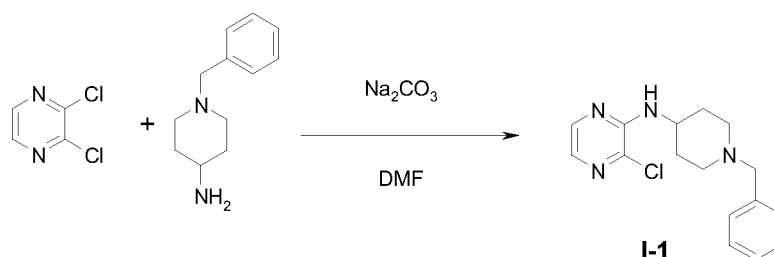
Experimental part

25 Hereinafter, "DCM" means dichloromethane, "THF" means tetrahydrofuran ; "DMF" means *N,N*-dimethylformamide ; "EtOAc" means ethyl acetate ; "DCE" means 1,2-dichloroethane ; "DMSO" means dimethylsulfoxide ; "TMSCN" means trimethylsilyl cyanide ; "Ti(iPrO)₄" means titanium(4+) salt 2-propanol ; "TFA" means trifluoro acetic acid ; "DCM" means dichloromethane ; "HATU" means O-(7-Azobenzotriazol-1-yl)-
30 1,1,3,3-tetramethyluronium hexafluorophosphate ; "DIPEA" means diisopropylethylamine ; "DIEA" means diethylamine ; "PS-TBD" is polymer-supported TBD and "PS-NCO" means polymer-supported isocyanate.

Microwave assisted reactions were performed in a single-mode reactor: EmrysTM 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.

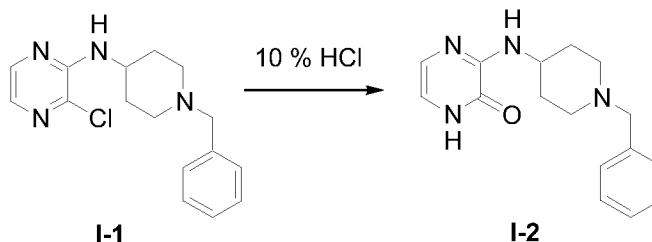
A. Preparation of the intermediate compounds

A1. Preparation of intermediate compound 1

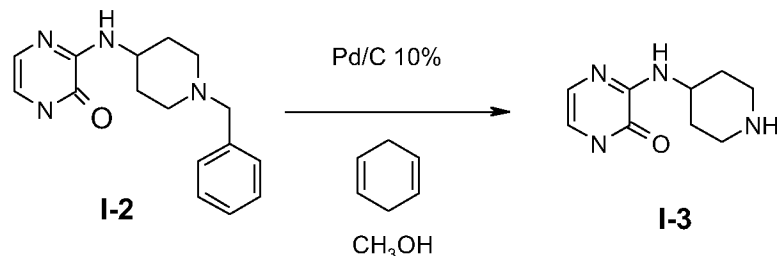


2,3-Dichloropyrazine (10 g, 62.12 mmol) and 1-(benzylamino)pyrrolidine (13.73 mL, 67.12 mmol) were dissolved in DMF (60 ml). Then Na_2CO_3 (10.09 g, 114.10 mmol) was added. The reaction was stirred at 130 °C for 16 hours. The solid was filtered off, washed with AcOEt and the solvent was evaporated till dryness. The product was dissolved in AcOEt, washed with H_2O and brine, dried with MgSO_4 and evaporated under vacuum yielding 15 g of the desired intermediate compound 1 (74 %). The product was used without any further purification.

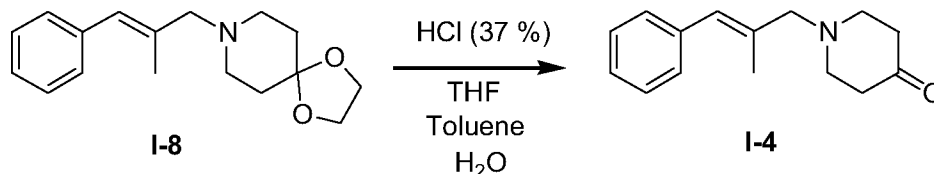
A2. Preparation of intermediate compound 2



Intermediate compound 1 (7 g, 23.11 mmol) was dissolved in 10 % HCl (70 ml) and heated in a sealed tube at 110 °C for 16 hours. A light brown solid was precipitated, which was filtered off, washed with water and dried under vacuum yielding 4.57 g of the desired intermediate compound 2 (70 %).

A3. Preparation of intermediate compound 3

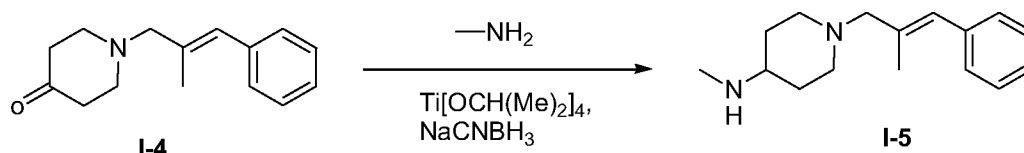
Intermediate compound **2** (4.17 g, 14.66 mmol) was dissolved in CH₃OH (62 mL), then Pd/C (4.17 g; 10 %) and 1,4-cyclohexadiene (27.96 mL, 293.2 mmol) were added. The reaction was heated in a sealed tube at 65 °C for 4 hours. The reaction was filtered over celite and the solvent was evaporated till dryness yielding 2.69 g of the desired intermediate compound **3** (94 %).

A4. Preparation of intermediate compound 4

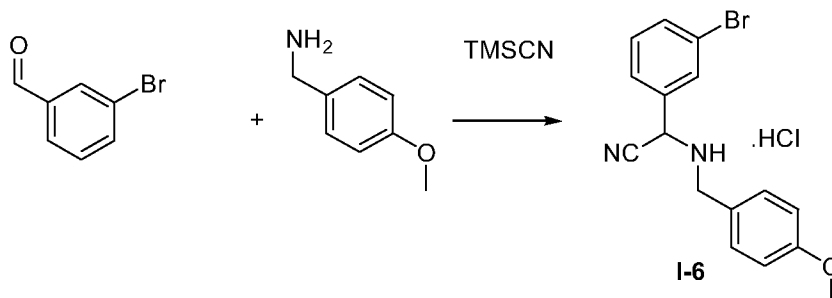
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Intermediate compound **8** (12.6 g, 0.046 mol) was dissolved in a mixture of 37% aq. HCl (27.24 ml), H₂O (37.01 ml) and THF (196 ml). The solution was stirred and refluxed for 2 days, then the cooled and crude mixture was evaporated and reverted to the starting material. The residue was mixed with conc. HCl (29.73 ml), H₂O (80 ml) and toluene (110 ml). Then, the reaction mixture was stirred and refluxed for 1 day. The organic layer was separated and discarded. The aqueous layer was cooled on an ice-water bath, neutralized with an excess NaHCO₃ (solid) and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered and the solvent was evaporated. The residue was purified by open column chromatography (eluent 1: CH₂Cl₂; eluent 2: CH₂Cl₂/2-propanone 95/5, 90/10; eluent 3: CH₂Cl₂/CH₃OH 96/4). The product fractions were collected and the solvent was evaporated. Yield: 4.98 g of intermediate compound **4** (47 %).

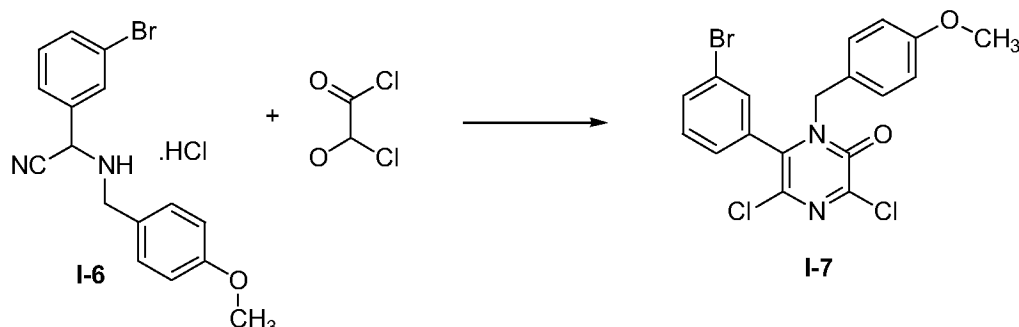
20

A5. Preparation of intermediate compound 5

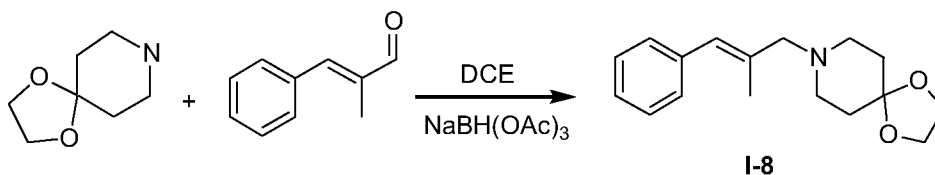
To a mixture of intermediate compound **4** (1 g, 4.361 mmol) and MeNH₂ (2.7 mL, 5.23 mmol) in THF (30 mL), Ti[OCH(Me)₂]₄ (1 mL, 4.361 mmol) was added at 0 °C under N₂ atmosphere. The reaction was stirred at room temperature for 3 hours. Then a solution of NaCNBH₃ (0.3 g, 4.61 mmol) in EtOH (2 mL) was added. The reaction was stirred 20 hours at room temperature. The organic phase was filtered and the solvent was evaporated to yield an oil. The crude was treated with water and extracted with DCM (3x 10 mL). The organic phase was evaporated and the residue was purified with DCM/MeOH 9:1 to obtain 0.6 g (60 %) as an oil of intermediate compound **5**.

A6. Preparation of intermediate compound 6

To a mixture of 3-bromobenzaldehyde (1.2 g, 6.48 mmol) and 4-methoxyaniline (9 g, 6.48 mmol) in DCM (150 mL) was added Ti-(i-PrOH)₄ (0.648 mmol). The reaction was stirred for 2 hours at room temperature. TMSCN (13.61 mmol) was added and the reaction was stirred 24 hours at room temperature. The solvent was evaporated and the oil was dissolved in Et₂O (100 mL); then a solution of i-PrOH/HCl 6 N (10 mL) was added. The precipitate was filtered off and washed with cold Et₂O to yield 5.2 g of intermediate compound **6** as a white solid (56 %).

A7. Preparation of intermediate compound 7

To a mixture of intermediate compound **6** (2.88 g, 7.85 mmol) and DCE (40 mL), ethanedioyl dichloride **6** (11.7 mL, 23.43 mmol) was added. The reaction was stirred
 5 for 4 days at room temperature. The crude was evaporated to dryness, to yield 2.8 g of intermediate compound **7** as a yellow oil (81 %). The crude was used in the next step without purification.

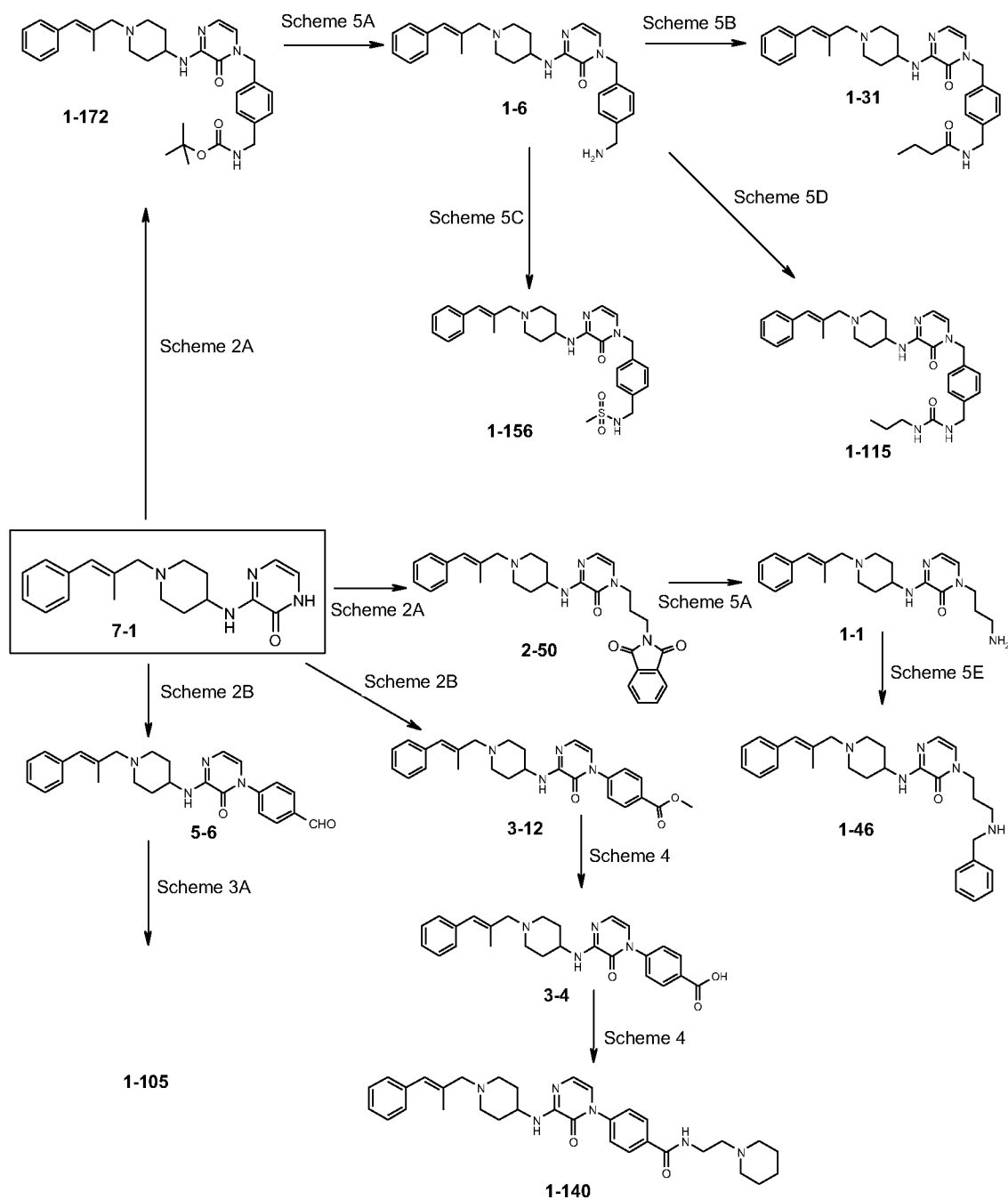
A8. Preparation of intermediate compound 8

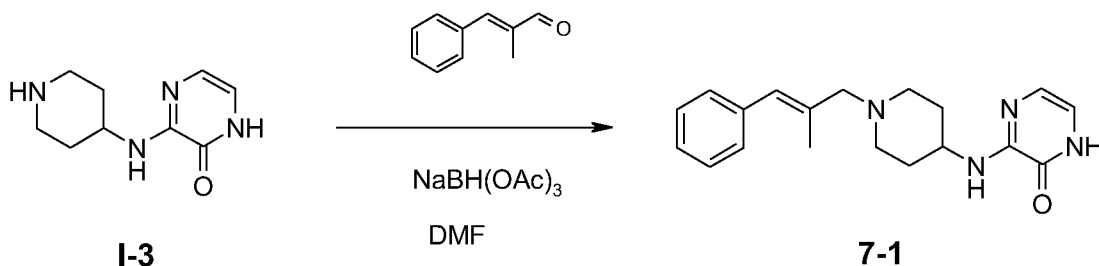
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A mixture of 1,4-dioxa-8-azaspiro[4.5]decane (6.7 g, 0.046 mol, 98 %), (2E)-2-methyl-3-phenyl-2-propenal (5.02 ml, 0.035 mol, 98 %) and sodium triacetoxyborohydride (10.02 g, 0.046 mol) in DCE (170 ml) was stirred at room temperature for 6 hours. The reaction mixture was treated with a 10 % NH_4Cl solution and extracted with DCM. The
 15 organic layer was dried over Na_2SO_4 , filtered and the solvent was evaporated. Yield: 12.79 g of intermediate compound **8** (quantitative, used as such without further purification).

B. Preparation of the final compounds

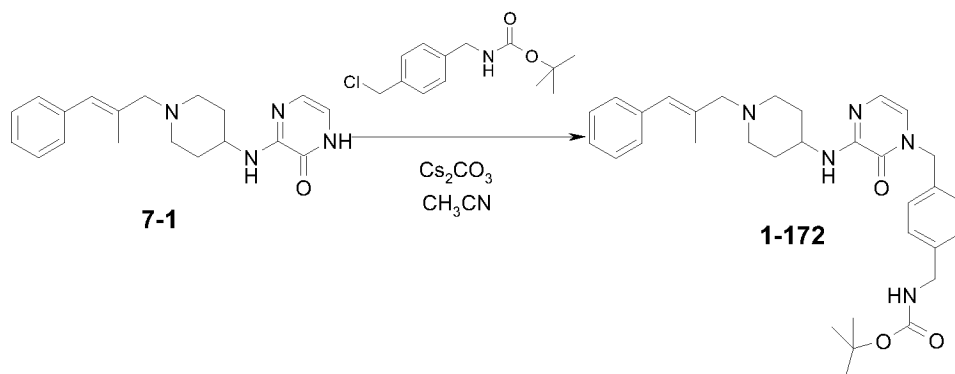
B1. Summary scheme 1



Preparation of final compound 7-1

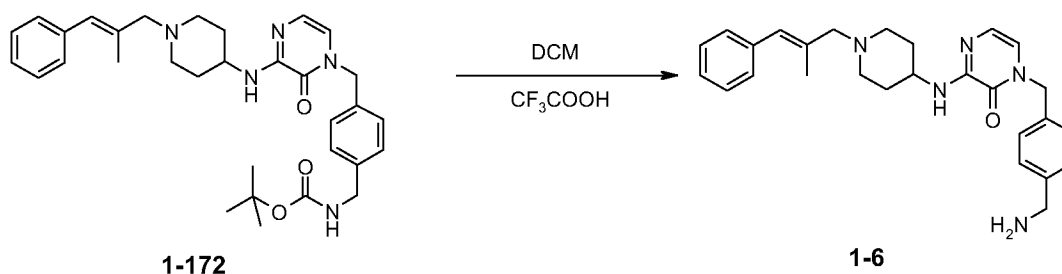
Intermediate compound **3** (2 g, 10.269 mmol) was dissolved in DMF (60 ml), then α -methylcinnamaldehyde (4.51 g, 30.87 mmol) and $\text{NaBH}(\text{OAc})_3$ (3.2 g, 15.45 mmol) was added. The reaction was stirred at room temperature for 16 hours. The solvent was removed, the product was dissolved in EtOAc, washed with NaHCO_3 and brine and dried with MgSO_4 . The solvent was evaporated till dryness and the product was purified by open chromatography using DCM/ CH_3OH 9/1 as eluent, yielding 3.2 g of the desired final compound **7-1** (96 %).

10

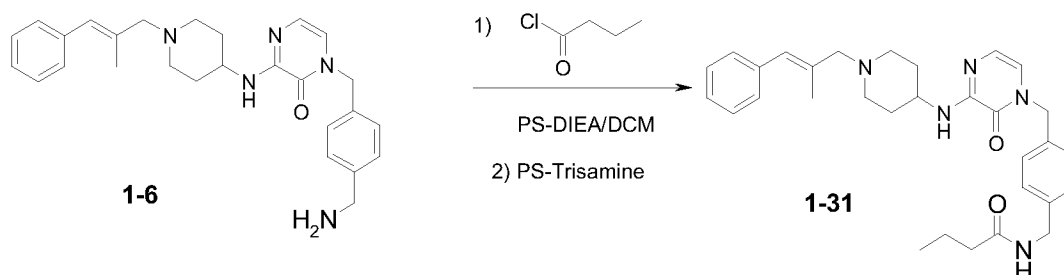
Preparation of final compound 1-172

Final compound **7-1** (2 g, 6.16 mmol), (4-tert-butoxyaminomethyl)-benzyl chloride (2.36 g, 9.24 mmol), and Cs_2CO_3 (7.6 g, 21.56 mmol) were suspended in CH_3CN (80 ml). The reaction was heated in the microwave at 130 °C for 20 minutes. The resin was filtered off, and the filtrate was concentrated under vacuum. The resulting crude was purified by HPLC yielding 2.84 g of the purified final compound **1-172** (85 %).

15

Preparation of final compound 1-6

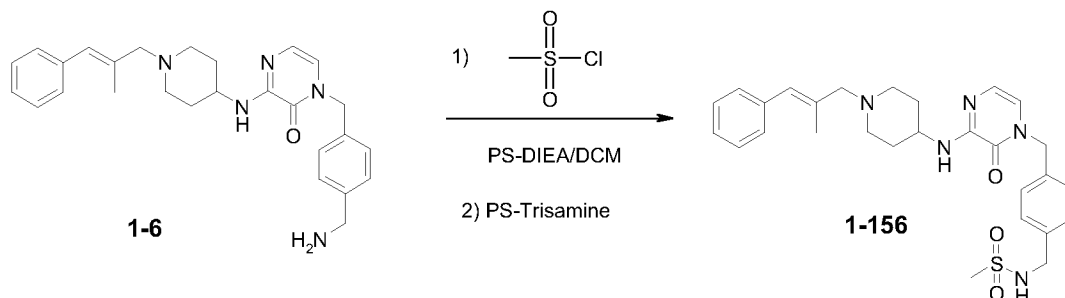
Final compound **1-172** (1.07 g, 1.96 mmol) was dissolved in DCM (25 ml), then TFA (25 ml) was added. The mixture was stirred at room temperature for 16 hours. The solvent was removed and the resulting crude was dissolved in EtOAc and washed with K_2CO_3 (aqueous saturated) and brine, and was then dried (MgSO_4). The organic layer was evaporated under vacuum yielding 773 mg of the final compound **1-6** (89 %).

Preparation of final compound 1-31

10

PS-DIEA (51.79 mg, 0.201 mmol) was suspended in DCM (4 ml), then compound **1-6** (30 mg, 0.067 mmol), and butyrylchloride (15.6 μl , 0.134 mmol) were added. The reaction mixture was stirred at room temperature for 3 hours, then PS-Trisamine (64.26 mg, 0.268 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. The resin was filtered off, washed with DCM and the solvent was concentrated under reduced pressure yielding 31.76 mg of the final compound **1-31** (65 %).

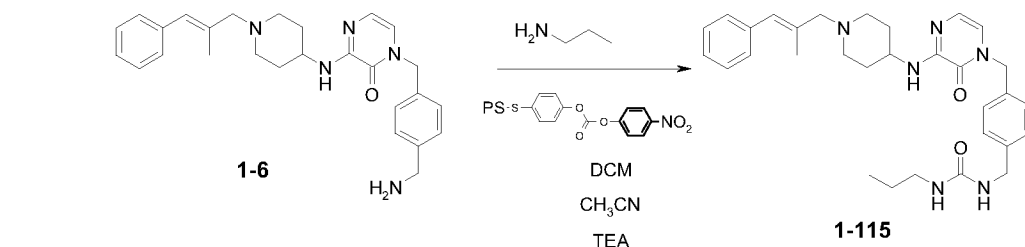
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Preparation of final compound 1-156

PS-DIEA (51.79 mg, 0.201 mmol) was suspended in DCM (4 ml), then compound **1-6** (30 mg, 0.067 mmol), and methanesulfonyl chloride (10.4 μl , 0.135 mmol) were added.

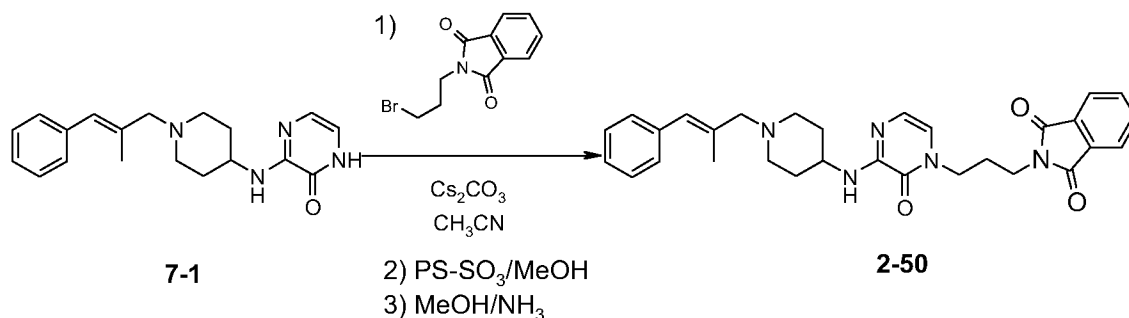
- 5 The reaction mixture was stirred at room temperature for 3 hours, then PS-Trisamine (64.74 mg, 0.270 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. The resin was filtered off, washed with DCM and the solvent was concentrated under reduced pressure yielding 25.5 mg of the final compound **1-156** (75 %).

10

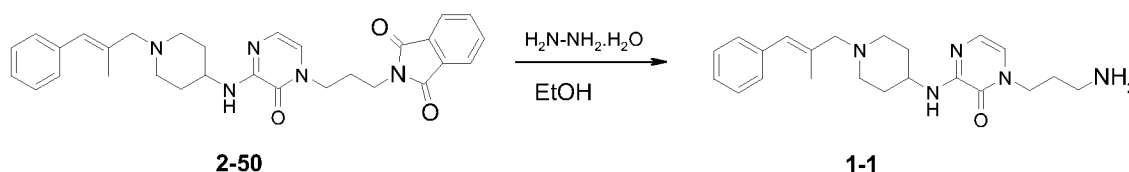
Preparation of final compound 1-115

PS-s- $\text{C}_6\text{H}_4\text{-O-CO-O-C}_6\text{H}_4\text{-NO}_2$, prepared according to Dressman, B.A.; Singh, U.; Kaldor, S.W. Tetrahedron Lett 1998, 39, 3631 (100 mg, 0.12 mmol) was suspended in DCM (4

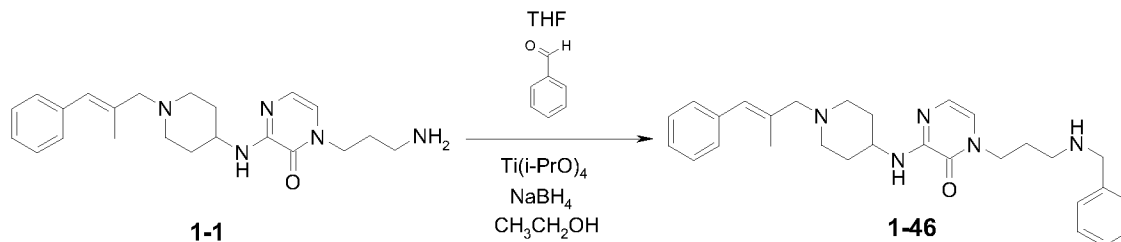
- 15 ml), and then propylamine (88.66 μl , 1.20 mmol) was added. The reaction was stirred at room temperature for 16 hours. The resin was filtered off, and washed with DCM, CH_3OH , THF and CH_3CN . The resin was suspended in CH_3CN (4 ml). Final compound **1-6** (30 mg, 0.067 mmol) and triethylamine (84 μl , 0.60 mmol) were added. The reaction was heated at 65 $^\circ\text{C}$ for 16 hours. The resin was filtered off, washed with CH_3CN ,
 20 DCM and CH_3OH , and the solvent was evaporated till dryness, to yield 32 mg of the final compound **1-115** (93 %).

Preparation of final compound 2-50

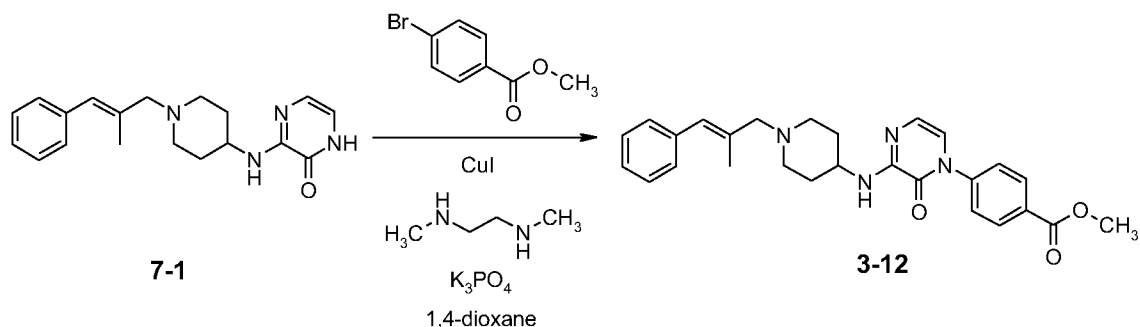
Final compound **7-1** (50 mg, 0.154 mmol), *N*-(3-bromopropyl)phthalimide (61.93 mg, 0.231 mmol), and Cs₂CO₃ (185 mg, 0.539 mmol) were suspended in CH₃CN (2 ml). The reaction was heated in a sealed tube for 16 hours at 110 °C. The reaction was filtered off, and the filtrate was concentrated under vacuum. The crude was dissolved in MeOH, then PS-SO₃ was added. The reaction was shaken at room temperature for 16 hours. The resin was filtered off, washed with MeOH and then suspended in MeOH/NH₃ 7N for 3 hours. The resin was filtered and the filtrate was concentrated under vacuum yielding 0.61 mg of the purified final compound **2-50** (77 %).

Preparation of final compound 1-1

Final compound **2-50** (300 mg, 0.586 mmol) and hydrazine monohydrate (0.172 ml, 3.51 mmol) were suspended in EtOH (9 ml). The reaction was heated in the microwave at 140 °C for 10 minutes. The solvent was concentrated under vacuum. The resulting crude was purified by HPLC yielding 111 mg of the purified final compound **1-1** (50 %).

Preparation of final compound 1-46

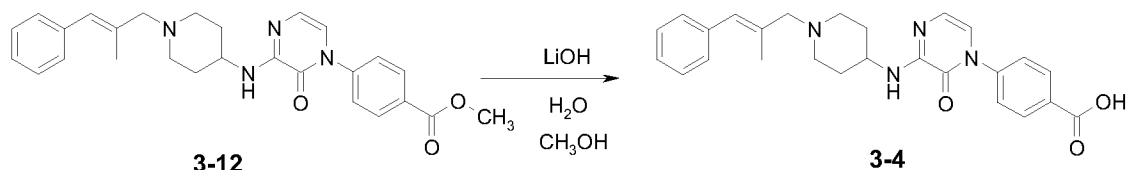
Final compound **1-1** (80 mg, 0.209 mmol) was dissolved in dry THF (3.2 ml). Benzaldehyde (32 μl , 0.314 mmol) and $\text{Ti}(\text{i-PrO})_4$ (119.42 mg, 0.418 mmol) were added. The reaction was stirred at room temperature for 16 hours. Then NaBH_4 (24.5 mg, 0.629 mmol) and $\text{CH}_3\text{CH}_2\text{OH}$ (1.1 ml) were added, stirring was continued at room temperature for 8 hours. Then NH_3 (aqueous solution) was added, a precipitate appeared which was filtered over celite and washed with Et_2O . The organic layer was separated and the remaining aqueous layer was extracted with Et_2O . The combined organic layers were treated with HCl (2N). The aqueous phase was then treated with NaOH (2N) to pH 10-12, and washed with EtOAc (3 x 10ml). The organic layer was washed with brine, dried (MgSO_4) and evaporated till dryness. The resulting crude was purified by open flash chromatography using DCM/ $(\text{CH}_3\text{OH}/\text{NH}_3)$ 9:1 to yield 40 mg of the purified final compound **1-46** (40 %).

Preparation of final compound 3-12

Final compound **7-1** (1 g, 2.93 mmol), 4-bromobenzoic acid methyl ester (756.7 mg, 3.51 mmol) and CuI (11.6 mg, 0.586 mmol) were suspended in 1,4-dioxane (20 ml) and stirred at room temperature for 1 minute. Then *N,N*'-dimethyl-1,2-ethanediamine (124 μl , 1.17 mmol) was added and the mixture was stirred for 5 minutes more. Finally K_3PO_4 (1.24 g, 5.86 mmol) was added, and the mixture was heated at 110 $^\circ\text{C}$ for 16

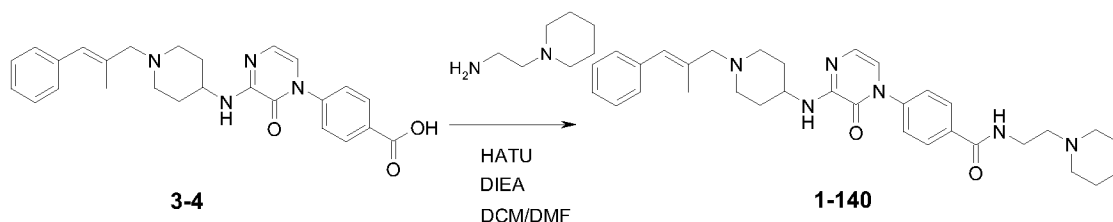
hours in a sealed tube. The crude product was filtered over celite, washed with DCM and the solvent was concentrated under vacuum. The resulting crude was washed with H₂O, brine and dried (MgSO₄). The solvent was evaporated under reduced pressure and the resulting crude was purified by open chromatography in DCM/(CH₃OH/NH₃) 9.5/0.5 to yield 1.12 g of the final compound **3-12** (83 %).

Preparation of final compound 3-4

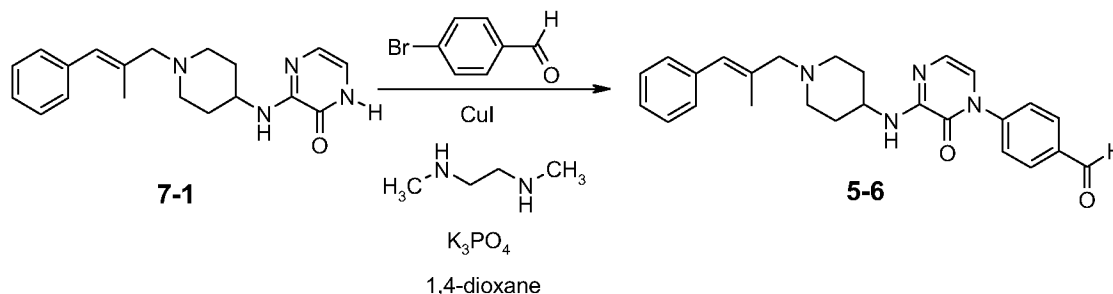


Final compound **3-12** (600 mg, 1.30 mmol), was suspended in CH₃OH (12 ml). Then LiOH (62.64 mg, 2.61 mmol) and H₂O (2.4 ml) were added and stirred for 16 hours at room temperature. The reaction was neutralized with HCl 10 %, the solvent was removed, and the product was triturated with Et₂O yielding 578 mg of the purified final compound **3-4** (quantitative).

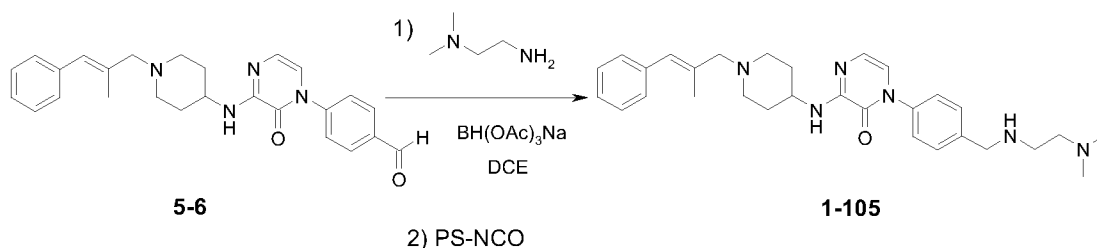
Preparation of final compound 1-140



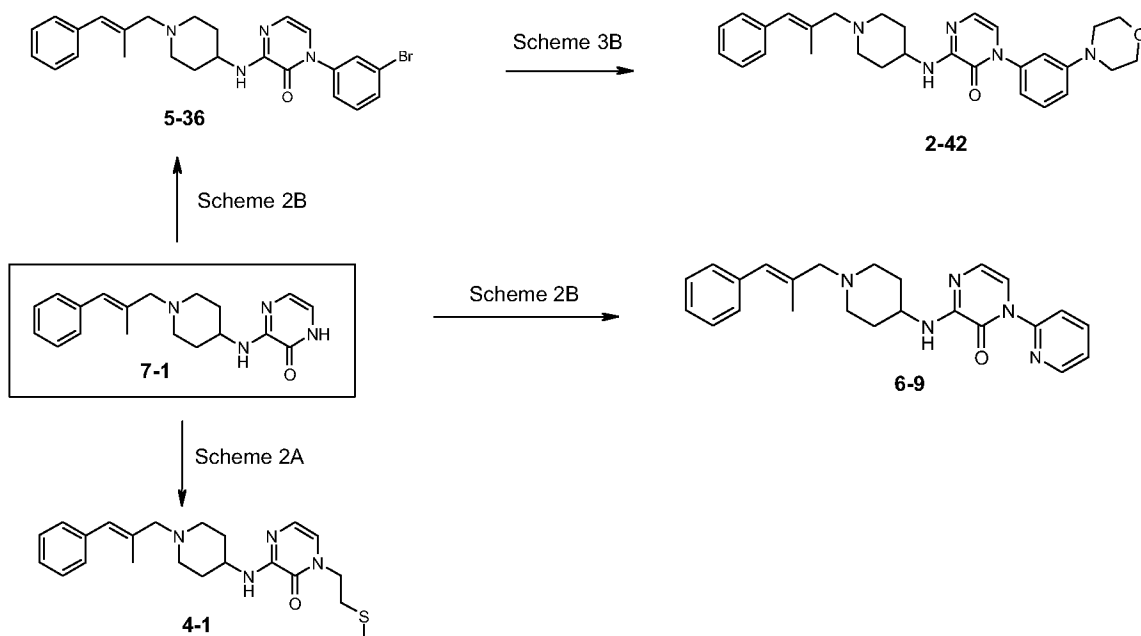
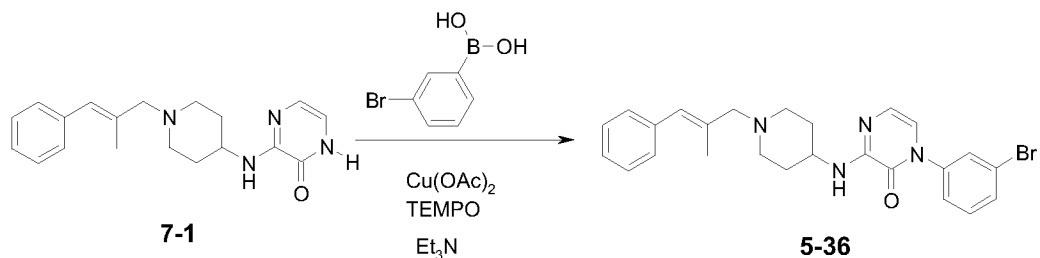
Final compound **3-4** (25 mg, 0.049 mmol) and HATU (22.3 mg, 0.058 mmol) were dissolved in DCM/DMF (2.58 ml, 2:1). Then 1-(2-aminoethyl)piperidine (6.4 μ l, 0.045 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. The solvent was removed under vacuum. The crude was dissolved in DCM, washed with NH₄Cl, and brine, then dried (MgSO₄). The solvent was concentrated under reduced pressure and the resulting crude purified by open chromatography in SiO₂ with DCM/(CH₃OH/NH₃) 9.5/0.5 to yield 16.2 mg of final compound **1-140** (60 %).

Preparation of final compound 5-6

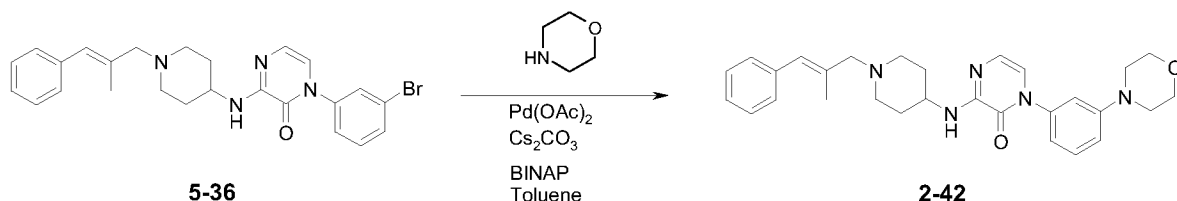
Final compound **7-1** (1 g, 2,93 mmol), 4-bromobenzaldehyde (650 mg, 3,51 mmol) and CuI (111 mg, 0,586 mmol) were suspended in 1,4-dioxane (20 ml). The reaction was stirred for 1 minute, and then *N,N*-dimethyl-1,2-ethanediamine (124 μ l, 1,17 mmol) was added while stirring for 5 minutes more. Finally K_3PO_4 (1,24 g, 5,86 mmol) was added and the reaction mixtures was heated in a sealed tube at 110 °C for 16 hours. The reaction was filtered over celite, washed with DCM and the solvent was evaporated till dryness. The crude compound was dissolved in EtOAc, washed with H_2O and brine, and dried ($MgSO_4$). The solvent was concentrated under vacuum, and the resulting crude purified by HPLC to yield 627 mg of the final compound **5-6** (50 %).

Preparation of final compound 1-105

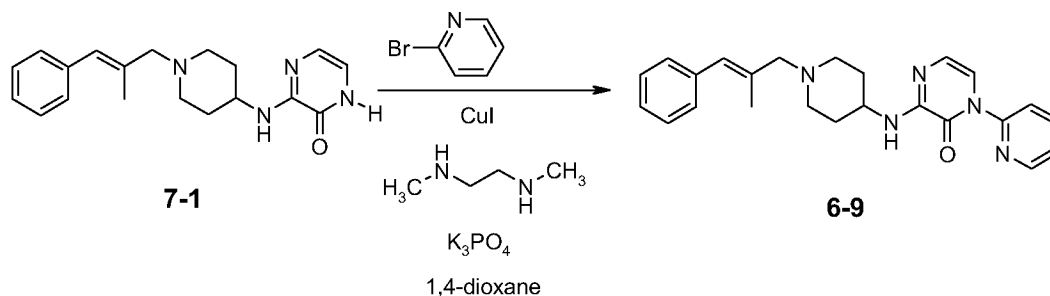
Final compound **5-6** (25 mg, 0,058 mmol), *N,N*-dimethylethylenediamine (8.35 μ l, 0.075 mmol) and $BH(OAc)_3Na$ (65.7 mg, 0,138 mmol) were suspended in DCE (3 ml). The reaction was stirred at room temperature for 16 hours. Then PS-NCO (78.43 mg, 0.12 mmol) was added. The reaction was stirred at room temperature for 4h. The resin was filtered off, washed with DCM and the solvent was evaporated till dryness yielding 18.8 mg of the final compound **1-105** (60 %).

B2. Summary scheme 2Preparation of final compound 5-36

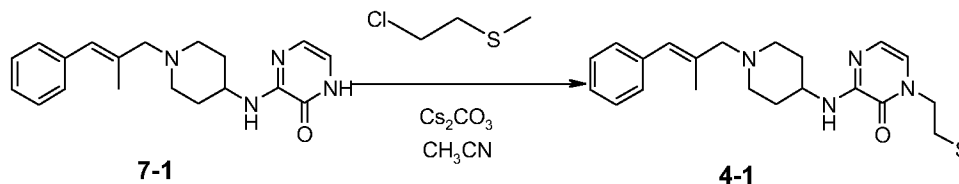
- 5 To a mixture of compound **7-1** (2 g, 6.16 mmol), 3-bromophenylboronic acid (2.5 g, 12.32 mmol) and copper acetate (0.115 g, 0.62 mmol) in DCM (20 ml), molecular sieves (0.7 g) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1.05 g, 6.77 mmol) were added. Finally, triethylamine (1.8 ml, 12.5 mmol) was also added to the mixture and the reaction was stirred at room temperature for 55 hours. The crude was filtered
- 10 off and the solvent was evaporated under reduced pressure. The residue was purified through a SCX cartridge, eluting twice with DCM and with methanol, and finally with saturated MeOH/NH_3 yielding after evaporation of the solvents 2.06 g of the final compound **5-36** (70 %).

Preparation of final compound 2-42

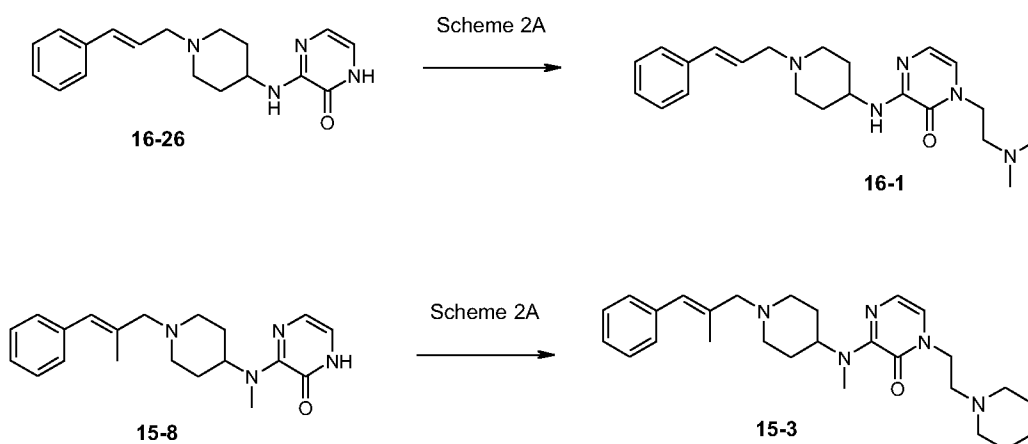
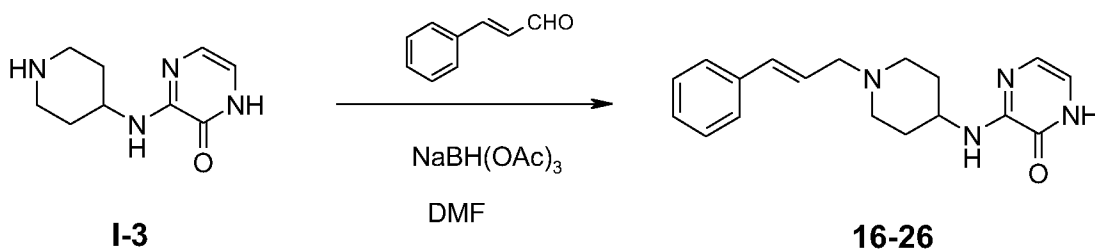
A mixture of final compound **5-36** (22 mg, 0.046 mmol), morpholine (4.8 mg, 0.055 mmol), palladium acetate (1 mg, 0.0025 mmol), cesium carbonate (22 mg, 0.0642 mmol) and BINAP (4.6 mg, 0.0075 mmol) in Toluene (3 ml) was stirred at reflux for 24 hours. The crude was treated with "resin-isocyanate", the mixture was filtered off through celite and the solvent was evaporated under reduced pressure. The residue was purified through a SCX cartridge, eluting twice with DCM and with methanol, and finally with saturated MeOH/NH₃ yielding after evaporation of the solvents 10 mg of the final compound **2-42** (45 %).

Preparation of final compound 6-9

Final compound **7-1** (0.3 g, 0.92 mmol), 2-bromopyridine (0.1 ml, 1.1 mmol) and CuI (35.2 mg, 0.18 mmol) were suspended in 1,4-dioxane (5 ml). The reaction was stirred for 1 minute, and then *N,N'*-dimethyl-1,2-ethanediamine (35 μ l, 0.37 mmol) was added while stirring for 5 minutes more. Finally K₃PO₄ (0.39 g, 1.85 mmol) was added and the reaction mixture was heated in a sealed tube at 110 °C for 16 hours. The reaction was filtered over celite, washed with DCM and the solvent was evaporated till dryness. The crude compound was dissolved in EtOAc, washed with H₂O and brine, and dried (MgSO₄). The solvent was concentrated under vacuum, and the resulting crude purified by open column chromatography using SiO₂ and DCM/(CH₃OH/NH₃) 9.7/0.3 as eluent, yielding 0.24 g of the final compound **6-9** (65 %).

Preparation of final compound 4-1

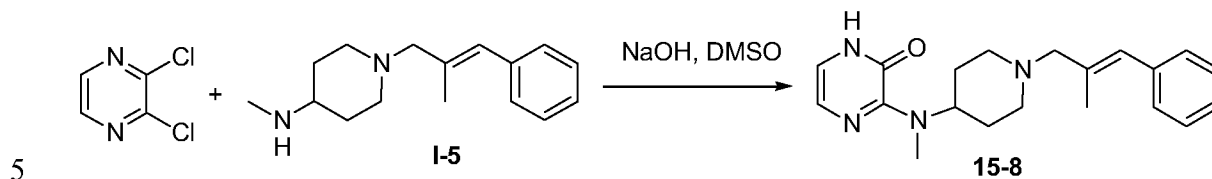
Final compound **7-1** (50 mg, 0.154 mmol), 2-chloroethylmethyl sulfide (25.5 mg, 0.231 mmol), and Cs_2CO_3 (0.185 g, 0.54 mmol) were suspended in CH_3CN (5 ml). The reaction mixture was stirred and heated at 90 °C for 16 hours. The mixture was filtered off through celite and the filtrate was concentrated under vacuum. The resulting crude was purified by HPLC yielding 28 mg of the purified final compound **4-1** (45 %).

B3. Summary scheme 3Preparation of final compound 16-26

Intermediate compound **3** (1.5 g, 7.72 mmol) was dissolved in DMF (30 ml), then trans-cinnamaldehyde (2.04 g, 15.44 mmol) and $\text{NaBH}(\text{OAc})_3$ (2.45 g, 11.58 mmol) were added. The reaction mixture was stirred at room temperature for 16 hours. The solvent was removed under vacuum and the residue dissolved in EtOAc, washed with NaHCO_3 and brine and dried over MgSO_4 . The solvent was evaporated till dryness and the

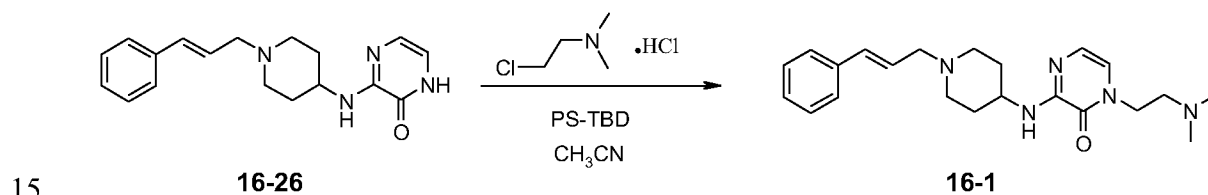
product was purified by recrystallization (Et₂O) to give 1.3 g of the desired final compound **16-26** as a white solid. Yield 54 %.

Preparation of final compound 15-8

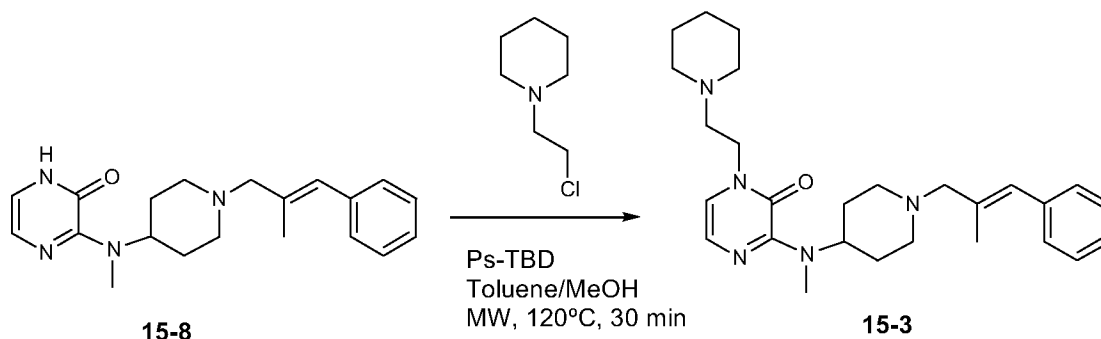


A mixture of 2,3-dichloropyrazine (0.78 g, 3.2 mmol), intermediate **5** (0.5 g 3.35 mmol) and NaOH (1 g, 7.46 mmol) was heated in a sealed tube at 150 °C for 4 hours. To this crude, a solution 0.8 ml of DMSO/NaOH(4M) 1:1 was added. The crude was heated at 150 °C for 5 hours. After cooling the reaction was treated with water (5 ml) and extracted with DCM (3x 5 mL). The organic phase was evaporated and the residue was purified with DCM/MeOH 9:1 to obtain 0.8 g (80 %) of final compound **15-8**.

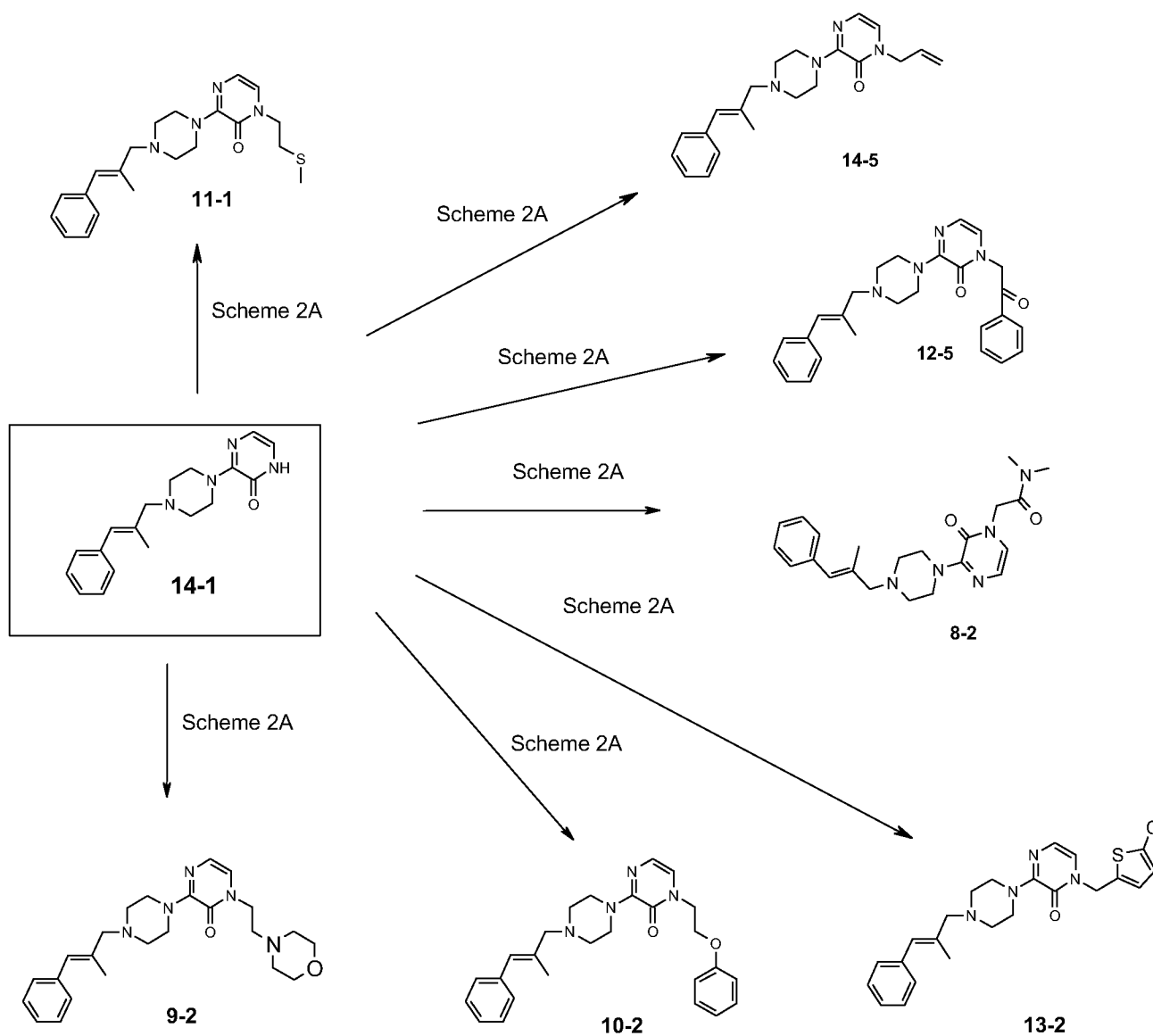
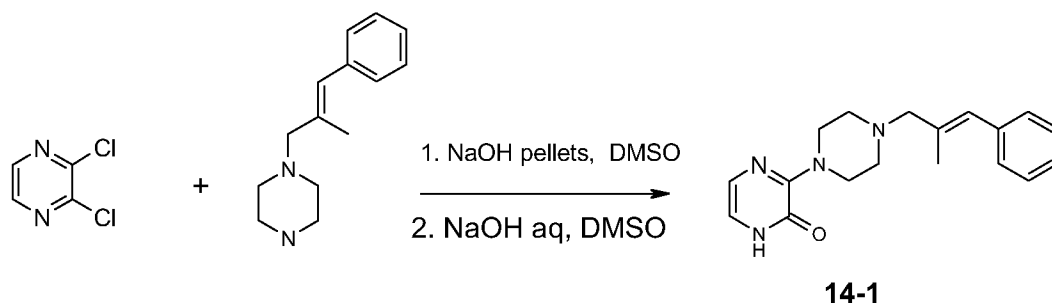
Preparation of final compound 16-1



Final compound **16-26** (23 mg, 0.073 mmol), 2-dimethylaminoethyl chloride hydrochloride (0.22 mmol), and PS-TBD (76 mg, 0.22 mmol) were suspended in CH₃CN (2 ml). The reaction was heated in the microwave at 120 °C for 20 minutes. The resin was filtered off, and the filtrate was concentrated under vacuum. The resulting crude was purified by HPLC yielding 0.024 g of the purified final compound **16-1** (85 %).

Preparation of final compound 15-3

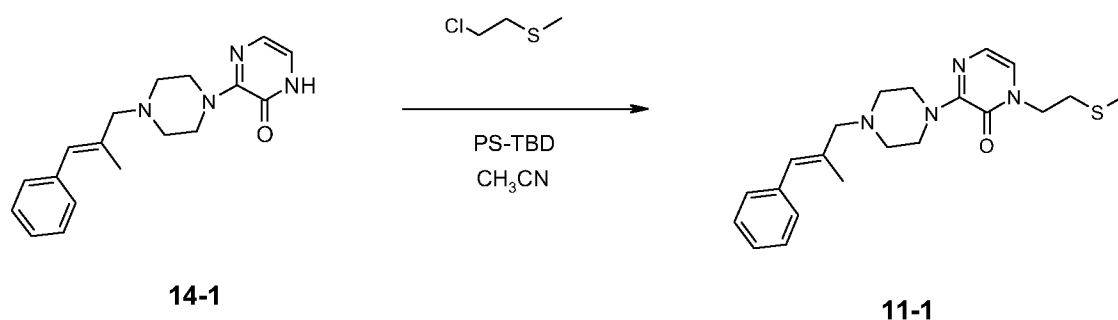
A mixture of final compound **15-8** (0.025 g 0.06502 mmol), 2-chloroethylpiperidine (0.19 g, 1.3 mmol), resin Ps-TBD (0.070 g, 0.196 mmol) in a mixture of 3 mL of toluene/MeOH 1:1 was heated under microwave irradiation at 120 °C for 30 min. The crude was filtered and the organic phase was evaporated to dryness. The residue was purified with DCM/MeOH 9:1 to obtain 0.019 g (65 %) of final compound **15-3** as an oil that precipitated in Et₂O.

B4. Summary scheme 4Preparation of final compound 14-1

2,3-Dichloropyrazine (448 mg, 3 mmol) and cinnamylpiperazine (CAS 152960-46-8, 2.9 mmol) were dissolved in DMSO (0.400 ml). Then NaOH pellets (1 g, 25 mmol) were added. The reaction was stirred at 150 °C under microwave irradiation for 0.5 hours.

Then 0.4 ml of NaOH 4 M and 0.4 ml of DMSO were added, heating at 150 °C in microwave for 0.5 hours more. The mixture was dissolved in AcOEt, washed with H₂O and brine, dried with MgSO₄ and evaporated under vacuum, yielding 650 mg of the desired final compound **14-1** (70 %).

Preparation of final compound 11-1

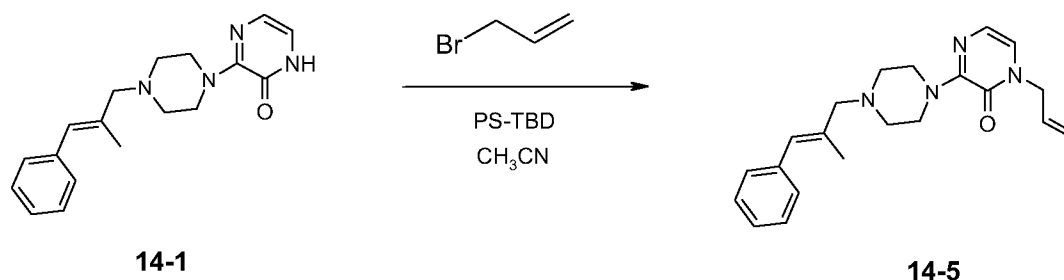


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Final compound **14-1** (31 mg, 0.1 mmol), 2-chloroethylmethyl sulfide (0.2 mmol), and PS-TBD (100 mg, 0.3 mmol) were suspended in CH₃CN (2 ml). The reaction was heated in the microwave at 120 °C for 20 minutes. The resin was filtered off, and the filtrate was concentrated under vacuum. The resulting crude was purified by HPLC yielding 0.015 g of the purified final compound **11-1** (40 %).

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Preparation of final compound 14-5

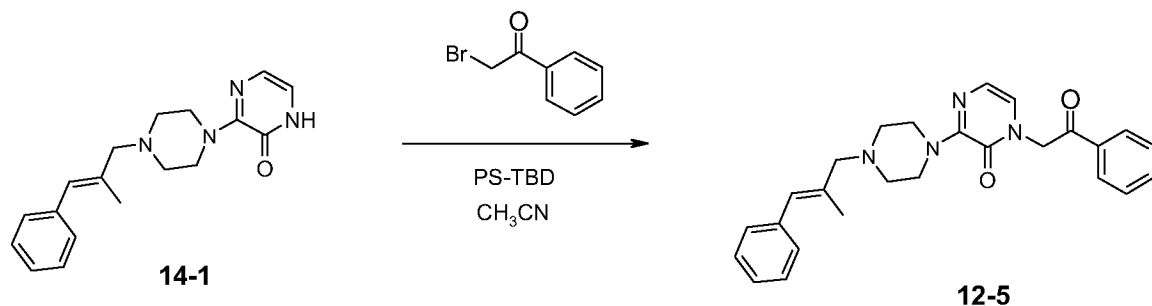


20

Final compound **14-1** (31 mg, 0.1 mmol), allyl bromide (0.2 mmol), and PS-TBD (100 mg, 0.3 mmol) were suspended in CH₃CN (2 ml). The reaction was heated in the microwave at 120 °C for 20 minutes. The resin was filtered off, and the filtrate was concentrated under vacuum. The resulting crude was purified by HPLC yielding 0.028 g of

the purified final compound **14-5** (80 %).

Preparation of final compound 12-5

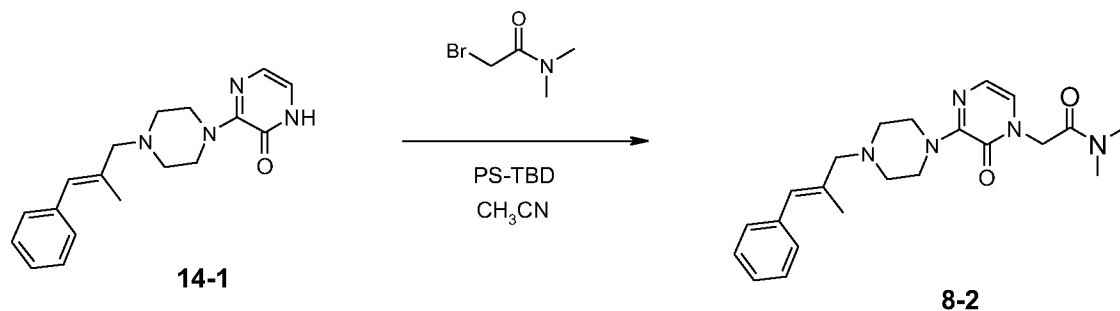


5

Compound **14-1** (31 mg, 0.1 mmol), 2-bromoacetophenone (0.2 mmol), and PS-TBD (100 mg, 0.3 mmol) were suspended in CH₃CN (2 ml). The reaction was heated in the microwave at 120 °C for 20 minutes. The resin was filtered off, and the filtrate was concentrated under vacuum. The resulting crude was purified by HPLC yielding 0.032 g of the purified final compound **12-5** (75 %).

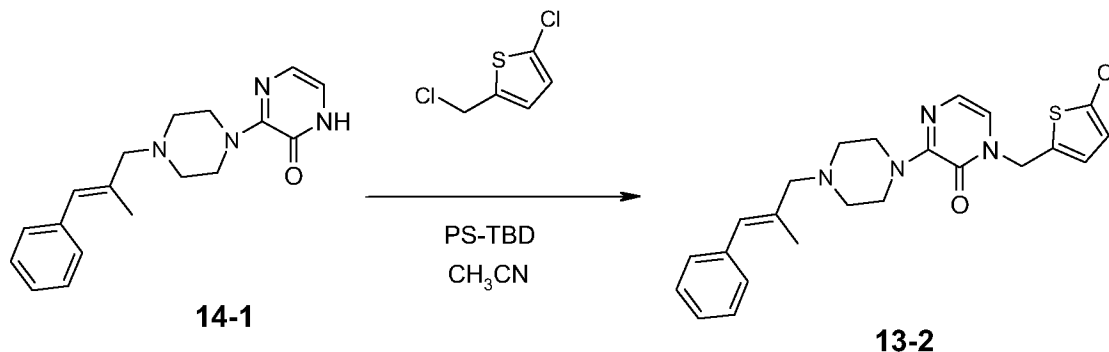
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Preparation of final compound 8-2

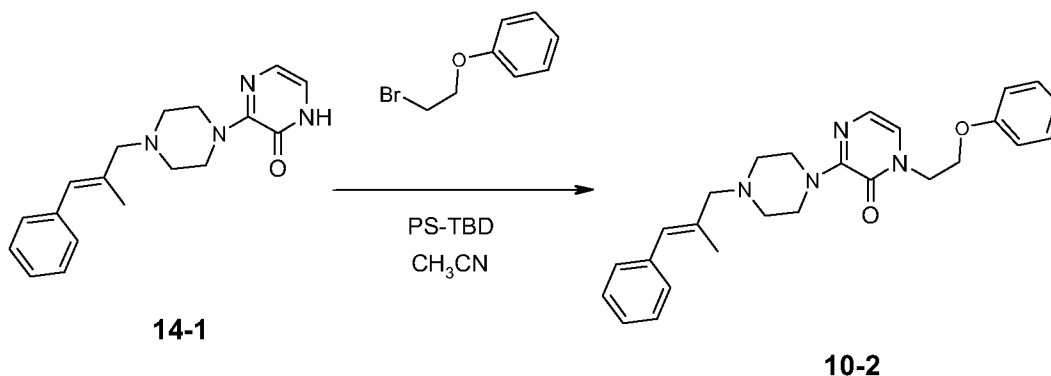


Compound **14-1** (31 mg, 0.1 mmol), 2-bromo-N,N-dimethylacetamide (0.2 mmol), and PS-TBD (100 mg, 0.3 mmol) were suspended in CH₃CN (2 ml). The reaction was heated in the microwave at 120 °C for 20 minutes. The resin was filtered off, and the filtrate was concentrated under vacuum. The resulting crude was purified by HPLC yielding 0.033 g of the purified final compound **8-2** (85 %).

20

Preparation of final compound 13-2

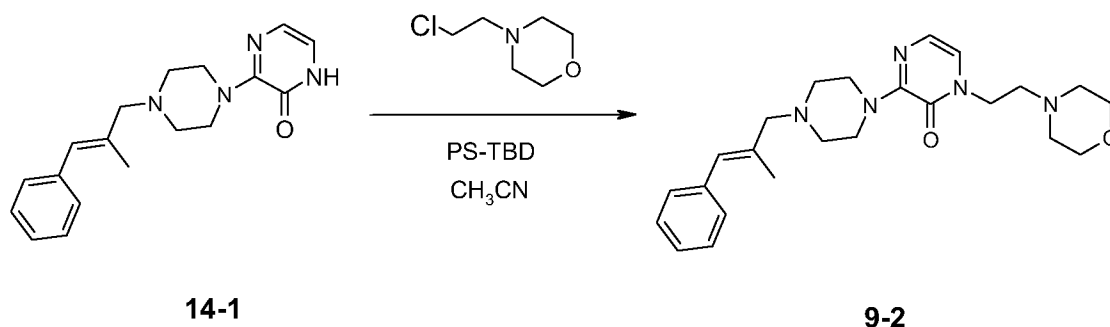
Compound **14-1** (31 mg, 0.1 mmol), 2-chloro-5-(chloromethyl) thiophene (0.2 mmol), and PS-TBD (100 mg, 0.3 mmol) were suspended in CH₃CN (2 ml). The reaction was heated in the microwave at 120 °C for 20 minutes. The resin was filtered off, and the filtrate was concentrated under vacuum. The resulting crude was purified by HPLC yielding 0.029 g of the purified final compound **13-2** (65 %).

Preparation of final compound 10-2

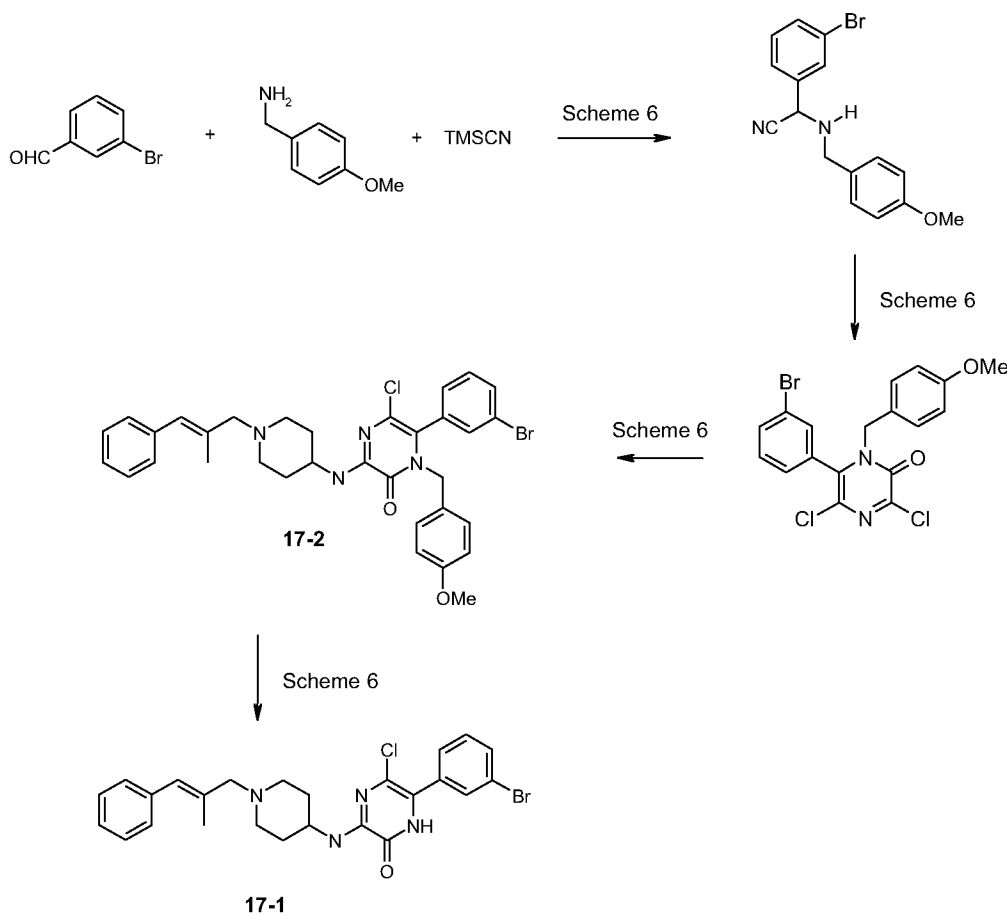
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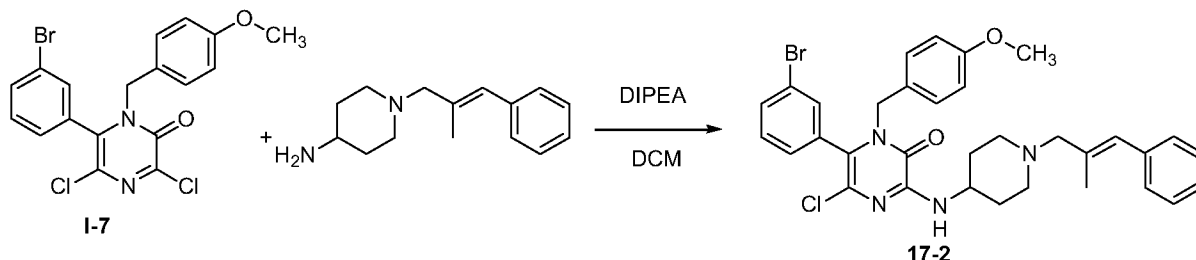
Compound **14-1** (31 mg, 0.1 mmol), beta-bromo phenetole (0.2 mmol), and PS-TBD (100 mg, 0.3 mmol) were suspended in CH₃CN (2 ml). The reaction was heated in the microwave at 120 °C for 20 minutes. The resin was filtered off, and the filtrate was concentrated under vacuum. The resulting crude was purified by HPLC yielding 0.024 g of the purified final compound **10-2** (55 %).

15

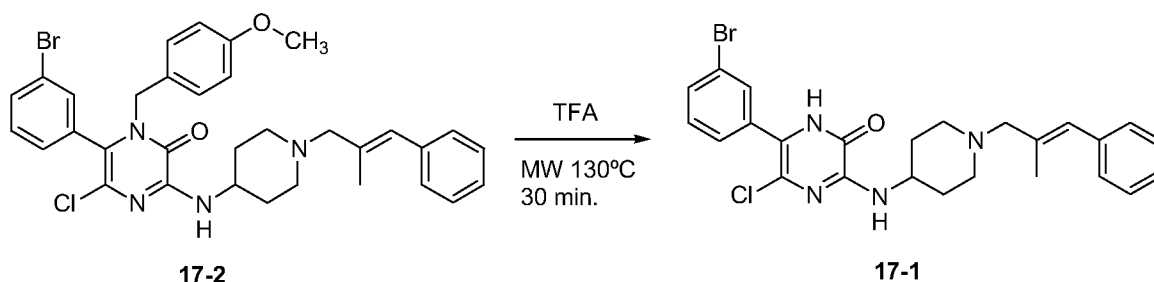
Preparation of final compound 9-2

Compound **14-1** (31 mg, 0.1 mmol), 4-(2-chloroethyl) morpholine hydrochloride (0.2 mmol), and PS-TBD (100 mg, 0.3 mmol) were suspended in CH₃CN (2 ml). The reaction was heated in the microwave at 120 °C for 20 minutes. The resin was filtered off, and the filtrate was concentrated under vacuum. The resulting crude was purified by HPLC yielding 0.021 g of the purified final compound **9-2** (50 %).

B5. Summary scheme 5

Preparation of final compound 17-2

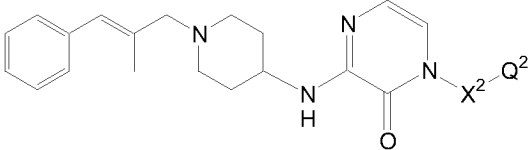
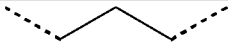
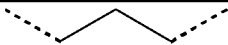
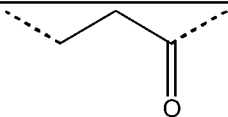
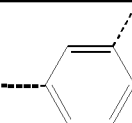
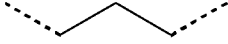
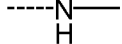
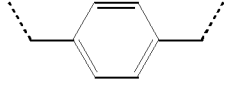
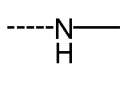
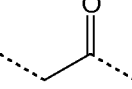
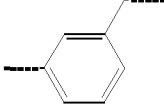
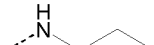
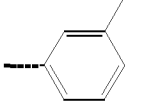
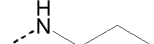
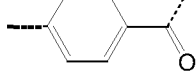
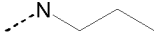
To a mixture of intermediate compound **7** (1 g, 2.27 mmol) and 4-amino-1-(2-methyl-
 5 cinnamyl)piperidine (0.57 g, 2.49 mmol) in DCE (30 mL), DIPEA (0.46 g, 4.6 mmol) was added. The reaction was stirred for 20 days at room temperature. The crude was evaporated to dryness, and purified by column chromatography (DCM/MeOH 9:1) to yield 0.45g of final compound **17-2** as a yellow oil (30%).

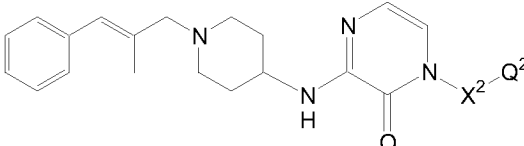
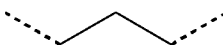
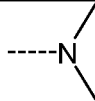
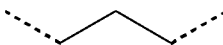
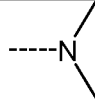
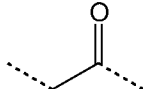
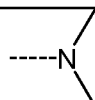
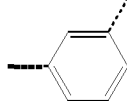
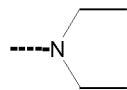
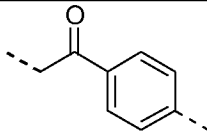
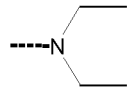
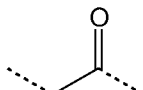
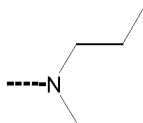
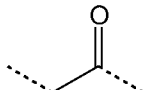
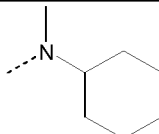
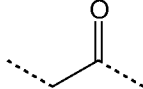
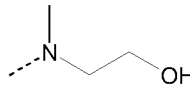
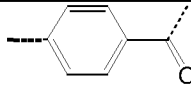
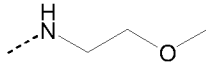
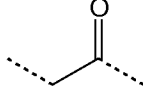
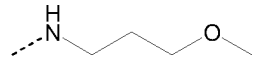
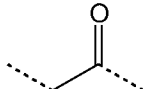
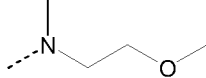
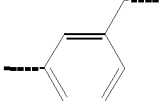
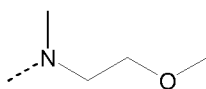
10 Preparation of final compound 17-1

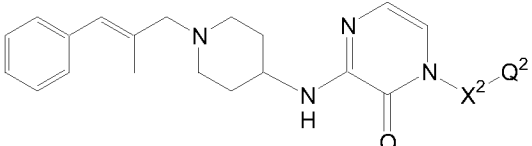
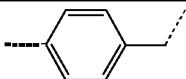
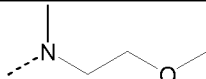
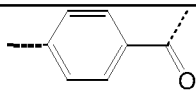
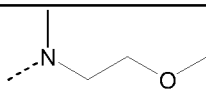
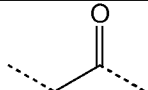
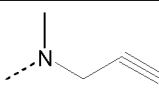
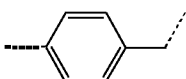
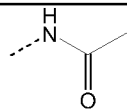
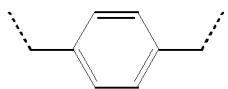
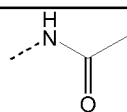
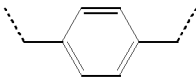
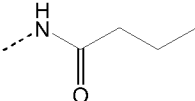
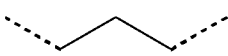
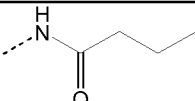
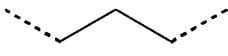
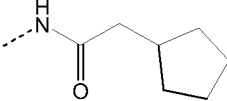
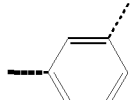
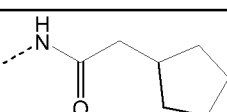
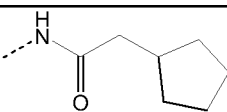
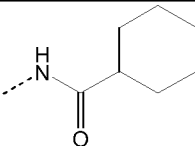
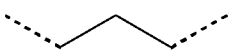
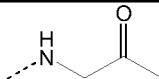
A solution of final compound **17-2** (0.02 g, 0.0315 mmol) in TFA (1 mL), was heated under microwave irradiation at 130 °C for 30 minutes. The TFA was evaporated to
 15 dryness and the crude was purified by column chromatography (DCM/MeOH 9:1) to yield 10 mg of the final compound **17-1** as an oil (63 %).

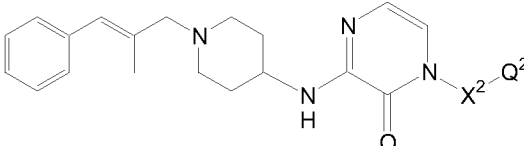
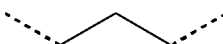
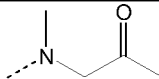
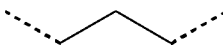
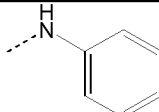
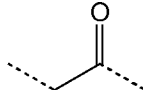
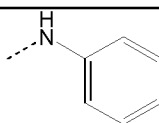
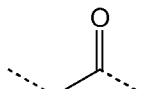
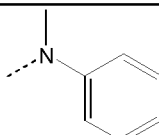
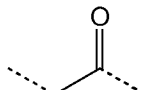
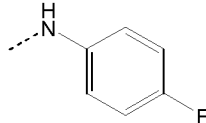
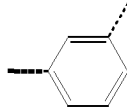
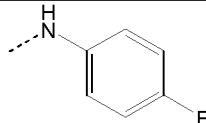
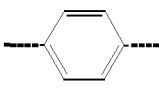
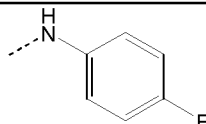
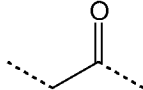
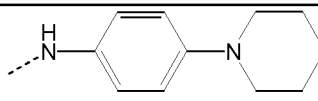
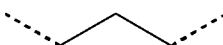
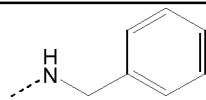
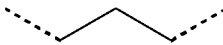
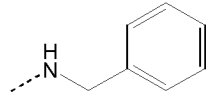
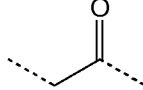
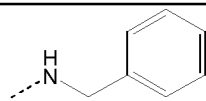
The following compounds were prepared according to the above examples, schemes and procedures.

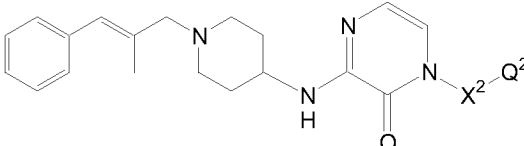
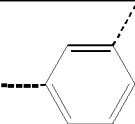
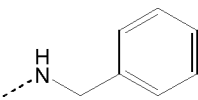
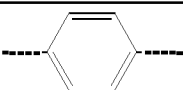
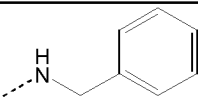
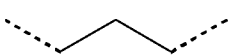
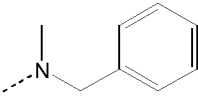
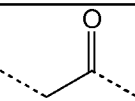
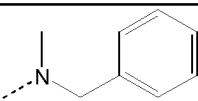
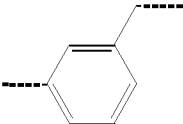
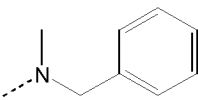
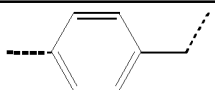
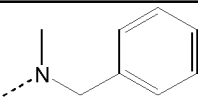
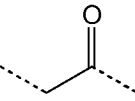
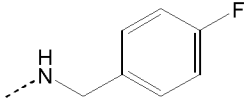
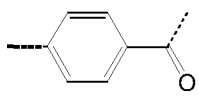
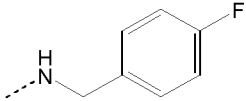
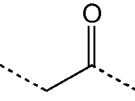
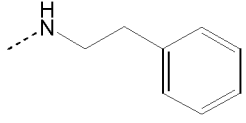
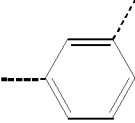
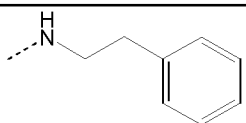
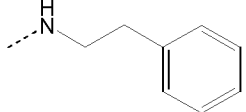
Table 1: List of compounds (with amino-piperidinyllinker) for which Q is a moiety of formula $-NR^1R^2$.

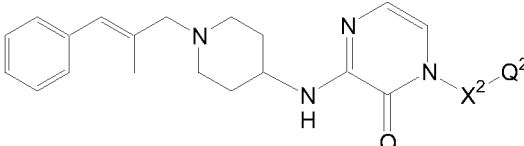
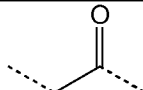
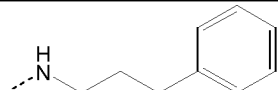
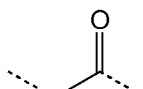
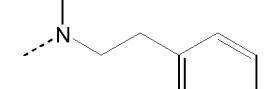
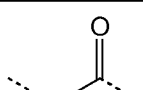
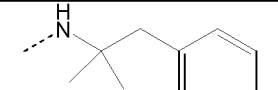
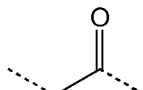
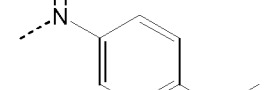
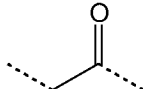
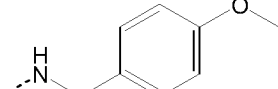
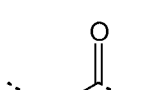
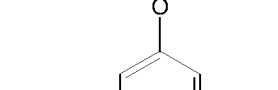
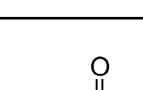
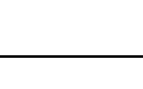
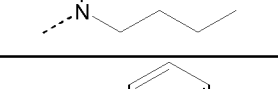
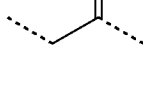
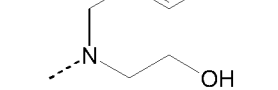
			
Co.Nr.	Scheme	$-X^2-$	$-Q^2$
1-1	5A		$-NH_2$
1-2	5A		$-NH_2$
1-3	4		$-NH_2$
1-4	5A		$-NH_2$
1-5	5A		$-NH_2$
1-6	5A		$-NH_2$
1-7	5A		$-NH_2$
1-8	5E		
1-9	5E		
1-10	4		
1-11	3A		
1-12	3A		
1-13	4		

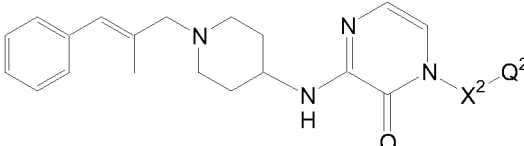
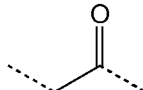
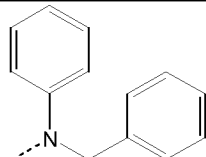
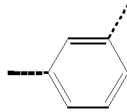
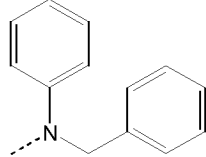
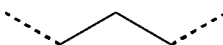
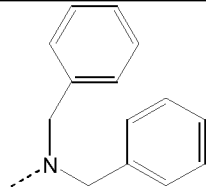
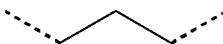
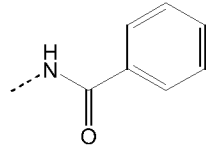
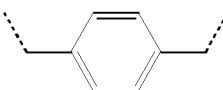
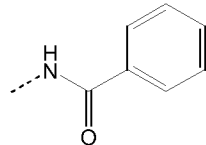
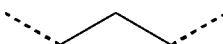
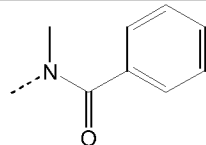
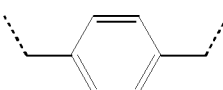
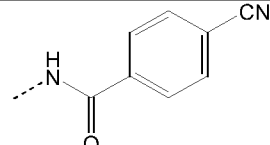
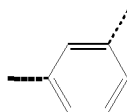
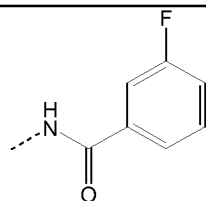
			
Co.Nr.	Scheme	--X²--	--Q²
1-14	2A		
1-15	2A		
1-16	2A		
1-17	3B		
1-18	2A		
1-19	4		
1-20	4		
1-21	4		
1-22	4		
1-23	4		
1-24	4		
1-25	3A		

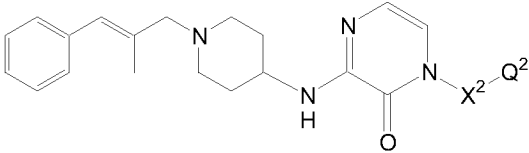
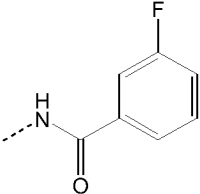
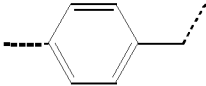
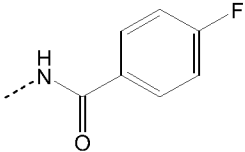
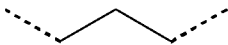
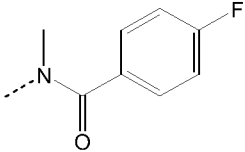
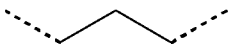
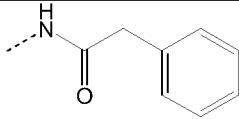
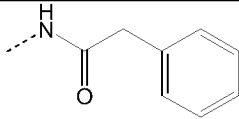
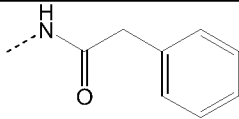
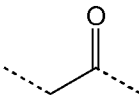
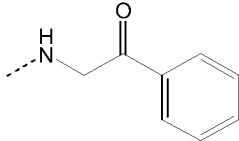
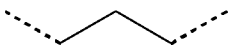
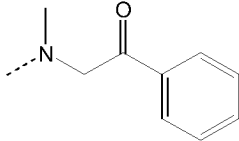
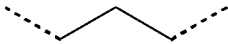
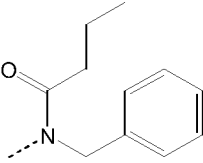
			
Co.Nr.	Scheme	--X²--	--Q²
1-26	3A		
1-27	4		
1-28	4		
1-29	5B		
1-30	5B		
1-31	5B		
1-32	5B		
1-33	5B		
1-34	5B		
1-35	5B		
1-36	5B		
1-37	5E		

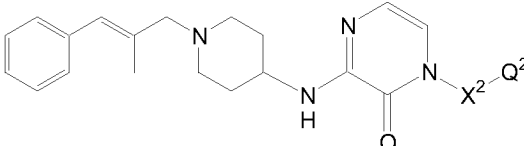
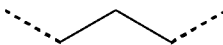
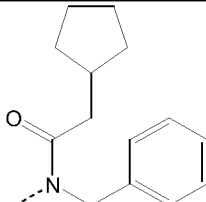
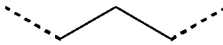
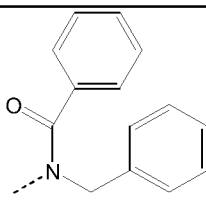
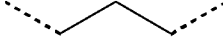
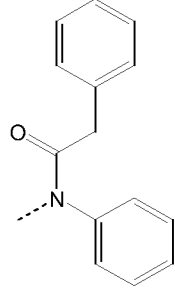
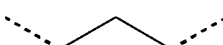
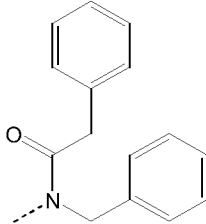
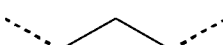
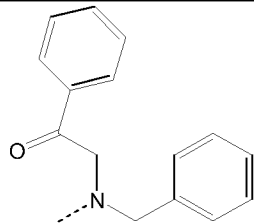
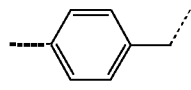
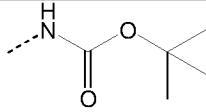
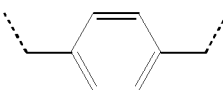
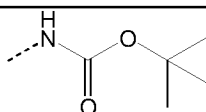
			
Co.Nr.	Scheme	--X²--	--Q²
1-38	5E		
1-39	2A		
1-40	4		
1-41	4		
1-42	4		
1-43	3B		
1-44	3B		
1-45	4		
1-46	5E		
1-47	5E		
1-48	4		

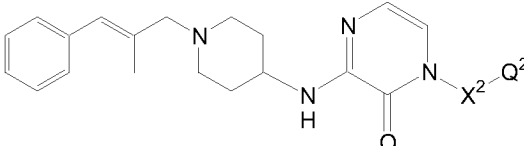
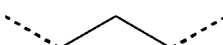
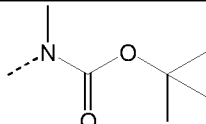
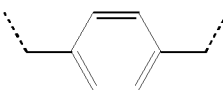
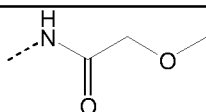
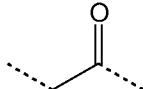
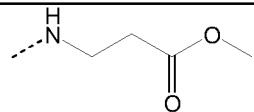
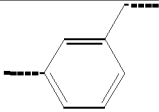
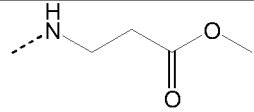
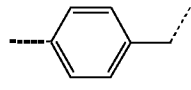
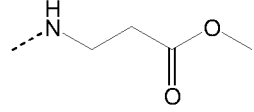
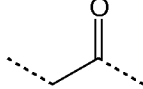
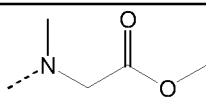
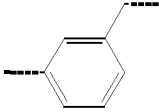
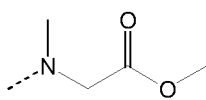
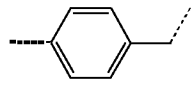
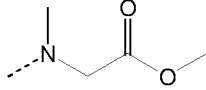
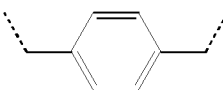
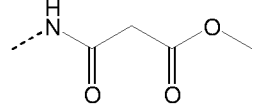
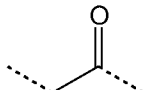
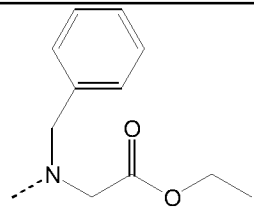
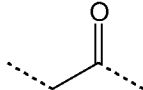
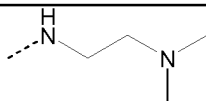
			
Co.Nr.	Scheme	--X²--	--Q²
1-49	3B		
1-50	3B		
1-51	5E		
1-52	4		
1-53	3A		
1-54	3A		
1-55	4		
1-56	4		
1-57	4		
1-58	3B		
1-59	3B		

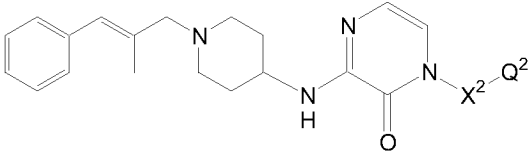
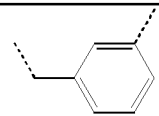
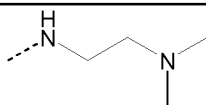
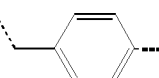
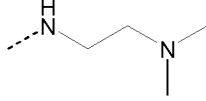
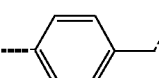
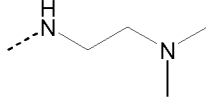
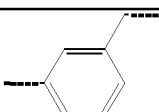
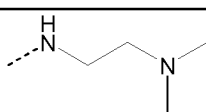
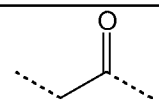
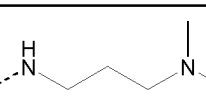
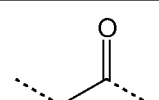
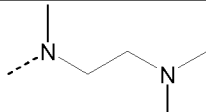
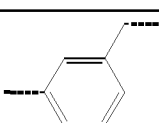
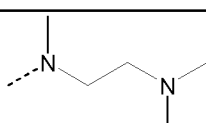
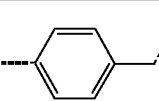
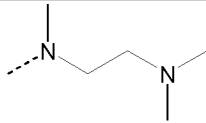
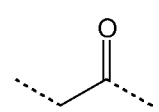
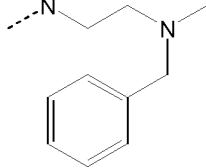
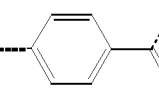
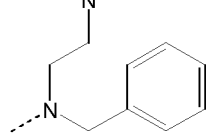
			
Co.Nr.	Scheme	--X²--	--Q²
1-60	4		
1-61	4		
1-62	4		
1-63	4		
1-64	4		
1-65	4		
1-66	4		
1-67	4		
1-68	4		

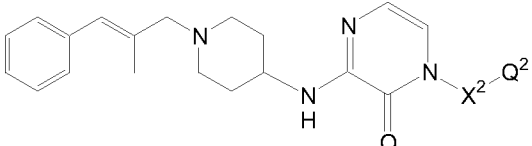
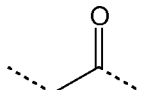
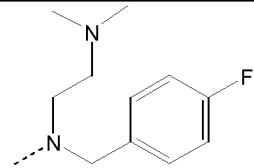
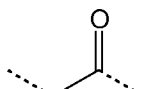
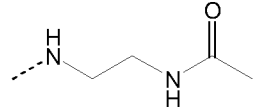
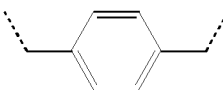
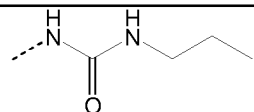
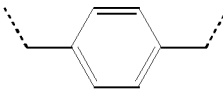
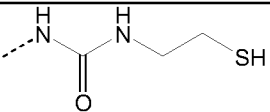
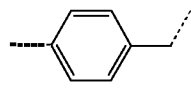
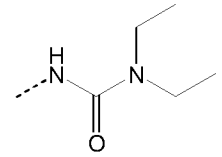
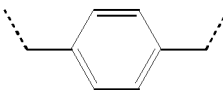
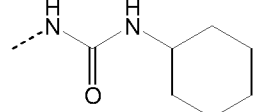
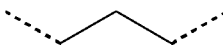
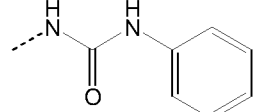
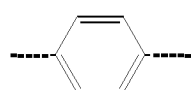
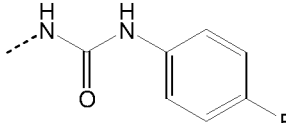
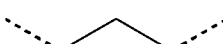
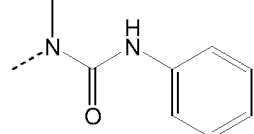
			
Co.Nr.	Scheme	--X²--	--Q²
1-69	4		
1-70	3B		
1-71	5E		
1-72	5B		
1-73	5B		
1-74	5B		
1-75	5B		
1-76	5B		

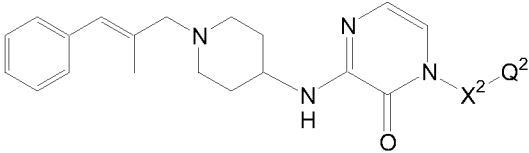
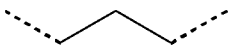
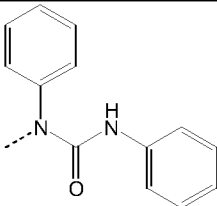
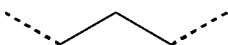
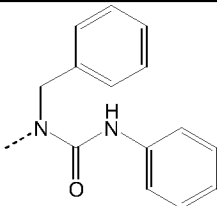
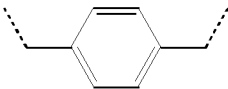
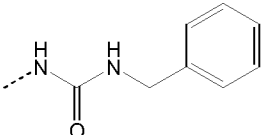
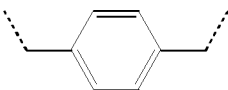
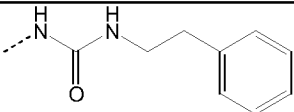
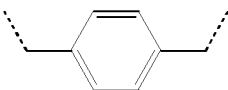
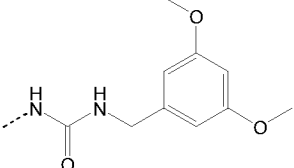
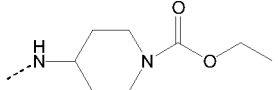
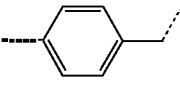
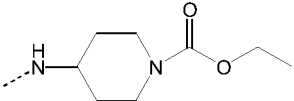
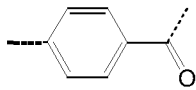
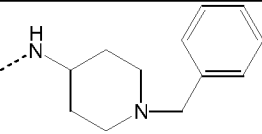
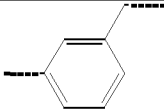
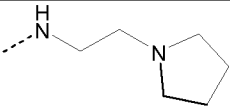
			
Co.Nr.	Scheme	--X²--	--Q²
1-77	5B		
1-78	5B		
1-79	5B		
1-80	5B		
1-81	5B		
1-82	5B		
1-83	4		
1-84	5E		
1-85	5B		

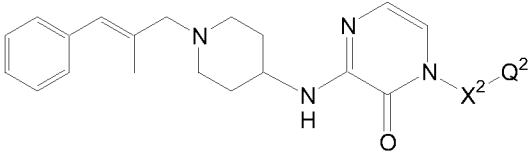
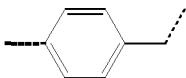
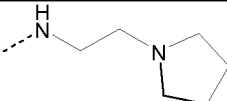
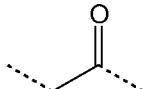
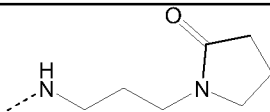
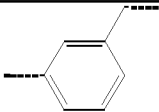
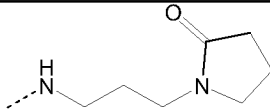
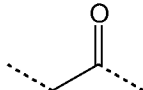
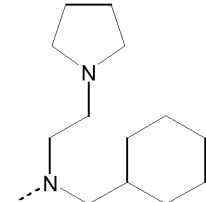
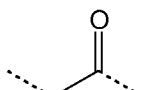
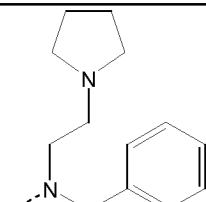
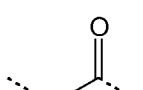
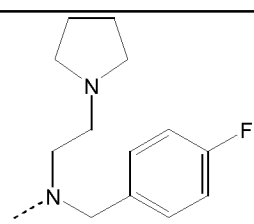
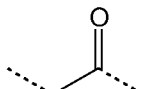
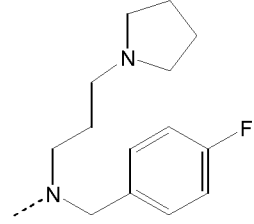
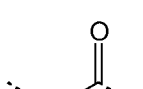
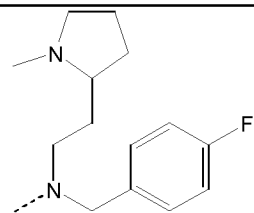
			
Co.Nr.	Scheme	--X²--	--Q²
1-86	5B		
1-87	5B		
1-88	5B		
1-89	5B		
1-90	5E		
1-91	2B		
1-172	2B		

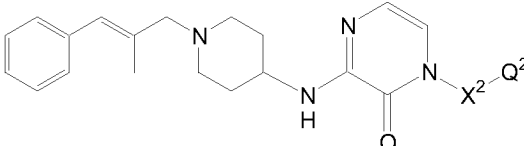
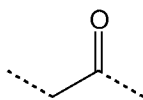
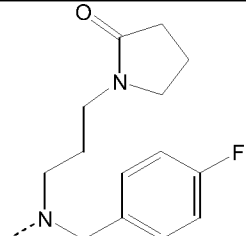
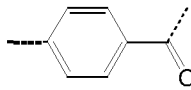
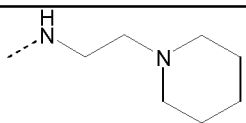
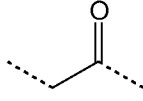
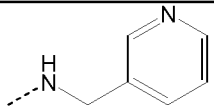
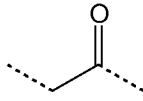
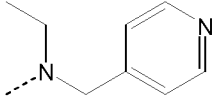
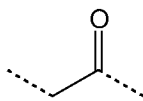
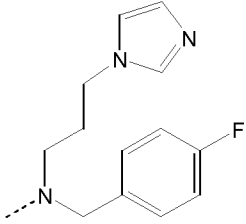
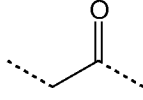
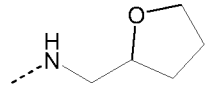
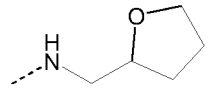
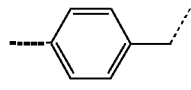
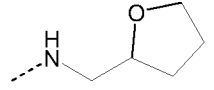
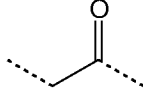
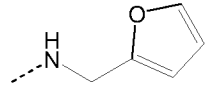
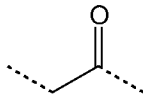
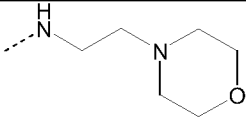
			
Co.Nr.	Scheme	--X ² --	--Q ²
1-92	2A		
1-93	5B		
1-94	4		
1-95	3A		
1-96	3A		
1-97	4		
1-98	5E		
1-99	5E		
1-100	5B		
1-101	4		
1-102	4		

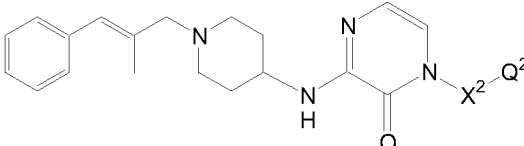
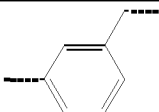
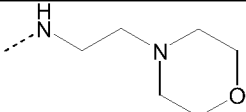
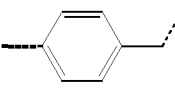
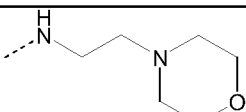
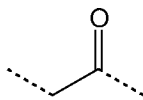
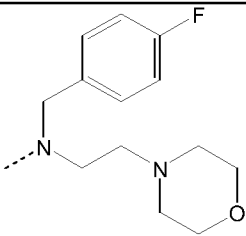
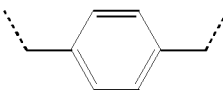
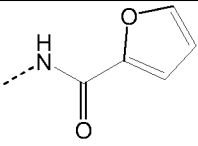
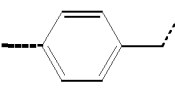
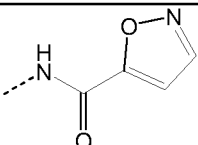
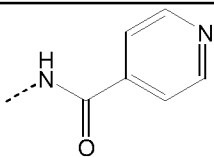
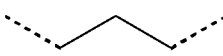
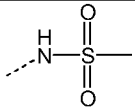
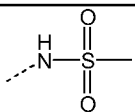
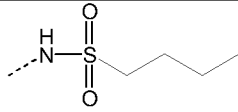
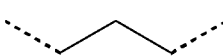
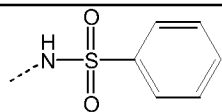
			
Co.Nr.	Scheme	--X²--	--Q²
1-103	3B		
1-104	3B		
1-105	3A		
1-106	3A		
1-107	4		
1-108	4		
1-109	3A		
1-110	3A		
1-111	4		
1-112	4		

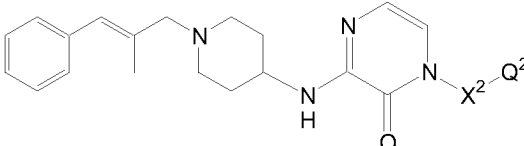
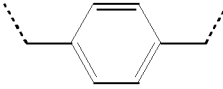
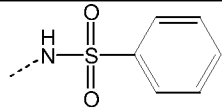
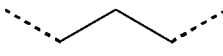
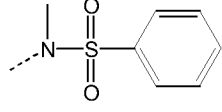
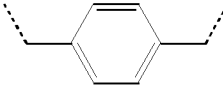
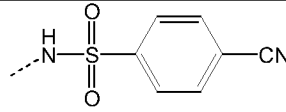
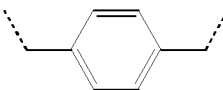
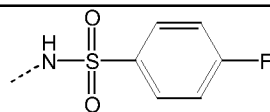
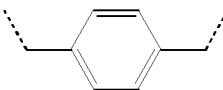
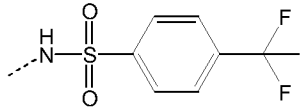
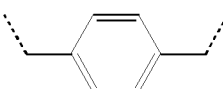
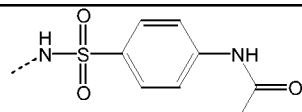
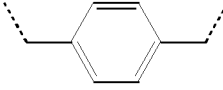
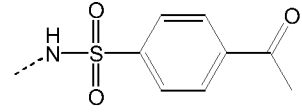
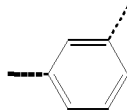
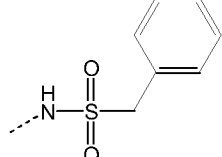
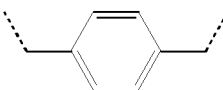
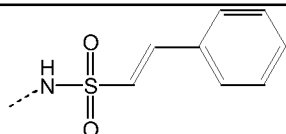
			
Co.Nr.	Scheme	--X²--	--Q²
1-113	4		
1-114	4		
1-115	5D		
1-116	5D		
1-117	5D		
1-118	5D		
1-119	5D		
1-120	5D		
1-121	5D		

			
Co.Nr.	Scheme	--X²--	--Q²
1-122	5D		
1-123	5D		
1-124	5D		
1-125	5D		
1-126	5D		
1-127	3A		
1-128	3A		
1-129	4		
1-130	3A		

			
Co.Nr.	Scheme	--X²--	--Q²
1-131	3A		
1-132	4		
1-133	3A		
1-134	4		
1-135	4		
1-136	4		
1-137	4		
1-138	4		

			
Co.Nr.	Scheme	--X²--	--Q²
1-139	4		
1-140	4		
1-141	4		
1-142	4		
1-143	4		
1-144	4		
1-145	3A		
1-146	3A		
1-147	4		
1-148	4		

			
Co.Nr.	Scheme	--X²--	--Q²
1-149	3A		
1-150	3A		
1-151	4		
1-152	5B		
1-153	5B		
1-154	5B		
1-155	5C		
1-156	5C		
1-157	5C		
1-158	5C		

			
Co.Nr.	Scheme	--X²--	--Q²
1-159	5C		
1-160	5C		
1-161	5C		
1-162	5C		
1-163	5C		
1-164	5C		
1-165	5C		
1-166	5C		
1-167	5C		

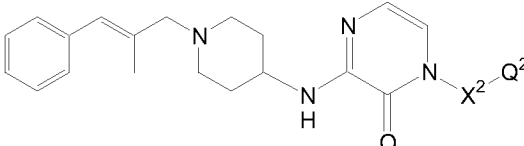
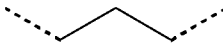
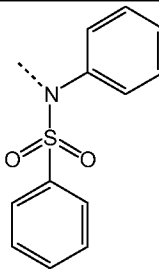
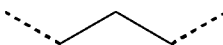
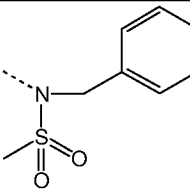
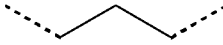
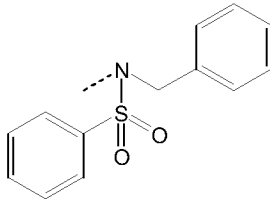
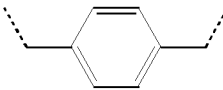
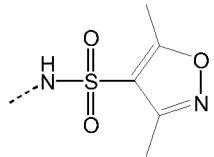
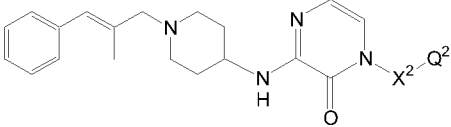
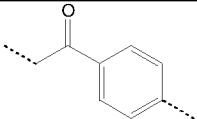
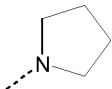
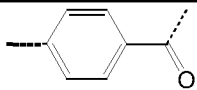
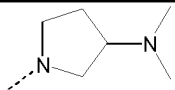
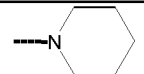
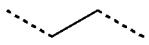
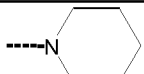
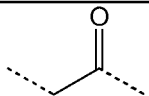
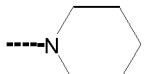
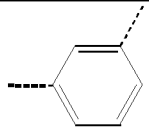
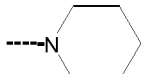
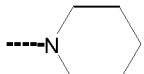
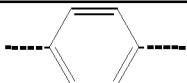
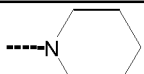
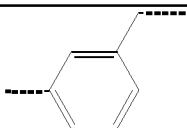
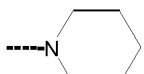
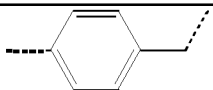
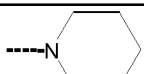
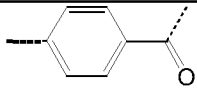
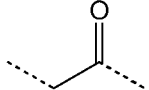
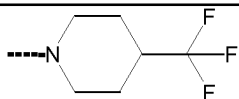
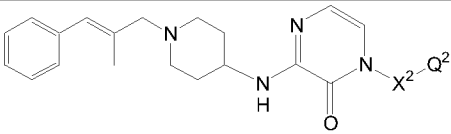
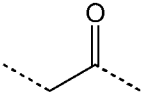
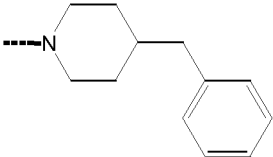
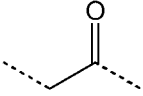
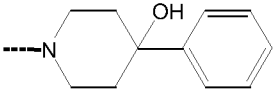
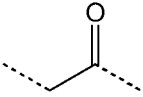
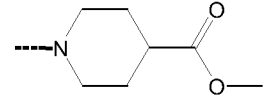
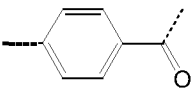
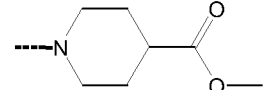
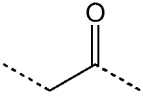
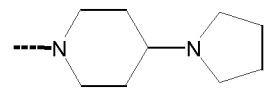
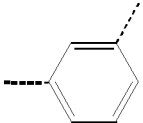
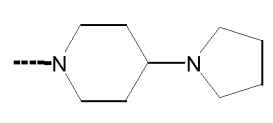
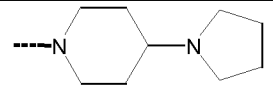
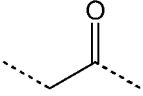
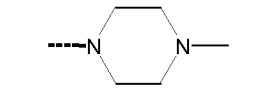
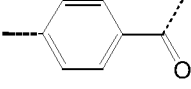
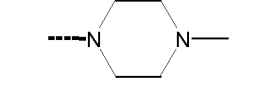
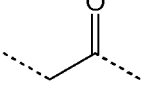
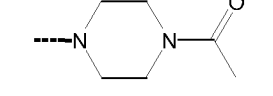
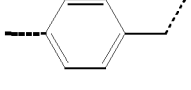
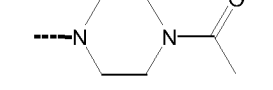
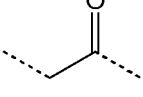
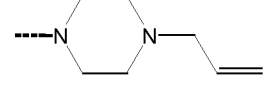
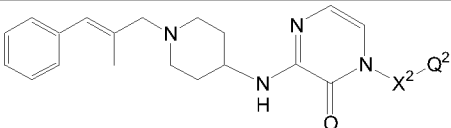
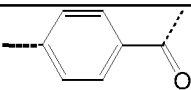
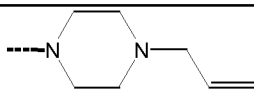
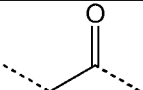
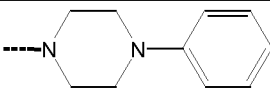
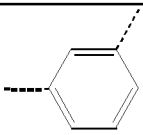
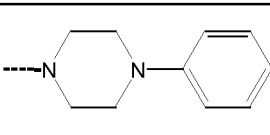
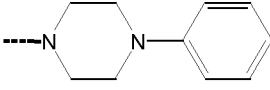
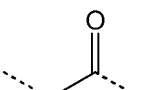
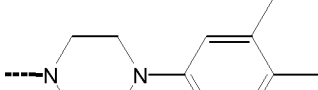
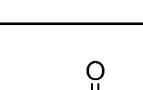
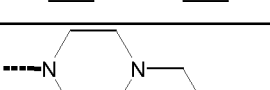
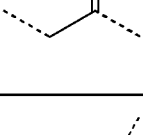
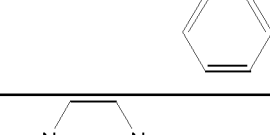
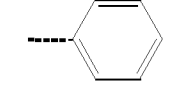
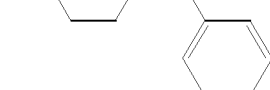
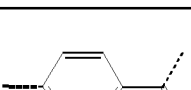
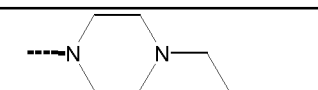
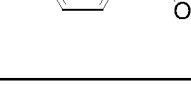
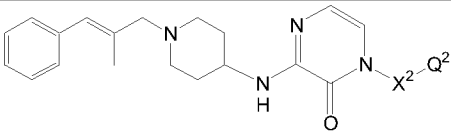
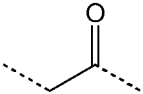
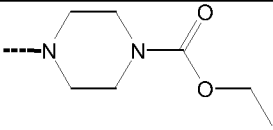
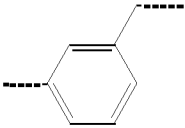
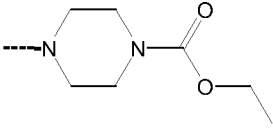
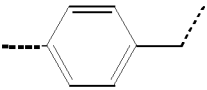
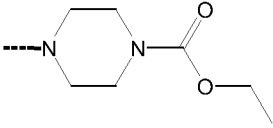
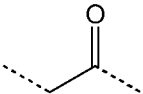
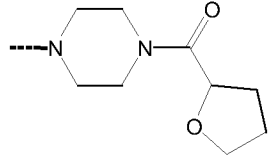
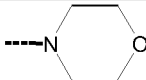
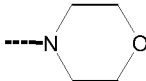
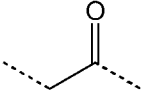
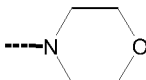
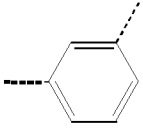
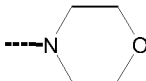
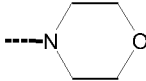
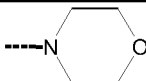
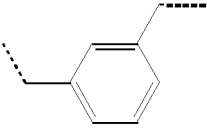
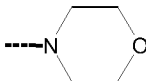
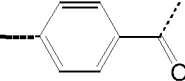
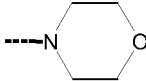
			
Co.Nr.	Scheme	--X²--	--Q²
1-168	5C		
1-169	5C		
1-170	5C		
1-171	5C		

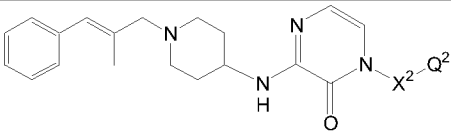
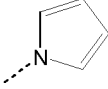
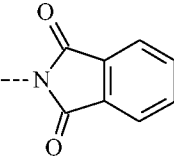
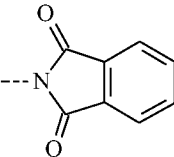
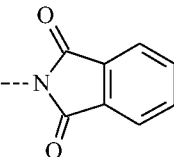
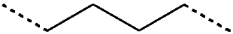
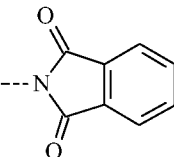
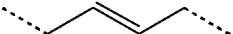
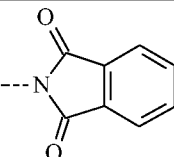
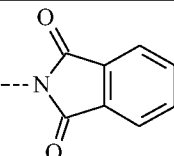
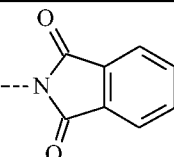
Table 2: List of compounds (with amino-piperidinyllinker) or which Q is a moiety of formula - Pir.

			
Co.Nr.	Scheme	--X ² --	--Q ²
2-1	2A		
2-2	4		
2-3	2A		
2-4	2A		
2-5	4		
2-6	3B		
2-7	3B		
2-8	3B		
2-9	3A		
2-10	3A		
2-11	4		
2-12	4		

			
Co.Nr.	Scheme	--X²--	--Q²
2-13	4		
2-14	4		
2-15	4		
2-16	4		
2-17	4		
2-18	3B		
2-19	3B		
2-20	4		
2-21	4		
2-22	4		
2-23	3A		
2-24	4		

			
Co.Nr.	Scheme	--X²--	--Q²
2-25	4		
2-26	4		
2-27	3B		
2-28	3B		
2-29	4		
2-30	4		
2-31	3B		
2-32	4		
2-33	4		
2-34	4		

			
Co.Nr.	Scheme	--X²--	--Q²
2-35	4		
2-36	3A		
2-37	3A		
2-38	4		
2-39	2A		
2-40	2A		
2-41	4		
2-42	3B		
2-43	3B		
2-44	3A		
2-45	3A		
2-46	4		

			
Co.Nr.	Scheme	--X²--	--Q²
2-47	2A		
2-48	2A	--CH₂--	
2-49	2A		
2-50	2A		
2-51	2A		
2-52	2A		
2-53	2A		
2-54	2A		

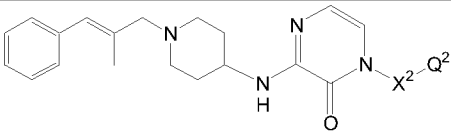
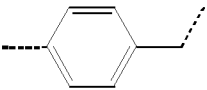
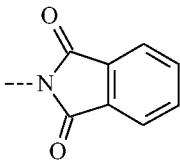
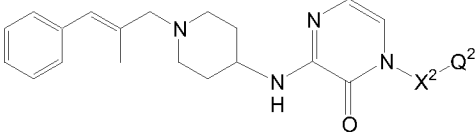
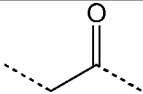
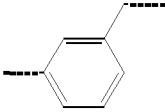
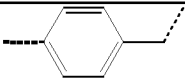
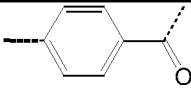
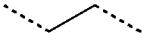
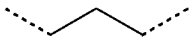
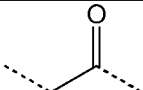
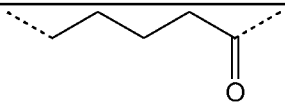
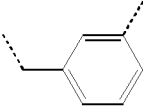
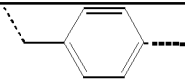
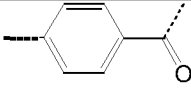
			
Co.Nr.	Scheme	--X ² --	--Q ²
2-55	2B		

Table 3: List of compounds (with amino-piperidinyllinker) for which Q is a moiety of formula –OR.

			
Co. Nr.	Scheme	--X ² --	--Q ²
3-1	4		--OH
3-2	2B		--OH
3-3	2B		--OH
3-4	4		--OH
3-5	2A		--OCH ₃
3-6	2A		--OCH ₃
3-7	2A		--OCH ₃
3-8	2A		--OCH ₃
3-9	2B		--OCH ₃
3-10	2A		--OCH ₃
3-11	2A		--OCH ₃
3-12	2B		--OCH ₃

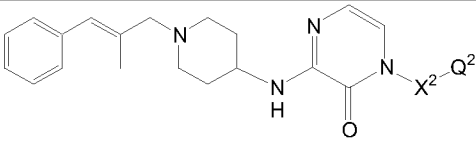
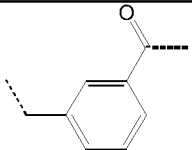
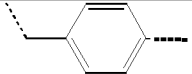
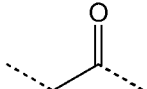
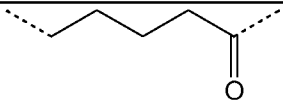
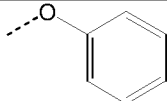
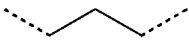
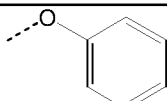
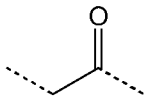
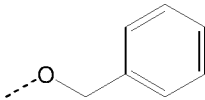
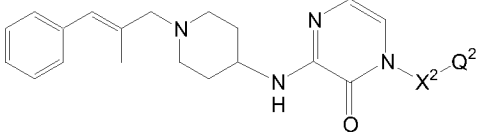
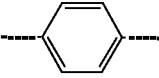
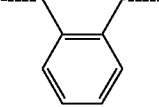
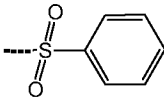
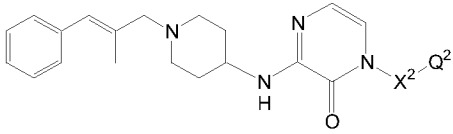
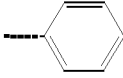
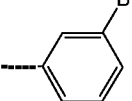
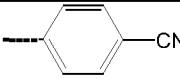
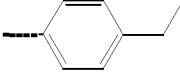
			
Co. Nr.	Scheme	--X²--	--Q²
3-13	2A		--OCH ₃
3-14	2A		--OCH ₃
3-15	2A		--OCF ₃
3-16	2A		--OCH ₂ CH ₃
3-17	2A		--OCH ₂ CH ₃
3-18	2A		
3-19	2A		
3-20	2A		
3-21	2A		

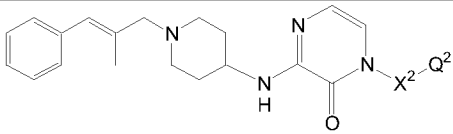
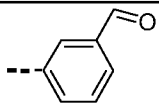
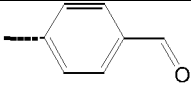
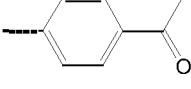
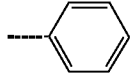
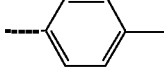
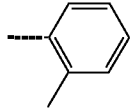
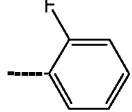
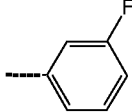
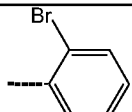
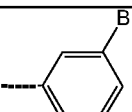
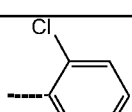
Table 4: List of compounds (with amino-piperidinyllinker) for which Q is a moiety of formula -SR or SO₂R

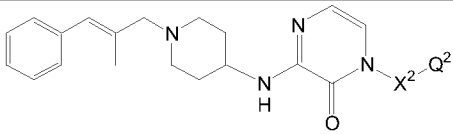
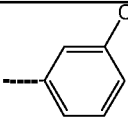
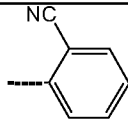
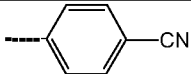
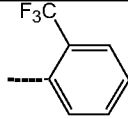
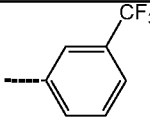
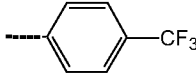
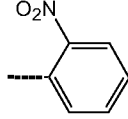
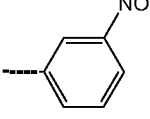
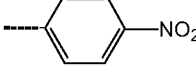
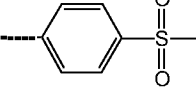
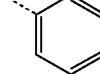
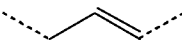
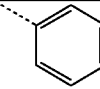
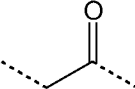
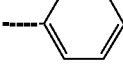
			
Co. Nr.	Scheme	--X ² --	--Q ²
4-1	2A		
4-2	2B		
4-3	2A		

5

Table 5: List of compounds (with amino-piperidinyllinker) for which Q is an aryl-moiety.

			
Co.Nr.	Scheme	--X ² --	--Q ²
5-1	2B	cb	
5-2	2B	cb	
5-36	2B	cb	
5-3	2B	cb	
5-4	2B	cb	

			
Co.Nr.	Scheme	--X²--	--Q²
5-5	2B	cb	
5-6	2B	cb	
5-7	2B	cb	
5-8	2A	--CH₂--	
5-9	2A	--CH₂--	
5-10	2A	--CH₂--	
5-11	2A	--CH₂--	
5-12	2A	--CH₂--	
5-13	2A	--CH₂--	
5-14	2A	--CH₂--	
5-15	2A	--CH₂--	
5-16	2A	--CH₂--	
5-17	2A	--CH₂--	

			
Co.Nr.	Scheme	--X²--	--Q²
5-18	2A	--CH₂--	
5-19	2A	--CH₂--	
5-20	2A	--CH₂--	
5-21	2A	--CH₂--	
5-22	2A	--CH₂--	
5-23	2A	--CH₂--	
5-24	2A	--CH₂--	
5-24	2A	--CH₂--	
5-25	2A	--CH₂--	
5-26	2A	--CH₂--	
5-27	2A	--CH₂CH₂--	
5-28	2A		
5-29	2A		

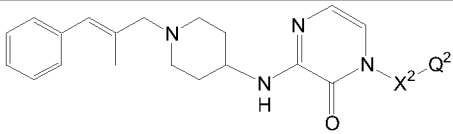
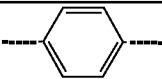
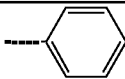
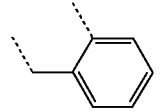
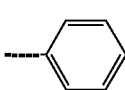
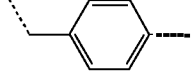
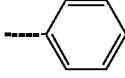
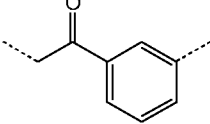
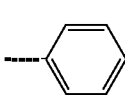
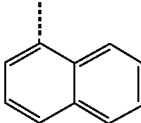
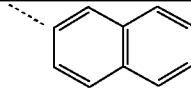
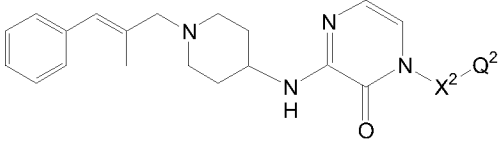
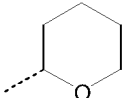
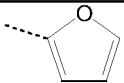
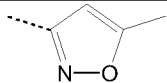
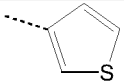
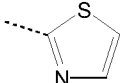
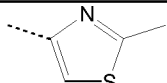
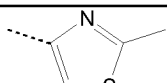
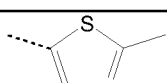
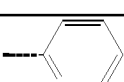
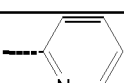
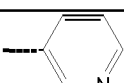
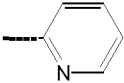
			
Co.Nr.	Scheme	--X ² --	--Q ²
5-30	2B		
5-31	2A		
5-32	2A		
5-33	2A		
5-34	2A	--CH ₂ --	
5-35	2A	--CH ₂ --	

Table 6: List of compounds (with amino-piperidinyll-linker) for which Q is a moiety of formula -Het.

			
Co.Nr.	Scheme	--X ² --	--Q ²
6-1	2A	--CH ₂ --	
6-2	2A	--CH ₂ --	
6-3	2A	--CH ₂ --	
6-4	2B	cb	
6-5	2B	cb	
6-6	2A	--CH ₂ --	
6-7	2A	--CH ₂ --	
6-8	2A	--CH ₂ --	
6-9	2B	cb	
6-10	2B	cb	
6-11	2B	cb	
6-12	2B	cb	
6-13	2A	--CH ₂ --	

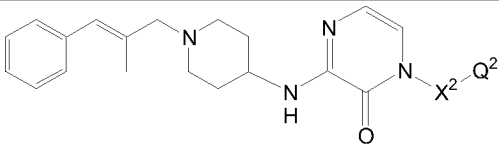
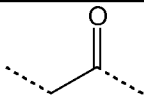
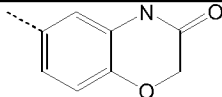
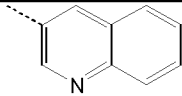
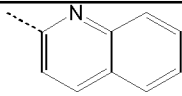
			
Co.Nr.	Scheme	--X²--	--Q²
6-14	2A	--CH₂--	
6-15	2A		
6-16	2B	cb	
6-17	2A	--CH₂--	

Table 7: List of compounds (with amino-piperidinyI-linker) for which Q is a moiety of formula -H.

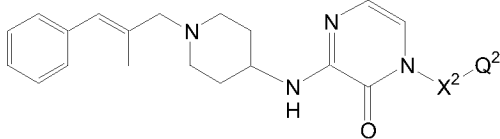
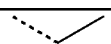
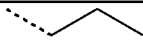
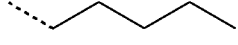
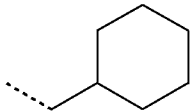
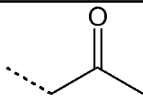
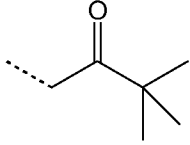
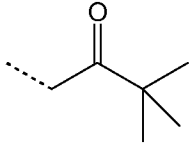
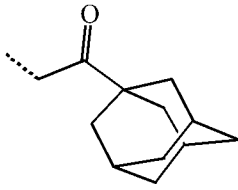
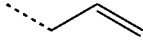
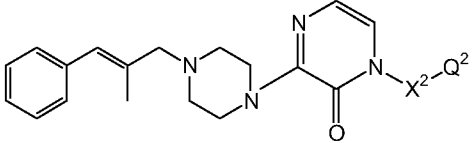
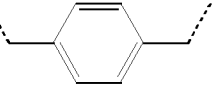
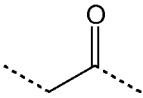
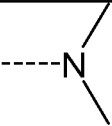
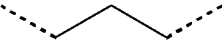
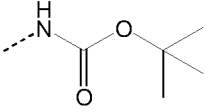
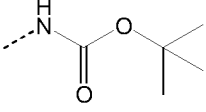
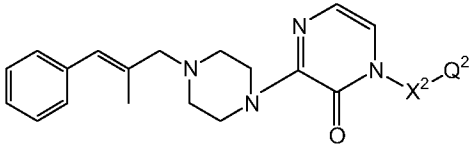
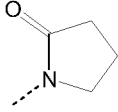
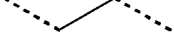
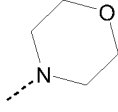
			
Co.Nr.	Scheme	--X²--	--Q²
7-1	1B	cb	H
7-2	1B	cb	H
7-3	2A		H
7-4	2A		H
7-5	2A		H
7-6	2A		H
7-7	2A		H
7-8	2A		H
7-9	2A		H
7-10	2A		H
7-11	2A		H

Table 8: List of compounds (with piperazinyllinker) for which Q is a moiety of formula – NR¹R².

			
Co.Nr.	Scheme	--X ² --	--Q ²
8-1	5		-NH ₂
8-2	2A		
8-3	2A		
8-4	2A		

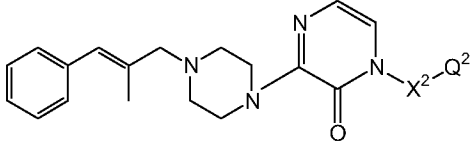
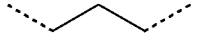
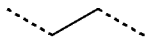
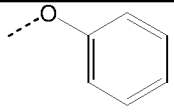
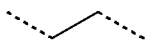
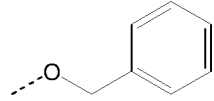
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Table 9: List of compounds (with piperazinyllinker) for which Q is a moiety of formula – Pir.

			
Co.Nr.	Scheme	--X ² --	--Q ²
9-1	2A		
9-2	2A		

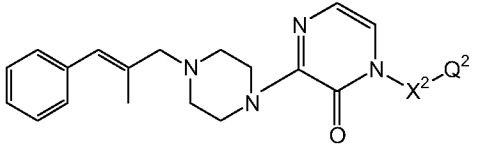
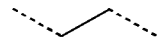
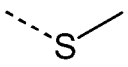
10

Table 10: List of compounds (with piperazinyl-linker) for which Q is a moiety of formula -OR.

			
Co.Nr.	Scheme	--X²--	--Q²
10-1	2A		--OCH ₃
10-2	2A		
10-3	2A		

5

Table 11: List of compounds (with piperazinyl-linker) for which Q is a moiety of formula -SR.

			
Co.Nr.	Scheme	--X²--	--Q²
11-1	2A		

10

Table 12: List of compounds (with piperazinyllinker) for which Q is an aryl moiety.

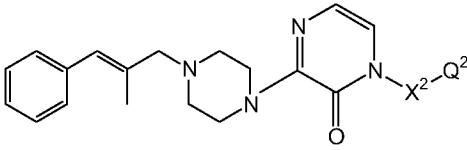
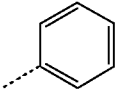
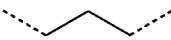
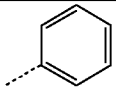
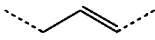
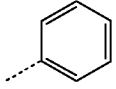
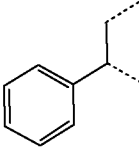
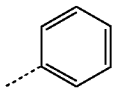
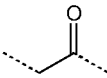
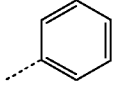
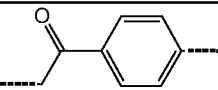
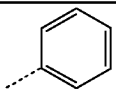
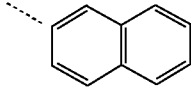
			
Co.Nr.	Scheme	--X²--	--Q²
12-1	2A	--CH₂--	
12-2	2A		
12-3	2A		
12-4	2A		
12-5	2A		
12-6	2A		
12-7	2A	--CH₂--	

Table 13: List of compounds (with piperazinyllinker) for which Q is a moiety of formula -Het.

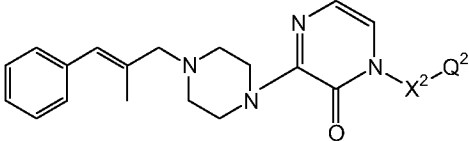
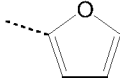
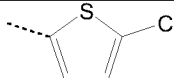
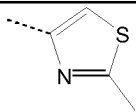
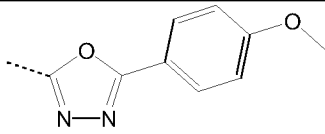
			
Co.Nr.	Scheme	--X²--	--Q²
13-1	2A	--CH₂--	
13-2	2A	--CH₂--	
13-3	2A	--CH₂--	
13-4	2A	--CH₂--	

Table 14: List of compounds (piperazinyI-linker) for which Q with is a moiety of formula -H.

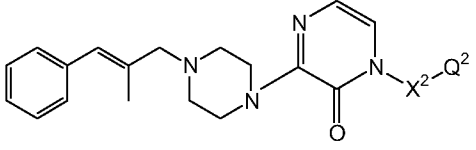
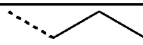
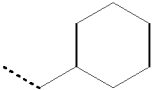
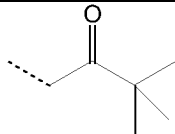
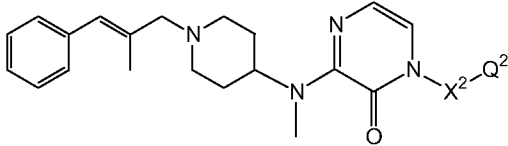
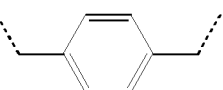
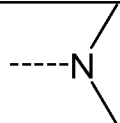
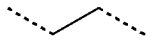
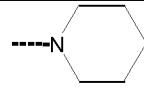
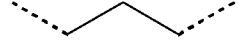
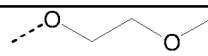
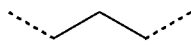
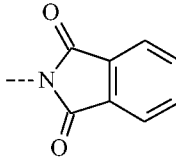
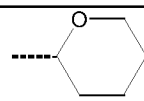
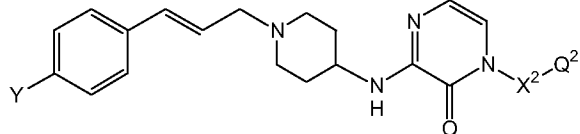
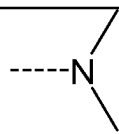
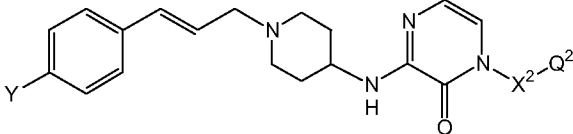
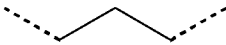
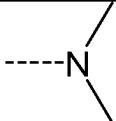
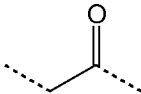
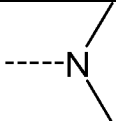
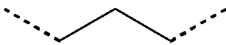
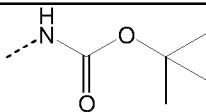
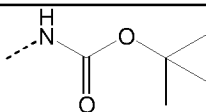
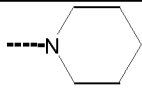
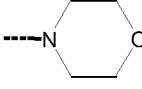
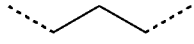
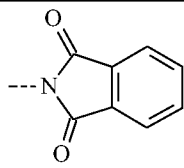
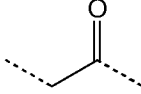
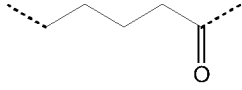
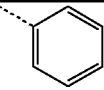
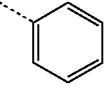
			
Co.Nr.	Scheme	--X²--	--Q²
14-1	1A	cb	H
14-2	2A		H
14-3	2A		H
14-4	2A		H
14-5	2A		H

Table 15: List of compounds where R⁴ is methyl

			
Co.Nr.	Scheme	--X ² --	--Q ²
15-1	5		-NH ₂
15-2	2A		
15-3	2A		
15-4	2A		-OH
15-5	2A		
15-6	2A		
15-7	2A	--CH ₂ --	
15-8	1A	cb	H

5 Table 16: List of compounds where R⁶ is hydrogen.

				
Co.Nr.	Scheme	--Y	--X ² --	--Q ²
16-1	2A	H		

				
Co.Nr.	Scheme	--Y	--X²--	--Q²
16-2	2A	H		
16-3	2A	H		
16-4	2A	H		
16-5	2A	H		
16-6	2A	H		
16-7	2A	H		
16-8	2A	H		
16-9	2A	H		--OCH ₃
16-10	2A	H		--OCH ₃
16-11	2A	H		--OCH ₂ CH ₃
16-12	2A	H		
16-13	2A	F	--CH ₂ --	
16-14	2A	H		

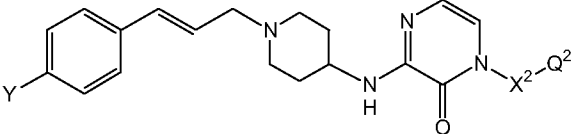
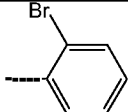
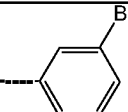
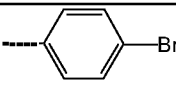
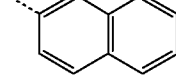
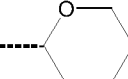
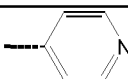
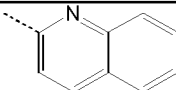
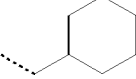
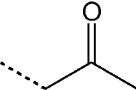
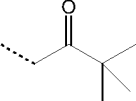
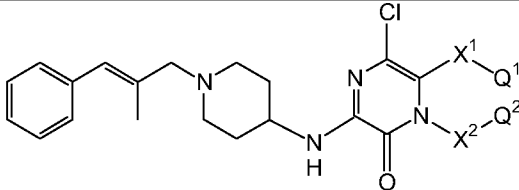
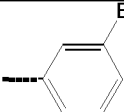
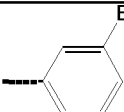
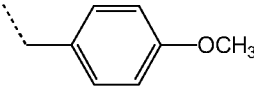
				
Co.Nr.	Scheme	--Y	--X²--	--Q²
16-15	2A	H	--CH₂--	
16-16	2A	H	--CH₂--	
16-17	2A	H	--CH₂--	
16-18	2A	H	--CH₂--	
16-19	2A	H	--CH₂--	
16-20	2A	H	--CH₂--	
16-21	2A	H	--CH₂--	
16-26	1A	H	cb	H
16-22	1A	H		H
16-23	2A	H		H
16-24	2A	H		H
16-25	2A	H		H

Table 17: List of compounds where R⁵ is Cl.

			
Co.Nr.	Scheme	--X ¹ -Q ¹	--X ² -Q ²
17-1	6		H
17-2	6		

5 C. Pharmacological exampleGeneral

The interaction of a compound of Formula (I) with α_2 -adrenoceptor receptors was assessed in *in vitro* radioligand binding experiments. In general, a low concentration of a radioligand with a high binding affinity for a particular receptor or transporter is incubated with a sample of a tissue preparation enriched in a particular receptor or transporter or with a preparation of cells expressing cloned human receptors in a buffered medium. During the incubation, the radioligand binds to the receptor or transporter. When equilibrium of binding is reached, the receptor bound radioactivity is separated from the non-bound radioactivity, and the receptor- or transporter-bound activity is counted. The interaction of the test compounds with the receptor is assessed in competition binding experiments. Various concentrations of the test compound are added to the incubation mixture containing the receptor- or transporter preparation and the radioligand. The test compound in proportion to its binding affinity and its concentration inhibits binding of the radioligand. The radioligand used for $h\alpha_{2A}$ and $h\alpha_{2C}$ receptor binding was [³H]-rauwolscine.

Example C.1 : Binding Experiment for α_2 -adrenoceptorCell culture and membrane preparation.

CHO cells, stable transfected with human adrenergic- α_{2A} and α_{2C} receptor cDNA, were cultured in Dulbecco's Modified Eagle's Medium (DMEM)/Nutrient mixture Ham's F12 (ratio 1:1)(Gibco, Gent-Belgium) supplemented with 10 % heat inactivated fetal calf serum (Life Technologies, Merelbeke-Belgium) and antibiotics (100 IU/ml penicillin G, 100 μ g/ml streptomycin sulphate, 110 μ g/ml pyruvic acid and 100 μ g/ml L-glutamine). One day before collection, cells were induced with 5 mM sodiumbutyrate. Upon 80-90 % of confluence, cells were scraped in phosphate buffered saline without Ca^{2+} and Mg^{2+} and collected by centrifugation at 1500 x g for 10 minutes. The cells were homogenised in Tris-HCl 50 mM using an Ultraturrax homogenizer and centrifuged for 10 minutes at 23,500 x g. The pellet was washed once by resuspension and rehomogenization and the final pellet was resuspended in Tris-HCl, divided in 1 ml aliquots and stored at -70°C .

15 Binding experiment for α_2 -adrenergic receptor subtypes

Membranes were thawed and re-homogenized in incubation buffer (glycylglycine 25 mM, pH 8.0). In a total volume of 500 μ l, 2-10 μ g protein was incubated with [^3H]rauwolscine (NET-722) (New England Nuclear, USA) (1 nM final concentration) with or without competitor for 60 minutes at 25 $^\circ\text{C}$ followed by rapid filtration over GF/B filter using a Filtermate196 harvester (Packard, Meriden, CT). Filters were rinsed extensively with ice-cold rinsing buffer (Tris-HCl 50 mM pH 7.4). Filter-bound radioactivity was determined by scintillation counting in a Topcount (Packard, Meriden, CT) and results were expressed as counts per minute (cpm). Non-specific binding was determined in the presence of 1 μ M oxymetazoline for the $\text{h}\alpha_{2A}$ receptor and 1 μ M spiroxatrine for $\text{h}\alpha_{2C}$ receptor.

Example C2 : Binding experiment for the 5HT-transporter

Human platelet membranes (Oceanix Biosciences Corporation, Hanover, MD, USA) were thawed, diluted in buffer (Tris-HCl 50 mM, 120 mM NaCl and 5 mM KCl) and quickly (max 3 s) homogenised with an Ultraturrax homogenizer. In a total volume of 250 μ L, 50-100 μ g protein was incubated with [^3H]paroxetine (NET-869) (New England Nuclear, USA) (0.5 nM final concentration) with or without competitor for 60 minutes at 25 $^\circ\text{C}$. Incubation was stopped by rapid filtration of the incubation mixture over GF/B

filters, pre-wetted with 0.1 % polyethylenamine, using a Filtermate196 harvester (Packard, Meriden, CT). Filters were rinsed extensively with ice-cold buffer and radio-activity on the filters was counted in a Topcount liquid scintillation counter (Packard, Meriden, CT). Data were expressed as cpm. Imipramine (at 1 μ M final concentration) was used to determine the non-specific binding.

Data analysis and results

Data from assays in the presence of compound were calculated as a percentage of total binding measured in the absence of test compound. Inhibition curves, plotting percent of total binding versus the log value of the concentration of the test compound, were automatically generated, and sigmoidal inhibition curves were fitted using non-linear regression. The pIC_{50} values of test compounds were derived from individual curves.

All compounds according to Formula (I) produced an inhibition at least at the $h\alpha_{2C}$ site (but often also at the $h\alpha_{2A}$ -site) of more than 50 % (pIC_{50}) at a test concentration ranging between 10^{-6} M and 10^{-9} M in a concentration-dependent manner.

Some compounds also show moderate 5-HTT activity.

For a selected number of compounds, covering most of the various embodiments of Formula (I), the results of the *in vitro* studies are given in Table 18.

Table 18. Pharmacological data for the compounds according to the invention.

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
2-9	9.2	9.7	6.7
1-136	8.0	9.5	6.2
1-138	8.1	9.1	5.9
1-135	7.9	9.1	6.1
1-137	7.9	9.1	6.0
1-46	7.4	9.1	6.5
1-111	7.3	9.1	5.4
1-11	8.5	9.0	6.2
1-12	8.4	9.0	6.1
1-25	8.3	9.0	5.8
2-50	7.5	9.0	6.9
1-51	7.3	9.0	6.0
2-18	7.9	8.9	6.1
1-145	7.7	8.9	6.1
1-95	7.6	8.9	5.9
1-98	7.5	8.9	6.0
1-55	7.2	8.9	6.5

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
1-153	6.9	8.9	6.1
1-17	8.3	8.8	6.0
1-130	8.2	8.8	6.7
1-134	7.9	8.8	6.3
1-106	7.9	8.8	6.1
2-17	7.6	8.8	5.7
2-10	7.5	8.8	6.6
1-107	7.5	8.8	5.7
1-108	7.3	8.8	5.2
1-110	7.7	8.7	6.3
1-133	7.5	8.7	5.6
1-102	7.5	8.7	5.5
2-52	7.3	8.7	7.5
1-26	7.2	8.7	5.8
2-30	7.1	8.7	6.1
1-90	6.9	8.7	6.2
1-151	6.9	8.7	5.9
1-53	8.4	8.6	6.7
2-6	8.4	8.6	6.5

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
1-109	8.2	8.6	6.5
1-104	7.9	8.6	6.7
1-6	7.9	8.6	6.4
1-47	7.6	8.6	6.3
1-27	7.5	8.6	6.3
1-52	7.2	8.6	6.2
1-96	7.1	8.6	6.0
1-146	7.0	8.6	6.3
2-42	8.1	8.5	6.1
1-43	7.9	8.5	7.3
6-10	7.9	8.5	6.3
1-7	7.8	8.5	6.1
1-131	7.6	8.5	6.8
1-103	7.6	8.5	6.7
15-2	7.5	8.5	6.0
1-112	7.4	8.5	6.7
1-40	7.3	8.5	6.0
1-147	7.3	8.5	5.5
1-8	7.3	8.5	5.4

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
2-4	7.2	8.5	5.6
2-20	7.2	8.5	5.6
1-143	7.1	8.5	5.7
1-41	7.0	8.5	6.4
1-50	7.0	8.5	6.2
1-67	7.0	8.5	6.0
2-24	7.0	8.5	5.3
1-62	6.9	8.5	6.0
1-72	6.9	8.5	5.8
1-142	6.8	8.5	6.0
2-53	6.7	8.5	7.2
1-139	6.7	8.5	5.6
1-49	7.6	8.4	6.6
1-149	7.6	8.4	5.5
2-46	7.5	8.4	6.1
1-9	7.5	8.4	5.8
1-140	7.4	8.4	6.7
15-6	7.3	8.4	6.9
1-54	7.3	8.4	6.7

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
1-15	7.3	8.4	5.1
2-12	7.2	8.4	5.7
1-14	7.2	8.4	5.2
1-20	7.1	8.4	6.0
1-37	7.1	8.4	5.9
2-51	7.0	8.4	6.8
1-42	7.0	8.4	6.3
1-65	7.0	8.4	6.1
1-150	7.0	8.4	6.1
1-57	6.9	8.4	5.5
2-15	6.9	8.4	5.4
1-113	6.9	8.4	5.1
1-94	6.8	8.4	5.6
6-9	7.6	8.3	5.3
5-1	7.5	8.3	5.9
1-4	7.5	8.3	5.5
1-105	7.4	8.3	6.2
2-16	7.3	8.3	6.3
2-19	7.3	8.3	6.2

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
2-7	7.3	8.3	5.9
2-2	7.2	8.3	6.4
1-99	7.1	8.3	6.0
1-28	7.1	8.3	5.6
2-13	7.0	8.3	6.6
1-71	7.0	8.3	6.4
2-34	7.0	8.3	6.2
1-44	7.0	8.3	6.1
1-48	6.9	8.3	5.7
1-119	6.8	8.3	6.8
1-78	6.7	8.3	7.1
1-117	6.7	8.3	6.3
1-83	6.7	8.3	6.0
4-2	7.9	8.2	6.8
1-58	7.6	8.2	6.4
2-48	7.5	8.2	6.8
2-31	7.5	8.2	6.4
6-4	7.4	8.2	6.0
1-2	7.4	8.2	5.7

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
5-6	7.4	8.2	5.7
2-44	7.3	8.2	5.7
2-11	7.2	8.2	6.3
1-1	7.2	8.2	5.7
2-3	7.2	8.2	5.5
1-158	7.0	8.2	6.8
1-61	7.0	8.2	5.9
1-92	7.0	8.2	5.9
1-141	7.0	8.2	5.8
1-5	7.0	8.2	5.7
2-54	6.9	8.2	7.3
1-101	6.9	8.2	5.8
2-5	6.9	8.2	5.3
1-121	6.8	8.2	6.1
1-144	6.8	8.2	5.5
1-23	6.7	8.2	5.6
3-9	8.3	8.1	7.3
5-30	7.6	8.1	6.4
6-5	7.3	8.1	6.5

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
6-12	7.3	8.1	5.8
1-39	7.1	8.1	6.7
1-13	7.1	8.1	6.4
7-9	7.1	8.1	5.3
1-122	7.0	8.1	6.7
1-80	7.0	8.1	6.5
1-29	7.0	8.1	6.0
2-25	6.9	8.1	6.3
2-26	6.9	8.1	6.1
1-24	6.9	8.1	5.5
2-14	6.9	8.1	5.3
1-148	6.6	8.1	5.9
5-29	7.8	8.0	6.1
15-1	7.6	8.0	6.3
5-7	7.6	8.0	6.2
5-2	7.5	8.0	6.4
2-8	7.4	8.0	6.3
2-45	7.3	8.0	6.1
5-3	7.3	8.0	6.0

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
7-10	7.3	8.0	5.9
1-127	7.3	8.0	5.5
5-24	7.2	8.0	6.4
1-60	7.1	8.0	6.1
1-59	7.1	8.0	5.9
2-21	7.0	8.0	6.3
1-84	7.0	8.0	5.9
2-36	7.0	8.0	5.8
3-7	7.0	8.0	5.1
1-19	6.9	8.0	5.8
1-10	6.9	8.0	5.7
1-97	6.9	8.0	5.6
1-168	6.8	8.0	6.7
2-55	6.8	8.0	6.6
1-85	6.8	8.0	5.9
1-169	6.7	8.0	6.5
1-74	6.6	8.0	5.5
7-4	7.6	7.9	6.2
7-11	7.5	7.9	5.7

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
5-4	7.4	7.9	6.4
1-18	7.4	7.9	6.0
8-1	7.4	7.9	6.0
5-14	7.3	7.9	6.7
7-7	7.3	7.9	5.0
1-166	7.2	7.9	6.5
5-24	7.2	7.9	6.5
1-66	7.1	7.9	6.1
5-5	7.1	7.9	6.0
3-2	7.1	7.9	5.3
1-22	7.0	7.9	6.2
1-63	7.0	7.9	6.2
1-128	7.0	7.9	5.9
1-88	6.9	7.9	6.2
2-41	6.9	7.9	5.4
7-8	6.9	7.9	<5
1-160	6.8	7.9	6.3
1-123	6.8	7.9	6.2
1-68	6.8	7.9	6.1

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
1-16	7.0	7.8	<5
2-33	6.9	7.8	6.7
1-77	6.9	7.8	6.6
3-17	6.9	7.8	6.1
3-16	6.9	7.8	<5
1-56	6.8	7.8	6.6
4-3	6.8	7.8	6.4
1-86	6.8	7.8	6.0
2-49	6.8	7.8	6.0
3-3	6.8	7.8	5.2
6-15	7.8	7.7	6.0
3-13	7.6	7.7	6.3
1-70	7.5	7.7	6.8
2-27	7.5	7.7	6.7
4-1	7.4	7.7	5.5
3-19	7.2	7.7	6.7
5-17	7.2	7.7	6.6
1-34	7.2	7.7	6.2
5-31	7.0	7.7	6.7

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
1-170	6.7	7.9	6.6
1-33	6.7	7.9	6.1
1-89	6.7	7.9	6.1
2-32	6.7	7.9	5.9
1-87	6.7	7.9	5.8
1-32	6.7	7.9	5.6
1-114	6.7	7.9	5.4
1-64	6.6	7.9	5.8
1-132	6.5	7.9	5.6
1-38	6.5	7.9	5.1
16-8	6.3	7.9	6.7
3-12	7.5	7.8	6.3
6-16	7.2	7.8	6.5
7-3	7.2	7.8	5.4
6-17	7.1	7.8	6.5
3-8	7.1	7.8	6.1
5-27	7.0	7.8	6.4
2-28	7.0	7.8	6.1
3-20	7.0	7.8	5.4

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
1-162	7.0	7.7	6.5
5-19	7.0	7.7	6.4
15-3	7.0	7.7	5.3
6-1	6.9	7.7	6.0
6-6	6.9	7.7	5.5
2-43	6.9	7.7	5.4
1-164	6.8	7.7	6.3
1-171	6.8	7.7	6.1
1-155	6.7	7.7	5.9
1-91	6.5	7.7	6.1
1-21	6.5	7.7	5.6
2-39	6.5	7.7	5.1
1-129	7.2	7.6	6.3
1-159	7.2	7.6	6.1
1-82	7.1	7.6	6.6
5-10	7.1	7.6	6.4
5-15	7.1	7.6	6.4
5-34	7.0	7.6	6.4
1-161	7.0	7.6	6.3

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
5-12	7.0	7.6	6.3
1-100	6.9	7.6	6.0
5-26	6.9	7.6	5.9
6-2	6.9	7.6	5.9
2-22	6.9	7.6	<5
7-2	6.9	7.6	<5
5-21	6.8	7.6	6.4
1-165	6.8	7.6	6.0
6-8	6.8	7.6	5.4
1-120	6.7	7.6	6.9
1-81	6.7	7.6	6.7
6-11	6.6	7.6	5.4
2-40	6.5	7.6	5.1
1-76	7.7	7.5	6.9
3-11	7.7	7.5	6.3
6-3	7.2	7.5	5.7
3-10	7.1	7.5	6.1
7-5	7.0	7.5	6.6
7-1	7.0	7.5	5.0

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
3-18	6.9	7.5	6.8
1-152	6.9	7.5	6.3
5-25	6.9	7.5	6.2
2-29	6.8	7.5	7.0
1-73	6.8	7.5	6.5
5-11	6.8	7.5	6.3
1-30	6.8	7.5	5.9
1-156	6.8	7.5	5.9
2-35	6.8	7.5	5.6
2-47	6.7	7.5	5.4
6-13	6.7	7.5	5.4
1-3	6.7	7.5	<5
2-37	6.4	7.5	5.2
2-1	7.5	7.4	5.9
5-35	7.2	7.4	6.4
15-4	7.2	7.4	5.6
15-7	7.1	7.4	5.5
13-2	7.1	7.4	5.4
1-154	6.9	7.4	6.4

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
5-18	6.9	7.4	6.2
1-45	6.9	7.4	5.7
15-5	6.9	7.4	5.7
1-36	6.8	7.4	6.4
1-69	6.8	7.4	6.1
1-163	6.8	7.4	6.1
6-14	6.8	7.4	5.6
14-1	6.8	7.4	5.4
2-38	6.8	7.4	5.1
1-167	6.7	7.4	6.2
1-126	6.6	7.4	6.3
6-7	6.6	7.4	5.7
3-1	6.6	7.4	<5
3-21	6.5	7.4	5.4
3-5	6.5	7.4	5.0
16-4	6.4	7.4	5.9
2-23	6.1	7.4	5.1
1-79	5.7	7.4	<5
1-75	6.9	7.3	6.7

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Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
12-2	6.7	7.2	5.9
1-124	6.6	7.2	6.3
14-4	6.4	7.2	<5
16-2	6.3	7.2	5.0
3-6	6.2	7.2	5.4
16-6	6.1	7.2	<5
8-4	6.8	7.1	5.9
5-23	6.7	7.1	6.1
1-115	6.6	7.1	6.1
11-1	6.5	7.1	5.2
13-3	6.5	7.1	5.2
10-1	6.5	7.1	5.1
1-118	6.4	7.1	6.3
10-3	6.4	7.1	5.9
8-3	6.4	7.1	5.6
3-4	6.2	7.1	<5
5-33	7.1	7.0	5.9
10-2	6.6	7.0	5.9
5-20	6.3	7.0	5.3

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
5-16	6.9	7.3	6.3
5-22	6.9	7.3	6.1
14-2	6.9	7.3	5.2
5-9	6.8	7.3	6.0
1-93	6.8	7.3	5.9
1-31	6.7	7.3	6.1
5-8	6.7	7.3	5.8
7-6	6.7	7.3	5.8
1-157	6.6	7.3	6.0
1-35	6.6	7.3	5.9
12-5	6.5	7.3	5.4
13-1	7.3	7.2	5.2
13-4	7.2	7.2	6.4
12-1	7.2	7.2	5.5
3-14	7.1	7.2	6.1
14-5	6.9	7.2	5.1
1-125	6.8	7.2	6.3
5-28	6.8	7.2	6.3
5-13	6.8	7.2	5.9

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Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
12-7	6.9	6.9	6.0
1-116	6.7	6.9	6.5
3-15	6.6	6.9	5.9
5-32	6.5	6.9	6.5
12-3	6.4	6.9	5.9
16-21	6.3	6.9	6.0
14-3	6.4	6.8	5.1
16-15	6.2	6.8	6.1
12-4	6.2	6.8	5.4
16-11	6.1	6.8	6.2
16-25	6.0	6.8	<5
8-2	5.8	6.8	<5
16-1	5.8	6.8	<5
16-16	6.3	6.7	6.0
16-14	6.1	6.7	6.1
17-1	6.0	6.7	6.5
9-2	6.0	6.7	5.1
16-10	6.0	6.7	<5
16-18	6.6	6.6	6.4

Co. Nr.	h- α 2A pIC ₅₀	h- α 2C pIC ₅₀	h-5HTT pIC ₅₀
12-6	6.4	6.6	5.7
16-22	6.1	6.6	5.2
9-1	5.7	6.6	5.0
16-20	5.7	6.6	<5
16-17	6.3	6.5	6.1
16-23	6.2	6.5	5.9
16-12	6.1	6.5	5.6
16-24	6.0	6.5	<5
16-19	5.8	6.5	5.3
16-3	5.6	6.5	<5
16-5	6.1	6.4	5.9
16-7	5.4	6.4	<5
16-13	6.6	6.3	5.7
17-2	6.1	6.3	5.8
16-9	5.5	6.2	<5

D. Composition examples

“Active ingredient” (a.i.) as used throughout these examples relates to a 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.

Example D.1 : oral drops

500 Grams of the a.i. is dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60~80 °c. After cooling to 30~40 °C there are added 35 l of polyethylene glycol and the mixture is stirred well. Then there is added a solution of 1750 grams of sodium saccharin in 2.5 l of purified water and while stirring there are added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of a.i. The resulting solution is filled into suitable containers.

Example D.2 : oral solution

9 Grams of methyl 4-hydroxybenzoate and 1 gram of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 grams of 2,3-dihydroxybutanedioic acid and thereafter 20 grams of the a.i. The latter solution is combined with the remaining part of the former solution and 12 l 1,2,3-propanetriol and 3 l of sorbitol 70 % solution are added thereto. 40 Grams of sodium saccharin are dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the active ingredient per teaspoonful (5 ml). The resulting solution is filled in suitable containers.

Example D.3 : film-coated tablets

Preparation of tablet core

A mixture of 100 grams of the a.i., 570 grams lactose and 200 grams starch is mixed well and thereafter humidified with a solution of 5 grams sodium dodecyl sulfate and 10 grams polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there is added 100 grams microcrystalline cellulose and 15 grams hydrogenated vegetable oil. The whole is mixed well and compressed into

tablets, giving 10,000 tablets, each containing 10 mg of the active ingredient.

Coating

To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there is added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 grams of polyethylene glycol is molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 grams of magnesium octadecanoate, 5 grams of polyvinylpyrrolidone and 30 ml of concentrated color suspension and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

Example D.4 : injectable solution

1.8 grams methyl 4-hydroxybenzoate and 0.2 grams propyl 4-hydroxybenzoate are dissolved in about 0.5 l of boiling water for injection. After cooling to about 50 °C there are added while stirring 4 grams lactic acid, 0.05 grams propylene glycol and 4 grams of the a.i.. The solution is cooled to room temperature and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of a.i.. The solution is sterilized by filtration and filled in sterile containers.

E. Physico-chemical data

General procedure A

The HPLC gradient was supplied by a HP 1100 from Agilent Technologies comprising a quaternary pump with degasser, an autosampler, a column oven (set at 40 °C), a diode-array detector (DAD) and a column as specified in the respective methods below. Flow from the column was split to the MS detector. MS detectors were 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 Mass-Lynx-Openlynx software.

General procedure B

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), a diode-array detector (DAD) and a column as specified in the respective methods below. Flow from the col-

umn 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.

E.1 LCMS - PROCEDURE 1

In addition to the general procedure A: Reversed phase HPLC was carried out on an XDB-C18 cartridge (3.5 µm, 4.6 x 30 mm) from Agilent, with a flow rate of 1 ml/min. 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 6.0 minutes, to 100 % B at 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.6 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 1.0 second using a dwell time of 1.0 second. 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.

E.2 LCMS - PROCEDURE 2

In addition to the general procedure A: Reversed phase HPLC was carried out on an XDB-C18 cartridge (3.5 µm, 4.6 x 30 mm) from Agilent, with a flow rate of 1 ml/min. 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 6.0 minutes, to 100 % B at 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.6 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.

E.3 LCMS - PROCEDURE 3

In addition to the general procedure A: Reversed phase HPLC was carried out on an

XDB-C18 cartridge (3.5 μ m, 4.6 x 30 mm) from Agilent, with a flow rate of 1 ml/min. 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 6.0 minutes, to 100 % B at 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.6 minutes until 9.0 minutes. Injection volume 5 μ l. 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.

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E.4 LCMS - PROCEDURE 4

In addition to the general procedure A: Reversed phase HPLC was carried out on an BONUS-RP column (3.5 μ m, 4.6 x 75 mm) from Agilent, with a flow rate of 1 ml/min. 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 8.0 minutes, to 100 % B at 9.0 minutes, equilibrated to initial conditions at 11.0 minutes until 13.0 minutes. Injection volume 5 μ l. High-resolution Mass spectra (Time of Flight, TOF) were acquired by scanning from 100 to 750 in 1.0 second using a dwell time of 1.0 second. 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.

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E.5 LCMS - PROCEDURE 5

In addition to the general procedure A: Reversed phase HPLC was carried out on an XDB-C8 cartridge (3.5 μ m, 4.6 x 30 mm) from Agilent, with a flow rate of 1 ml/min. 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 6.0 minutes, to 100 % B at 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.6 minutes until 9.0 minutes. Injection volume 5 μ l. 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.

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E.6 LCMS - PROCEDURE 6

In addition to the general procedure A: Reversed phase HPLC was carried out on an XDB-C18 cartridge (3.5 μ m, 4.6 x 30 mm) from Agilent, with a flow rate of 1 ml/min. 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 6.0 minutes, to 100 % B at 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.6 minutes until 9.0 minutes. Injection volume 5 μ l. High-resolution mass spectra (Time of Flight, TOF) were acquired only in positive ionization mode by scanning from 100 to 900 in 1.0 second using dwell time of 1.0 second. 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.

E.7 LCMS - PROCEDURE 7

In addition to the general procedure A: Reversed phase HPLC was carried out on an XDB-C18 cartridge (3.5 μ m, 4.6 x 30 mm) from Agilent, with a flow rate of 1 ml/min. 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 6.0 minutes, to 100 % B at 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.6 minutes until 9.0 minutes. Injection volume 5 μ l. 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.

E.8 LCMS - PROCEDURE 8

In addition to the general procedure A: same as procedure 3, but using 10 μ l of injection volume.

E.9 LCMS - PROCEDURE 9

In addition to the general procedure A: Reversed phase HPLC was carried out on an XDB-C18 cartridge (3.5 μ m, 4.6 x 30 mm) from Agilent, with a flow rate of 1 ml/min. 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 6.0 minutes, to 100 % B at 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.6 minutes until 9.0 minutes. Injection volume 5 μ l. High-resolution mass spectra (Time of Flight,

TOF) were acquired only in positive ionization mode by scanning from 100 to 750 in 1.0 second using a dwell time of 1.0 second. 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.

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E.10 LCMS - PROCEDURE 10

In addition to the general procedure A: Reversed phase HPLC was carried out on an XT-C18 column (3.5 μ m, 4.6 x 30 mm) from Waters, with a flow rate of 1 ml/min. The gradient conditions used are: 80 % A (1 g/l ammonium bicarbonate solution), 10 % B (acetonitrile), 10 % C (methanol) to 50 % B and 50 % C in 6.0 minutes, to 100 % B at 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.6 minutes until 9.0 minutes. Injection volume 10 μ l. 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.

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E.11 LCMS - PROCEDURE 11

In addition to the general procedure B: Reversed phase UPLC was carried out on a bridged ethylsiloxane/silica (BEH) C18 column (1.7 μ m, 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 H₂O/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 μ l was used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

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E12. Melting points

For a number of compounds, melting points were determined in open capillary tubes on a Mettler FP62 apparatus. Melting points were measured with a temperature gradient of 3 or 10 °C/minute. Maximum temperature was 300 °C. The melting point was read from a digital display.

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For a number of compounds, melting points were determined with a DSC823e (Mettler-Toledo). Melting points were measured with a temperature gradient of 30 °C/minute. Maximum temperature was 400 °C.

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Table 19: Analytical data

Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
1-1	3.01	382	1	
1-2	3.01	382	1	HCl-salt (.3HCl) Mp: decomposes
1-3	3.56	396	3	
1-4	4.76	416	2	
1-5	4.64	416	2	
1-6	nd	nd	-	Mp: 286 °C
1-7	0.70	444	11	Mp: 231 °C HCl-salt (.3HCl)
1-8	3.15	396	2	
1-9	3.57	458	1	Trifluoroacetate salt (.3CF ₃ COOH)
1-10	4.25	424	1	
1-11	4.82	472	3	HCl-salt (.2HCl)
1-12	4.77	472	3	
1-13	5.17	486	2	
1-14	3.67	410	1	Mp: 254 °C
1-15	nd	nd	-	HCl-salt (.3HCl)
1-16	4.01	410	1	Mp: 128 °C
1-17	6.46	472	2	
1-18	5.74	514	1	
1-19	4.51	438	1	
1-20	5.27	478	1	
1-21	3.55	440	1	
1-22	4.73	502	2	
1-23	4.02	454	1	
1-24	4.15	454	1	
1-25	5.63	502	2	
1-26	5.55	502	2	
1-27	4.93	516	2	
1-28	4.14	434	1	
1-29	4.66	472	3	Mp: 142 °C
1-30	4.49	486	1	
1-31	5.04	514	1	

Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
1-32	4.59	452	1	
1-33	5.44	492	1	
1-34	6.03	526	2	
1-35	5.99	526	2	
1-36	5.67	554	1	
1-37	4.19	438	2	Mp: 160 °C
1-38	4.59	452	2	
1-39	5.78	458	2	
1-40	4.84	458	1	
1-41	5.03	472	1	
1-42	4.94	476	2	
1-43	6.22	510	2	
1-44	6.20	510	2	
1-45	4.63	543	1	
1-46	4.91	472	2	
1-47				Mp: 270 °C HCl-salt (.3HCl)
1-48	4.67	472	1	
1-49	6.25	506	2	
1-50	6.21	506	2	
1-51	6.04	486	2	
1-52	5.04	486	1	
1-53	6.74	534	2	
1-54	6.77	534	3	
1-55	4.79	490	1	
1-56	5.61	552	2	
1-57	4.97	486	1	
1-58	6.41	520	2	
1-59	6.42	520	2	
1-60	5.28	500	1	
1-61	5.25	500	1	
1-62	5.66	514	1	
1-63	4.74	488	1	
1-64	4.76	502	1	
1-65	4.93	532	1	

Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
1-66	5.77	528	1	
1-67	4.72	516	1	
1-68	5.70	562	1	
1-69	5.70	548	2	
1-70	6.92	582	2	
1-71	6.96	562	2	
1-72	5.02	486	1	
1-73	5.31	548	1	
1-74	4.99	500	2	
1-75	5.22	573	1	
1-76	5.79	538	2	
1-77	5.78	538	2	
1-78	5.55	552	2	
1-79	4.95	518	2	
1-80	5.07	492	1	
1-81	5.63	534	2	
1-82	5.38	562	1	
1-83	4.65	452	1	
1-84	5.28	514	2	
1-85	5.92	542	2	
1-86	6.44	582	2	
1-87	5.94	576	2	
1-88	6.21	576	2	
1-89	6.10	590	2	
1-90	6.64	590	2	
1-91	nd	nd	-	
1-92	5.84	496	2	
1-93	4.72	516	1	
1-94	4.02	468	1	
1-95	5.10	516	3	
1-96	5.05	516	3	
1-97	3.96	468	1	
1-98	5.62	516	2	
1-99	5.62	516	2	
1-100	4.66	544	1	

Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
1-101	5.44	558	1	
1-102	3.30	453	1	
1-103	4.84	501	2	
1-104	4.76	501	2	
1-105	4.46	501	4	
1-106	4.53	501	4	
1-107	3.40	467	1	
1-108	3.65	467	1	
1-109	4.41	515	5	
1-110	4.57	515	3	mp: 115 °C
1-111	5.44	543	2	
1-112	5.71	605	6	
1-113	5.10	561	2	
1-114	3.56	467	1	
1-115	4.90	529	1	
1-116	6.58	547	1	
1-117	5.32	529	2	
1-118	5.53	569	1	
1-119	5.05	501	2	
1-120	5.72	553	2	
1-121	5.13	515	2	
1-122	6.00	577	2	
1-123	6.01	591	2	
1-124	5.24	577	1	
1-125	5.31	591	1	
1-126	5.27	637	1	
1-127	5.58	585	2	
1-128	5.53	585	2	
1-129	5.90	617	3	
1-130	4.66	527	4	
1-131	4.55	527	4	
1-132	3.83	507	1	
1-133	4.62	555	4	
1-134	5.67	575	2	
1-135	4.76	569	1	

Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
1-136	5.15	587	2	
1-137	4.78	601	2	
1-138	5.00	601	2	
1-139	5.14	615	2	
1-140	4.77	555	6	
1-141	3.88	473	1	
1-142	4.32	501	1	
1-143	5.06	598	2	
1-144	4.15	466	1	
1-145	5.20	514	2	
1-146	5.13	514	2	
1-147	4.41	462	1	
1-148	3.86	495	1	
1-149	4.91	543	4	
1-150	4.10	543	5	
1-151	5.32	603	2	
1-152	4.97	538	1	mp: 103 °C
1-153	4.91	525	2	
1-154	4.72	549	1	
1-155	4.12	460	2	
1-156	4.66	522	1	
1-157	5.39	564	1	
1-158	5.11	522	2	
1-159	5.44	584	1	mp: 128 °C
1-160	5.40	536	2	
1-161	5.33	609	1	
1-162	5.52	602	1	
1-163	5.87	652	1	
1-164	4.89	641	1	
1-165	5.35	626	1	mp: 110 °C
1-166	5.63	570	2	
1-167	5.71	610	1	
1-168	5.89	598	2	
1-169	5.51	550	2	
1-170	6.14	612	2	

Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
1-171	5.31	603	1	
2-1	5.71	512	1	
2-2	5.16	541	10	
2-3	5.51	436	1	
2-4	5.24	436	1	Mp: 294 °C HCl-salt (.3HCl)
2-5	4.49	450	1	Mp: 170 °C
2-6	6.59	484	2	
2-7	6.54	484	2	
2-8	6.55	484	7	HCl-salt (.HCl)
2-9	5.65	498	2	
2-10	5.83	498	2	
2-11	5.88	526	2	
2-12	4.95	518	1	
2-13	5.77	540	1	
2-14	4.78	542	1	
2-15	4.35	508	1	
2-16	5.20	570	2	
2-17	3.59	519	1	
2-18	4.85	553	2	
2-19	5.02	553	2	
2-20	3.87	465	1	
2-21	4.71	527	2	
2-22	3.59	493	1	
2-23	5.06	541	2	
2-24	4.45	491	1	
2-25	5.37	553	2	
2-26	5.18	527	1	
2-27	6.60	561	2	
2-28	6.63	561	2	
2-29	5.72	555	1	
2-30	5.24	541	1	
2-31	6.65	575	2	
2-32	6.04	603	6	
2-33	6.06	617	6	

Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
2-34	5.36	591	2	
2-35	4.42	523	1	
2-36	6.00	571	2	
2-37	6.02	571	2	
2-38	4.00	549	1	
2-39	4.63	438	1	
2-40	nd	nd	-	Mp: decomposes HCl-salt (.3HCl)
2-41	3.82	452	1	
2-42	5.63	486	2	
2-43	5.55	486	2	
2-44	5.50	500	8	HCl-salt (.2HCl)
2-45	5.50	514	2	
2-46	4.70	514	2	
2-47	5.25	418	3	
2-48	5.17	484	1	Mp: decomposes Trifluoroacetate salt (.2CF ₃ COOH)
2-49	4.91	498	1	
2-50	5.46	512	1	
2-51	5.49	526	1	
2-52	5.74	524	2	
2-53	nd	nd	-	
2-54	5.50	522	3	Mp: 67 °C Trifluoroacetate salt (.CF ₃ COOH)
2-55	1.10	560	11	
3-1	3.44	382	1	
3-2	4.70	431	3	
3-3	4.69	431	3	
3-4	3.14	445	2	
3-5	4.33	383	1	
3-6	4.67	397	1	
3-7	4.39	397	1	
3-8	5.00	439	1	

Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
3-9	5.59	431	2	
3-10	5.49	445	1	
3-11	5.45	445	1	
3-12	5.64	459	2	
3-13	5.41	473	1	
3-14	5.38	473	1	
3-15	6.05	499	1	Mp: 99 °C
3-16	4.6	411	1	
3-17	5.37	453	1	
3-18	5.7	445	1	
3-19	5.94	459	1	
3-20	5.4	473	1	
3-21	4.59	427	1	
4-1	5.03	399	1	
4-2	5.93	447	2	
4-3	5.59	569	1	Mp: 112 °C
5-1	5.52	401	2	
5-2	5.58	419	2	
5-3	5.26	426	2	
5-4	6.20	429	2	
5-5	5.06	429	2	
5-6	5.15	429	2	
5-7	5.32	443	2	
5-8	5.47	415	1	
5-9	5.83	429	1	
5-10	5.81	429	1	
5-11	5.58	433	1	
5-12	5.56	433	1	
5-13	1.04	433	11	Mp: decomposes
5-14	5.95	493	1	
5-15	5.95	493	1	
5-16	5.97	493	1	
5-17	5.86	449	1	
5-18	5.85	449	1	
5-19	5.14	440	1	

Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
5-20	5.07	440	1	Mp: decomposes
5-21	5.97	483	1	
5-22	5.90	483	1	
5-23	5.94	483	1	
5-24	5.36	460	1	
5-24	5.38	460	1	
5-25	5.45	460	1	Mp: 123 °C
5-26	4.52	493	1	
5-27	5.81	429	1	
5-28	5.98	441	1	
5-29	5.07	443	1	
5-30	6.45	477	2	
5-31	6.32	491	1	
5-32	6.30	491	1	
5-33	5.84	519	1	
5-34	6.06	465	1	
5-35	6.13	465	1	
6-1	5.47	423	9	
6-2	5.11	405	1	
6-3	5.02	420	1	Mp: 107 °C
6-4	5.43	407	3	Mp: 210 °C
6-5	6.05	408	3	
6-6	4.97	436	1	
6-7	4.92	436	1	HCl-salt (.2HCl)
6-8	4.89	436	1	
6-9	5.01	402	3	
6-10	5.10	402	3	HCl-salt (.2HCl)
6-11	4.51	402	3	Mp: decomposes
6-12	4.58	402	3	
6-13	4.49	416	1	
6-14	4.31	416	1	
6-15	4.58	514	1	
6-16	5.41	452	3	
6-17	5.52	466	1	
7-1	4.04	325	1	

Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
7-2	nd	nd	-	Mp: decomposes HCl-salt (.2HCl)
7-3	4.93	353	1	
7-4	5.25	367	1	
7-5	5.98	395	1	
7-6	6.2	421	1	
7-7	3.98	381	1	
7-8	5.12	423	1	
7-9	5.15	423	1	HCl-salt (.2HCl)
7-10	6.32	501	1	
7-11	5.06	365	1	Mp: 126 °C
8-1	4.29	430	1	Trifluoroacetate salt (.2CF ₃ COOH)
8-2	4.36	396	1	
8-3	5.78	468	1	
8-4	6.01	530	1	
9-1	4.70	436	1	
9-2	4.98	424	1	
10-1	5.30	383	1	
10-2	6.05	431	1	
10-3	6.00	445	1	
11-1	5.53	385	1	
12-1	5.92	401	1	
12-2	6.28	429	1	
12-3	6.18	427	1	
12-4	6.34	491	1	
12-5	5.51	429	1	
12-6	6.18	505	1	
12-7	6.35	451	1	
13-1	5.59	391	1	
13-2	6.23	441	1	
13-3	5.38	422	1	
13-4	5.61	499	1	
14-1	4.42	311	1	

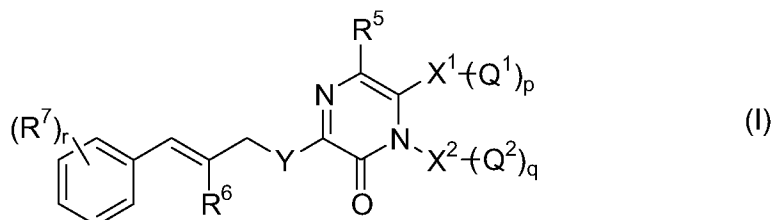
Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
14-2	5.55	353	1	
14-3	6.41	407	1	
14-4	5.60	409	1	
14-5	6.93	407	1	
15-1	4.00	458	1	Trifluoroacetate salt (.3CF ₃ COOH)
15-2	3.51	486	1	
15-3	5.61	450	1	
15-4	4.10	397	1	
15-5	4.80	441	1	
15-6	5.49	526	1	
15-7	5.65	437	1	
16-1	3.69	382	1	
16-2	2.90	396	1	
16-3	2.90	396	1	
16-4	4.90	468	1	
16-5	5.18	530	1	
16-6	4.33	422	1	
16-7	3.56	424	1	
16-8	4.72	498	1	Trifluoroacetate salt (.CF ₃ COOH)
16-9	3.62	369	1	
16-10	3.49	383	1	
16-11	4.62	439	1	
16-12	4.17	385	1	
16-13	5.29	405	1	
16-14	5.01	415	1	
16-15	5.35	479	1	
16-16	5.33	479	1	
16-17	5.36	479	1	
16-18	5.47	451	1	
16-19	4.68	409	1	
16-20	3.52	402	1	
16-21	4.78	452	1	
16-22	4.24	353	1	

Co. Nr.	R _t	(MH) ⁺	Proce- dure	Physico-chemical data
16-23	5.65	407	1	
16-24	3.22	367	1	
16-25	4.37	409	1	
17-1	nd	nd	-	
17-2	1.28	633	11	

nd = not determined

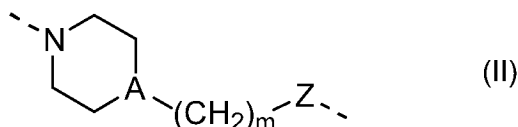
CLAIMS

1. Compound according to the general Formula (I)



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

Y is a bivalent radical of Formula (II)



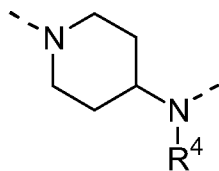
wherein

- A is a nitrogen or a carbon-atom ;
- 10 m is an integer equal to zero, 1 or 2 ; and
- Z is a covalent bond or N-R⁴ ; wherein R⁴ is selected from the group of hydrogen ; (C₁₋₃)alkyl and phenylcarboxyl(C₁₋₃)alkyl ;
- R⁵ is selected from the group of hydrogen and halo ;
- R⁶ is selected from the group of hydrogen and (C₁₋₃)alkyl ;
- 15 R⁷ is selected from the group of hydrogen, (C₁₋₃)alkyl; (C₁₋₃)alkyloxy; halo; cyano ; nitro ; formyl ; ethanoyl ; hydroxy ; amino ; trifluoromethyl ; mono- and di((C₁₋₃)alkyl)amino ; mono- and di((C₁₋₃)alkylcarbonyl)amino ; carboxyl; morpholinyl ; and thio ; and r is an integer equal to zero, 1, 2, 3, 4, or 5.;
- 20 X¹, X² are each, independently from each other, a bond, a saturated or an unsaturated bivalent (C₁₋₈)-hydrocarbon radical, wherein one or more bivalent -CH₂-units may optionally be replaced by a respective bivalent phenyl-unit ; and wherein one or more hydrogen atoms may be replaced by a radical selected from the group of oxo ; (C₁₋₃)alkyloxy ;
- 25 halo ; cyano ; nitro ; formyl ; hydroxy ; amino ; trifluoromethyl ; mono- and di((C₁₋₃)alkyl)amino ; carboxyl ; and thio ;

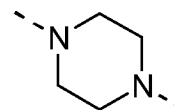
- Q¹, Q² are each, independently from each other, a radical selected from the group of hydrogen ; -NR¹R² ; Pir ; -OR^{3a} ; SR^{3b} ; SO₂R^{3c} ; aryl ; and Het; wherein two radicals -OR^{3a} may be taken together to form a bivalent radical -O-(CH₂)_r-O- wherein r is an integer equal to 1, 2 or 3 ;
- 5 p, q are each, independently from each other, an integer equal to 1 or 2;
- R¹ and R² are each, independently from each other, a radical selected from the group of hydrogen ; alkyl ; alkenyl ; alkynyl ; aryl ; arylalkyl ; diarylalkyl ; alkylcarbonyl ; alkylcarbonylalkyl ; alkenylcarbonyl ; alkyloxy ; alkyloxyalkyl ; alkyloxycarbonyl ; alkyloxyalkylcarbonyl ; alkyloxycarbonylalkyl ; alkyloxycarbonylalkylcarbonyl ; alkylsulfonyl ; arylsulfonyl ; arylalkylsulfonyl ; arylalkenylsulfonyl ; Het-sulfonyl ; arylcarbonyl ; arylalkylcarbonyl ; Het ; Het-alkyl ; Het-alkylcarbonyl ; Het-carbonyl ; Het-carbonylalkyl ; alkyl-NR^aR^b ; carbonyl-NR^aR^b ; carbonylalkyl-NR^aR^b ; alkylcarbonyl-NR^aR^b ; and alkylcarbonylalkyl-NR^aR^b ;
- 10 wherein R^a and R^b are each independently selected from the group of hydrogen, alkyl, alkylcarbonyl, alkyloxyalkyl, alkyloxycarbonylalkyl, aryl, arylalkyl, Het and alkyl-NR^cR^d, wherein R^c and R^d are each independently from each other hydrogen or alkyl ;
- Pir is a radical containing at least one N, by which it is attached to the X-radical, selected from the group of pyrrolidinyl ; imidazolidinyl ; pyrazolidinyl ; piperidinyl ; piperazinyl ; pyrrolyl ; pyrrolinyl ; imidazolinyl ; pyrrazolinyl ; pyrrolyl ; imidazolyl ; pyrazolyl ; triazolyl ; azepyl ; diazepyl ; morpholinyl ; thiomorpholinyl ; indolyl ; isoindolyl ; indolinyl ; indazolyl ; benzimidazolyl ; and 1,2,3,4-tetrahydro-isoquinolinyl ;
- 20 wherein each Pir-radical is optionally substituted by 1, 2 or 3 radicals selected from the group of hydroxy ; halo ; oxo ; (C₁₋₃)alkyl ; (C₁₋₃)alkenyl ; (C₁₋₃)alkyloxycarbonyl ; Het-carbonyl ; (C₁₋₃)alkylamino ; trifluoromethyl ; (phenylC₀₋₃)alkyl ; pyrimidinyl ; pyrrolidinyl ; and pyridinyloxy ;
- 30 R^{3a}, R^{3b}, R^{3c} are each, independently from each other, a radical selected from the group of hydrogen ; alkyl ; trihaloalkyl ; aryl ; arylalkyl ; alkyloxyalkyl ; Het ; and Het-alkyl ;
- Het is a heterocyclic radical selected from the group of pyrrolidinyl ; imidazolidinyl ; pyrazolidinyl ; piperidinyl ; piperazinyl ; pyrrolyl ; pyrrolinyl ; imidazolinyl ; pyrrazolinyl ; pyrrolyl ; imidazolyl ; pyrazolyl ; triazolyl ;
- 35

- pyridinyl ; pyridazinyl ; pyrimidinyl ; pyrazinyl ; triazinyl ; azepyl ; diazepyl ; morpholinyl ; thiomorpholinyl ; indolyl ; isoindolyl ; indolinyl ; indazolyl ; benzimidazolyl ; 1,2,3,4-tetrahydro-isoquinolinyl ; furyl ; thienyl ; oxazolyl ; isoxazolyl ; thiazolyl ; thiadiazolyl ; isothiazolyl ; dioxolyl ; dithianyl ; tetrahydrofuryl ; tetrahydropyranyl ; quinolinyl ; isoquinolinyl ; quinoxalinyl ; benzoxazolyl ; benzisoxazolyl ; benzothiazolyl ; benzisothiazolyl ; benzofuranyl ; benzothienyl ; benzopiperidinyl ; benzomorpholinyl ; chromenyl ; and imidazo[1,2-*a*]pyridinyl ; wherein each Het-radical is optionally substituted by one or more radicals selected from the group of halo ; oxo ; (C₁₋₃)alkyl ; (C₁₋₃)alkylcarbonyl ; (C₁₋₃)alkenylthio ; imidazolyl-(C₁₋₃)alkyl ; aryl(C₁₋₃)alkyl and (C₁₋₃)alkyl-oxycarbonyl ;
- aryl is naphthyl or phenyl, each optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of oxo ; (C₁₋₃)alkyl ; (C₁₋₃)alkyloxy ; halo ; cyano ; nitro ; formyl ; ethanoyl ; hydroxy ; amino ; trifluoromethyl ; mono- and di((C₁₋₃)alkyl)amino ; mono- and di((C₁₋₃)alkylcarbonyl)amino ; carboxyl ; morpholinyl ; and thio ;
- alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 8 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 8 carbon atoms ; wherein each radical is optionally substituted on one or more carbon atoms with one or more radicals selected from the group of oxo ; (C₁₋₃)alkyloxy, halo ; cyano ; nitro ; formyl ; hydroxy ; amino ; carboxyl ; and thio ;
- alkenyl is an alkyl radical as defined above, further having one or more double bonds ;
- alkynyl is an alkyl radical as defined above, further having one or more triple bonds ; and
- arylalkyl is an alkyl radical as defined above, further having one or more CH₃-groups replaced by phenyl.

2. Compound according to any one of claims 1 and 2, characterized in that Y is a bivalent radical of Formula (II-a) or (II-b).



(II-a)

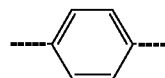


(II-b)

3. Compound according to any one of claims 1 to 2, characterized in that R⁴ is hydrogen or methyl.
4. Compound according to any one of claims 1 to 3, characterized in that R⁵ is hydrogen or chloro.
5. Compound according to any one of claims 1 to 4, characterized in that R⁶ is hydrogen or methyl.
6. Compound according to any one of claims 1 to 5, characterized in that R⁷ is hydrogen.
7. Compound according to any one of claims 1 to 6, characterized in that X¹ is a bond and Q¹ is hydrogen and X² is a bond or a (C₁₋₈)-hydrocarbon radical, more preferably a (C₁₋₆)-hydrocarbon radical, even more preferably a (C₁₋₅)-hydrocarbon radical, most preferably a (C₁₋₄)-hydrocarbon radical..
8. Compound according to claim 7, characterized in that in X² one bivalent -CH₂-unit of the hydrocarbon radical X² is replaced by a bivalent phenyl-unit; or two hydrogen atoms of the hydrocarbon radical X² are replaced by an oxo-radical.
9. Compound according to any one of claims 1 to 8, characterized in that each of X¹ and X², independently from each other, is selected from the group of a bond and any one of the radicals as defined below:

-CH₂-

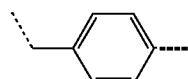
(aa)



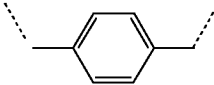
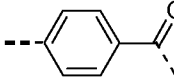
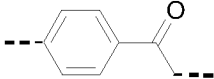
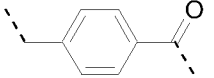
(ba)

-CH₂CH₂-

(ab)



(bb)

$-\text{CH}_2\text{CH}_2\text{CH}_2-$	(ac)		(be)
$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$	(ad)		(bg)
$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$	(ae)		(bh)
$-\text{CH}_2\text{CH}=\text{CH}-$	(af)		(bk)
$-\text{CH}_2\text{CH}=\text{CHCH}_2-$	(ag)		
$-\text{CH}_2\text{C}\equiv\text{CCH}_2-$	(ah)		
	(aj)		
$-\text{C}(=\text{O})\text{CH}_2-$	(al)		
$-\text{C}(=\text{O})\text{CH}_2\text{CH}_2-$	(am)		
$-\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$	(ao)		
$-\text{CH}_2\text{C}(=\text{O})\text{CH}_2-$	(ap)		
$-\text{CH}_2\text{C}(=\text{O})\text{C}(\text{CH}_3)_2\text{CH}_2-$	(ar)		

10. Compound according to any one of claims 1 to 9, characterized in that X^1 is a bond, $p=1$ and Q^1 is hydrogen and $q=1$ and Q^2 is selected from the group of hydrogen ; $-\text{NR}^1\text{R}^2$; Pir ; $-\text{OR}^{3a}$; SR^{3b} ; SO_2R^{3c} ; aryl ; and Het.

5

11. Compound according to any one of claims 1 to 10, characterized in that R^1 and R^2 are each, independently from each other, a radical selected from the group of hydrogen ; alkyl ; alkynyl ; aryl ; arylalkyl ; diarylalkyl ; alkylcarbonyl ; alkylcarbonylalkyl ; alkyloxycarbonyl ; alkyloxyalkylcarbonyl ; alkyloxycarbonylalkyl ; alkyloxy-carbonylalkylcarbonyl ; alkylsulfonyl ; arylsulfonyl ; arylalkylsulfonyl ; arylalkenyl-sulfonyl ; Het-sulfonyl ; arylcarbonyl ; arylalkylcarbonyl ; Het ; Het-alkyl ; Het-carbonyl ; alkyl- NR^aR^b ; and carbonyl- NR^aR^b ; wherein R^a and R^b are each independently selected from the group of hydrogen, alkyl, alkylcarbonyl, aryl, and arylalkyl.

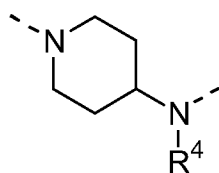
10

12. Compound according to any one of claims 1 to 11, characterized in that Pir is a radical containing at least one N, by which it is attached to the radical X^1 or X^2 , selected from the group of pyrrolidinyl ; piperidinyl ; piperazinyl ; pyrrolyl ; mor-

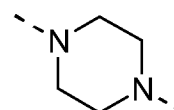
15

pholinyl ; and isoindolyl ; wherein each Pir-radical is optionally substituted by 1, 2 or 3 radicals selected from the group of hydroxy ; (C₁₋₃)alkyl ; (C₁₋₃)alkenyl ; (C₁₋₃)alkyloxycarbonyl ; Het-carbonyl ; (C₁₋₃)alkylamino ; trifluoromethyl ; (C₀₋₃)alkylphenyl ; and pyrrolidinyl.

- 5 13. Compound according to any one of claims 1 to 10, characterized in that R^{3a}, R^{3b}, R^{3c} are each, independently from each other, a radical selected from the group of hydrogen ; alkyl ; trihaloalkyl ; aryl ; arylalkyl ; and alkyloxyalkyl.
14. Compound according to any one of claims 1 to 10, characterized in that Het is a heterocyclic radical selected from the group of pyrrolidinyl ; piperidinyl ; imidazolyl
10 ; pyridinyl ; morpholinyl ; furyl ; thienyl ; isoxazolyl ; thiazolyl ; tetrahydrofuryl ; tetrahydropyranyl ; quinolinyl ; benzomorpholinyl ; wherein each Het-radical is optionally substituted by one or more radicals selected from the group of halo ; oxo ; (C₁₋₃)alkyl ; aryl(C₁₋₃)alkyl and (C₁₋₃)alkyloxycarbonyl.
15. Compound according to any one of claims 1 to 10, characterized in that aryl is
15 phenyl, optionally substituted with 1 or 2 substituents, each independently from each other, selected from the group of (C₁₋₃)alkyloxy ; halo ; cyano ; ethanoyl ; trifluoromethyl ; mono- and di((C₁₋₃)alkylcarbonyl)amino ; and morpholinyl.
16. Compound according to claim 1, characterized in that :
Y is a bivalent radical of Formula (II-a) or (II-b)



(II-a)



(II-b)

- 20 wherein R⁴ is hydrogen or methyl ;
- R⁵ is hydrogen or chloro ;
- R⁶ is hydrogen or methyl ;
- R⁷ is hydrogen ;
- 25 X¹, X² are each, independently from each other, a bond, a saturated or an unsaturated bivalent (C₁₋₈)-hydrocarbon radical, wherein one or more bivalent -CH₂-units may optionally be replaced by a respective bivalent phenyl-unit ; and wherein one or more hydrogen atoms may be replaced by an oxo-radical ;

Q^1, Q^2 are each, independently from each other, a radical selected from the group of hydrogen ; $-NR^1R^2$; Pir ; $-OR^{3a}$; SR^{3b} ; SO_2R^{3c} ; aryl ; and Het ;

p, q are each, independently from each other, an integer equal to 1 ;

5 R^1 and R^2 are each, independently from each other, a radical selected from the group of hydrogen ; alkyl ; alkynyl ; aryl ; arylalkyl ; diarylalkyl ; alkylcarbonyl ; alkylcarbonylalkyl ; alkyloxycarbonyl ; alkyloxyalkylcarbonyl ; alkyloxycarbonylalkyl ; alkyloxycarbonylalkylcarbonyl ; alkylsulfonyl ; arylsulfonyl ; arylalkylsulfonyl ; arylalkenylsulfonyl ; Het-sulfonyl ; arylcarbonyl ; arylalkylcarbonyl ; Het ; Het-alkyl ; Het-carbonyl ; alkyl-
10 NR^aR^b ; and carbonyl- NR^aR^b ; wherein R^a and R^b are each independently selected from the group of hydrogen, alkyl, alkylcarbonyl, aryl, and arylalkyl ;

Pir is a radical containing at least one N, by which it is attached to the radical X^1 or X^2 , selected from the group of pyrrolidinyl ; piperidinyl ; piperazinyl ; pyrrol-
15 rolyl ; morpholinyl ; and isoindolyl ; wherein each Pir-radical is optionally substituted by 1, 2 or 3 radicals selected from the group of hydroxy ; (C_{1-3}) alkyl ; (C_{1-3}) alkenyl ; (C_{1-3}) alkyloxycarbonyl ; Het-carbonyl ; (C_{1-3}) alkylamino ; trifluoromethyl ; (C_{0-3}) alkylphenyl ; and pyrrolidinyl ;

20 R^{3a}, R^{3b}, R^{3c} are each, independently from each other, a radical selected from the group of a radical selected from the group of hydrogen ; alkyl ; trihaloalkyl ; aryl ; arylalkyl ; and alkyloxyalkyl.

Het is a heterocyclic radical selected from the group of pyrrolidinyl ; piperidinyl ; imidazolyl ; pyridinyl ; morpholinyl ; furyl ; thienyl ; isoxazolyl ; thiazolyl ; tetrahydrofuryl ; tetrahydropyranyl ; quinolinyl ; benzomorpholinyl ;
25 wherein each Het-radical is optionally substituted by one or more radicals selected from the group of halo ; oxo ; (C_{1-3}) alkyl ; aryl (C_{1-3}) alkyl and (C_{1-3}) alkyloxycarbonyl.

aryl is phenyl, optionally substituted with 1 or 2 substituents, each independently from each other, selected from the group of (C_{1-3}) alkyloxy ; halo ;
30 cyano ; ethanoyl ; trifluoromethyl ; mono- and di $((C_{1-3})$ alkylcarbonyl)amino ; and morpholinyl ;

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 8 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms ; or is a cyclic saturated hydrocarbon radical
35 having from 3 to 7 carbon atoms attached to a straight or branched satu-

rated hydrocarbon radical having from 1 to 8 carbon atoms ; wherein each radical is optionally substituted on one or more carbon atoms with one or more radicals selected from the group of (C₁₋₃)alkyloxy ; hydroxy ; and thio ;

5 alkenyl is an alkyl radical as defined above, further having one or more double bonds ;

alkynyl is an alkyl radical as defined above, further having one or more triple bonds ; and

10 arylalkyl is an alkyl radical as defined above, further having one or more CH₃-groups replaced by phenyl.

17. Compound according to any one of claims 1 to 16 for use as a medicine.
18. Pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a therapeutically effective amount of a compound according to any one of claims 1 to 16.
- 15 19. Pharmaceutical composition according to claim 18, characterized in that it comprises further one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics.
20. Pharmaceutical composition according to any one of claims 18 and 19, characterized in that it is in a form suitable to be orally administered.
- 20 21. Process for the preparation of a pharmaceutical composition as claimed in any one of claims 18 to 20, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as claimed in any one of claims 1 to 16.
22. Process for the preparation of a pharmaceutical composition as claimed in any
25 one of claims 18 to 20, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as claimed in any one of claims 1 to 16 and one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics.
23. Use of a compound according to any one of claims 1 to 16 for the preparation of a
30 medicament for the prevention and/or treatment of diseases where antagonism of the α_2 -adrenergic receptor, in particular antagonism of the α_{2C} -adrenergic receptor is of therapeutic use.

24. Use of a compound according to any one of claims 1 to 16 for the preparation of a medicament for the prevention and/or treatment of central nervous system disorders, mood disorders, anxiety disorders, stress-related disorders associated with depression and/or anxiety, cognitive disorders, personality disorders, schizoaffective disorders, Parkinson's disease, dementia of the Alzheimer's type, chronic pain conditions, neurodegenerative diseases, addiction disorders, mood disorders and sexual dysfunction.
25. Use of a compound according to any one of claims 1 to 16 in combination with one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics for the preparation of a medicament for the prevention and/or treatment of central nervous system disorders, mood disorders, anxiety disorders, stress-related disorders associated with depression and/or anxiety, cognitive disorders, personality disorders, schizoaffective disorders, Parkinson's disease, dementia of the Alzheimer's type, chronic pain conditions, neurodegenerative diseases, addiction disorders, mood disorders and sexual dysfunction.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/053821

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D413/14 C07D405/14 C07D401/14 C07D401/12 C07D409/14
 C07D417/14 C07D239/36 C07D403/06 C07D405/06 C07D409/06
 C07D417/06 C07D413/06 A61K31/513 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/28300 A (ALLERGAN SALES, INC) 10 June 1999 (1999-06-10) claim 1	1-25
A	UHLEN S ET AL: "THE NOVEL ALPHA-2 ADRENERGIC RADIOLIGAND 3H-MK912 IS ALPHA-2C SELECTIVE AMONG HUMAN ALPHA-2A, ALPHA-2B AND ALPHA-2C ADRENOCEPTORS" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND, US, vol. 271, no. 3, December 1994 (1994-12), pages 1558-1565, XP001083702 ISSN: 0022-3565 table 1	1-25



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	UHLEN S ET AL: "COMPARISON OF THE BINDING ACTIVITIES OF SOME DRUGS ON ALPHA2A, ALPHA2B AND ALPHA2C-ADRENOEPTORS AND NON-ADRENERGIC IMIDAZOLINE SITES IN THE GUINEA PIG" PHARMACOLOGY AND TOXICOLOGY, MUNKSGAARD INTERNATIONAL PUBLISHERS, COPENHAGEN,, DK, vol. 76, June 1995 (1995-06), pages 353-364, XP001084676 ISSN: 0901-9928 table 1 -----	1-25

INTERNATIONAL SEARCH REPORT

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