



(43) International Publication Date
25 June 2015 (25.06.2015)

(10) International Publication Number
WO 2015/091988 A1

(51) International Patent Classification:

C07D 401/14 (2006.01) *A61P 25/04* (2006.01)
C07D 401/06 (2006.01) *A61P 25/06* (2006.01)
A61K 31/4439 (2006.01)

(21) International Application Number:

PCT/EP2014/078811

(22) International Filing Date:

19 December 2014 (19.12.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

13384005.8 20 December 2013 (20.12.2013) EP

(71) Applicant: **LABORATORIOS DEL DR. ESTEVE, S.A.**
[ES/ES]; Av. Mare de Déu de Montserrat 221, E-08041
Barcelona (ES).

(72) Inventors: **CUEVAS CORDOBES, Felix**; Pza. Hermano
Ramon Quiroga 2, 4^oF, E-28342 Valdemoro, Madrid (ES).
ALMANSA-ROSALES, Carmen; Teodora Lamadrid 41,
E-08022 Barcelona (ES). **AYET GARCERA, Eva Maria**;
Sardenya, 493, 6^o-2a, E-08025 Barcelona (ES). **SER-
AFINI CABANES, Maria Teresa**; Sol, 262, 7^o-2a, E-
08201 Sabadell (ES). **GARCIA LOPEZ, Monica**; Gran
Via de les Corts Catalanes, 911, 2^o-1a, E-08028 Barcelona
(ES).

(74) Agent: **PETERS, Hajo**; Zacco GmbH, Bayerstr. 83, 80335
Munich (DE).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: PIPERIDINE COMPOUNDS HAVING MULTIMODAL ACTIVITY AGAINST PAIN

(57) Abstract: The present invention relates to compounds having dual pharmacological activity towards both the sigma (σ) receptor, and the μ -opioid receptor and more particularly to piperidine compounds having this pharmacological activity, to processes of preparation of such compounds, to pharmaceutical compositions comprising them, and to their use in therapy, in particular for the treatment of pain.



WO 2015/091988 A1

Piperidine Compounds having multimodal activity against pain

FIELD OF THE INVENTION

The present invention relates to compounds having dual pharmacological activity towards both the sigma (σ) receptor, and the μ -opioid receptor (MOR or mu-opioid) and more particularly to piperidine compounds having this pharmacological activity, to processes of preparation of such compounds, to pharmaceutical compositions comprising them, and to their use in therapy, in particular for the treatment of pain.

BACKGROUND OF THE INVENTION

The adequate management of pain constitutes an important challenge, since currently available treatments provide in many cases only modest improvements, leaving many patients unrelieved [Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. *Lancet* 377, 2226-2235 (2011)]. Pain affects a big portion of the population with an estimated prevalence of around 20% and its incidence, particularly in the case of chronic pain, is increasing due to the population ageing. Additionally, pain is clearly related to comorbidities, such as depression, anxiety and insomnia, which lead to important productivity losses and socio-economical burden [Goldberg DS, McGee SJ. Pain as a global public health priority. *BMC Public Health*. 11, 770 (2011)]. Existing pain therapies include non-steroidal anti-inflammatory drugs (NSAIDs), opioid agonists, calcium channel blockers and antidepressants, but they are much less than optimal regarding their safety ratio. All of them show limited efficacy and a range of secondary effects that preclude their use, especially in chronic settings.

As mentioned before, there are few available therapeutic classes for the treatment of pain, and opioids are among the most effective, especially when addressing severe pain states. They act through three different types of opioid receptors (mu, kappa and gamma) which are transmembrane G-protein coupled receptors (GPCRs). Still, the main analgesic action is attributed to the activation of the μ -opioid receptor (MOR). However, the general administration of MOR agonists is limited due to their important side effects, such as constipation, respiratory depression, tolerance, emesis and physical dependence [Meldrum, M.L. (Ed.). Opioids and Pain Relief: A Historical Perspective. Progress in Pain Research and Management, Vol 25. IASP Press,

Seattle, 2003]. Additionally, MOR agonists are not optimal for the treatment of chronic pain as indicated by the diminished effectiveness of morphine against chronic pain conditions. This is especially proven for the chronic pain conditions of neuropathic or inflammatory origin, in comparison to its high potency against acute pain. The finding
5 that chronic pain can lead to MOR down-regulation may offer a molecular basis for the relative lack of efficacy of morphine in long-term treatment settings [Dickenson, A.H., Suzuki, R. *Opioids in neuropathic pain: Clues from animal studies*. Eur J Pain 9, 113-6 (2005)]. Moreover, prolonged treatment with morphine may result in tolerance to its analgesic effects, most likely due to treatment-induced MOR down-regulation,
10 internalization and other regulatory mechanisms. As a consequence, long-term treatment can result in substantial increases in dosing in order to maintain a clinically satisfactory pain relief, but the narrow therapeutic window of MOR agonists finally results in unacceptable side effects and poor patient compliance.

The sigma-1 (σ_1) receptor was discovered 35 years ago and initially assigned to a
15 new subtype of the opioid family, but later on and based on the studies of the enantiomers of SKF-10,047, its independent nature was established. The first link of the σ_1 receptor to analgesia was established by Chien and Pasternak [Chien CC, Pasternak GW. Sigma antagonists potentiate opioid analgesia in rats. *Neurosci. Lett.* 190, 137-9 (1995)], who described it as an endogenous anti-opioid system, based on
20 the finding that σ_1 receptor agonists counteracted opioid receptor mediated analgesia, while σ_1 receptor antagonists, such as haloperidol, potentiated it.

Many additional preclinical evidences have indicated a clear role of the σ_1 receptor in the treatment of pain [Zamanillo D, Romero L, Merlos M, Vela JM. σ_1 receptor: A new therapeutic target for pain. *Eur. J. Pharmacol*, 716, 78-93 (2013)]. The development
25 of the σ_1 receptor knockout mice, which show no obvious phenotype and perceive normally sensory stimuli, was a key milestone in this endeavour. In physiological conditions the responses of the σ_1 receptor knockout mice to mechanical and thermal stimuli were found to be undistinguishable from WT ones but they were shown to possess a much higher resistance to develop pain behaviours than WT mice when
30 hypersensitivity entered into play. Hence, in the σ_1 receptor knockout mice capsaicin did not induce mechanical hypersensitivity, both phases of formalin-induced pain were reduced, and cold and mechanical hypersensitivity were strongly attenuated after partial sciatic nerve ligation or after treatment with paclitaxel, which are models

of neuropathic pain. Many of these actions were confirmed by the use of σ_1 receptor antagonists and led to the advancement of one compound, S1RA, into clinical trials for the treatment of different pain states. Compound S1RA exerted a substantial reduction of neuropathic pain and anhedonic state following nerve injury (i.e.,
5 neuropathic pain conditions) and, as demonstrated in an operant self-administration model, the nerve-injured mice, but not sham-operated mice, acquired the operant responding to obtain it (presumably to get pain relief), indicating that σ_1 receptor antagonism relieves neuropathic pain and also address some of the comorbidities (i.e., anhedonia, a core symptom in depression) related to pain states.

10 Pain is multimodal in nature, since in nearly all pain states several mediators, signaling pathways and molecular mechanisms are implicated. Consequently, monomodal therapies fail to provide complete pain relief. Currently, combining existing therapies is a common clinical practice and many efforts are directed to assess the best combination of available drugs in clinical studies [Mao J, Gold MS,
15 Backonja M. Combination drug therapy for chronic pain: a call for more clinical studies. *J. Pain* 12, 157-166 (2011)]. Hence, there is an urgent need for innovative therapeutics to address this unmet medical need.

As mentioned previously, opioids are among the most potent analgesics but they are also responsible for various adverse effects which seriously limit their use.

20 Accordingly, there is still a need to find compounds that have an alternative or improved pharmacological activity in the treatment of pain, being both effective and showing the desired selectivity, and having good "drugability" properties, i.e. good pharmaceutical properties related to administration, distribution, metabolism and excretion.

25 Thus, the technical problem can therefore be formulated as finding compounds that have an alternative or improved pharmacological activity in the treatment of pain.

In view of the existing results of the currently available therapies and clinical practices, the present invention offers a solution by combining in a single compound
30 binding as a ligand to two different receptors relevant for the treatment of pain. This was mainly achieved by providing the compound according to the invention that bind both to the μ -opioid receptor and to the σ_1 receptor.

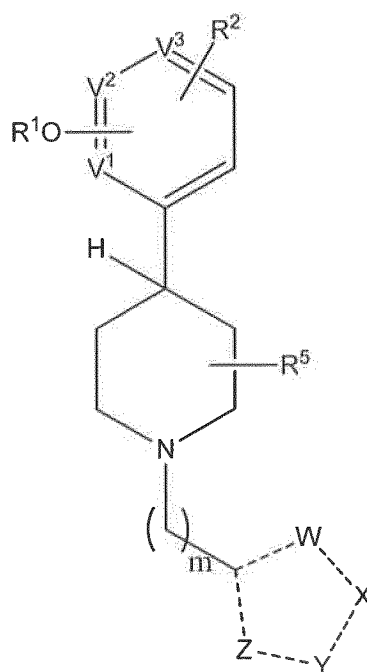
SUMMARY OF THE INVENTION

In this invention a family of structurally distinct piperidine derivatives which have a dual pharmacological activity towards both the sigma (σ) receptor, and the μ -opioid receptor was identified thus solving the above problem of identifying alternative or improved pain treatments by offering such dual compounds.

The invention is in one aspect directed to a compound having a dual activity binding to the σ_1 receptor and the μ -opioid receptor for use in the treatment of pain.

As this invention is aimed at providing a compound or a chemically related series of compounds which act as dual ligands of the σ_1 receptor and the μ -opioid receptor it is a very preferred embodiment if the compound has a binding expressed as K_i which is < 100 nm for both receptors, the μ -opioid receptor and the σ_1 receptor.

The invention is directed in a main aspect to a compound of general formula (I),



(I)

wherein R^1 , R^2 , R^5 , V^1 , V^2 , V^3 , W , X , Y , Z and m are as defined below in the detailed description.

DETAILED DESCRIPTION OF THE INVENTION

5 The invention is directed to a family of structurally distinct piperidine derivatives which have a dual pharmacological activity towards both the sigma (σ) receptor, and the μ -opioid receptor was identified thus solving the above problem of identifying alternative or improved pain treatments by offering such dual compounds.

The invention is in one aspect directed to a compound having a dual activity binding to the σ_1 receptor and the μ -opioid receptor for use in the treatment of pain.

10 As this invention is aimed at providing a compound or a chemically related series of compounds which act as dual ligands of the σ_1 receptor and the μ -opioid receptor it is a very preferred embodiment if the compound has a binding expressed as K_i which is < 100 nm for both receptors, the μ -opioid receptor and the σ_1 receptor.

15 The applicant has surprisingly found that the problem on which the present invention is based can be solved by using a multimodal balanced analgesic approach combining two different synergistic activities in a single drug (i.e., dual ligands which are bifunctional and bind to MOR and to σ_1 receptor), thereby enhancing the opioid analgesia through the σ_1 activation without increasing the undesirable side effects. This supports the therapeutic value of a dual MOR/ σ_1 receptor compound whereby
20 the σ_1 receptor binding component acts as an intrinsic adjuvant of the MOR binding component.

This solution offered the advantage that the two mechanisms complement each other in order to treat pain and chronic pain using lower and better tolerated doses needed based on the potentiation of analgesia but avoiding the adverse events of μ -opioid
25 receptor agonists.

A dual compound that possess binding to both the μ -opioid receptor and to the σ_1 receptor shows a highly valuable therapeutic potential by achieving an outstanding analgesia (enhanced in respect to the potency of the opioid component alone) with a reduced side-effect profile (safety margin increased compared to that of the opioid
30 component alone) versus existing opioid therapies.

Advantageously, the dual compounds according to the present invention would in addition show one or more the following functionalities: σ_1 receptor antagonism and MOR agonism. It has to be noted, though, that both functionalities “antagonism” and “agonism” are also sub-divided in their effect into subfunctionalities like partial agonism or inverse agonism. Accordingly, the functionalities of the dual compound should be considered within a relatively broad bandwidth.

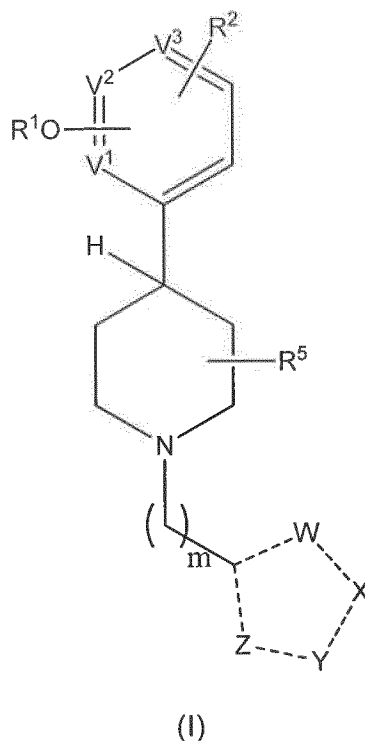
An antagonist on one of the named receptors blocks or dampens agonist-mediated responses. Known subfunctionalities are neutral antagonists or inverse agonists.

An agonist on one of the named receptors increases the activity of the receptor above its basal level. Known subfunctionalities are full agonists, or partial agonists.

In addition, the two mechanisms complement each other since MOR agonists are only marginally effective in the treatment of neuropathic pain, while σ_1 receptor antagonists show outstanding effects in preclinicalneuropathic pain models. Thus, the σ_1 receptor component adds unique analgesic actions in opioid-resistant pain. Finally, the dual approach has clear advantages over MOR agonists in the treatment of chronic pain as lower and better tolerated doses would be needed based on the potentiation of analgesia but not of the adverse events of MOR agonists.

A further advantage of using designed multiple ligands is a lower risk of drug-drug interactions compared to cocktails or multi-component drugs, thus involving simpler pharmacokinetics and less variability among patients. Additionally, this approach may improve patient compliance and broaden the therapeutic application in relation to monomechanistic drugs, by addressing more complex aetiologies. It is also seen as a way of improving the R&D output obtained using the “one drug-one target” approach, which has been questioned over the last years [Bornot A, Bauer U, Brown A, Firth M, Hellawell C, Engkvist O. Systematic Exploration of Dual-Acting Modulators from a Combined Medicinal Chemistry and Biology Perspective. *J. Med. Chem*, 56, 1197-1210 (2013)].

In a particular aspect, the present invention is directed to compounds of general formula (I):



wherein

m is 1 or 2;

- 5 one of V^1 , V^2 and V^3 is selected from nitrogen or carbon while the others are carbon;

R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycl;

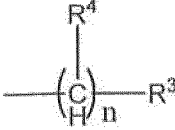
- 10 R^2 is hydrogen, halogen, $-\text{NR}^8\text{R}^9$, $-\text{SR}^7$, $-\text{OR}^7$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycl;

- 15 R^5 is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl;

R^6 , R^7 , R^8 and R^9 are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or

unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl; or R⁶ and R⁷ or R⁸ and R⁹ together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring;

- 5 and wherein W, X, Y and Z are selected from carbon, nitrogen, or oxygen while W-X-Y-Z are forming together with the bridging C-atom, that is connected to the core scaffold, a 5-membered heterocyclic ring, which is either substituted on one

of W, X, Y or Z by  or in which this said 5-membered heterocyclic ring - being otherwise unsubstituted - is fused at W and X to a further ringsystem;

- 10 wherein

n is 0 or 1;

- 15 R³ is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl; and

R⁴ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

- 20 optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof.

- 25 In another embodiment the compound according to the invention – especially according to general formula (I) - is optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or

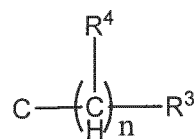
diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

In another embodiment the compound according to the invention – especially according to general formula (I) – is optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof.

In another embodiment the compound according to the invention – especially according to general formula (I) – is optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio.

In one embodiment one or more of the following provisos apply:

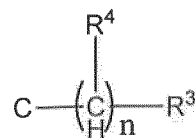
- with the proviso that if V^1 , V^2 and V^3 are carbon and either X or Y is



with $n = 0$ and R^3 being CH_3 , then OR^1 may not be $-\text{OCH}_3$ in meta position;

and/or

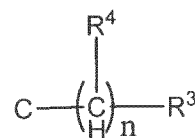
- with the proviso that if V^1 , V^2 and V^3 are carbon and either X or Y is



then R^3 may not be alkyl;

and/or

- with the proviso that if V^1 , V^2 and V^3 are carbon and either X or Y is



then R^5 may not be OH;

and/or

with the proviso that the compound may not be 3-Piperidinol, 4-(3-methoxyphenyl)-1-[(2-methyl-1H-imidazol-5-yl)methyl];

and/or

- 5 with the proviso that the compound may not be 1H-Pyrazole-3-carboxylic acid, 4-[[[(3R,4R)-3-hydroxy-4-(3-methoxyphenyl)-1-piperidinyl]methyl].

When different radicals R¹ to R⁸ are present simultaneously in the different Formulas of the present invention they may be identical or different.

10 In the context of this invention, alkyl is understood as meaning saturated, linear or branched hydrocarbons, which may be unsubstituted or substituted once or several times. It encompasses e.g. -CH₃ and -CH₂-CH₃. In these radicals, C₁₋₂-alkyl represents C1- or C2-alkyl, C₁₋₃-alkyl represents C1-, C2- or C3-alkyl, C₁₋₄-alkyl represents C1-, C2-, C3- or C4-alkyl, C₁₋₅-alkyl represents C1-, C2-, C3-, C4-, or C5-alkyl, C₁₋₆-alkyl represents C1-, C2-, C3-, C4-, C5- or C6-alkyl, C₁₋₇-alkyl represents
15 C1-, C2-, C3-, C4-, C5-, C6- or C7-alkyl, C₁₋₈-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7- or C8-alkyl, C₁₋₁₀-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9- or C10-alkyl and C₁₋₁₈-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9-, C10-, C11-, C12-, C13-, C14-, C15-, C16-, C17- or C18-alkyl. The alkyl radicals are preferably methyl, ethyl, propyl, methylethyl, butyl, 1-methylpropyl, 2-methylpropyl,
20 1,1-dimethylethyl, pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl, 1-methylpentyl, if substituted also CHF₂, CF₃ or CH₂OH etc. Preferably alkyl is understood in the context of this invention as C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl.

25 Alkenyl is understood as meaning unsaturated, linear or branched hydrocarbons, which may be unsubstituted or substituted once or several times. It encompasses groups like e.g. -CH=CH-CH₃. The alkenyl radicals are preferably vinyl (ethenyl), allyl (2-propenyl). Preferably in the context of this invention alkenyl is C₂₋₁₀-alkenyl or C₂₋₈-alkenyl like ethylene, propylene, butylene, pentylene, hexylene, heptylene or
30 octylene; or is C₁₋₆-alkenyl like ethylene, propylene, butylene, pentylene, or hexylene; or is C₁₋₄-alkenyl, like ethylene, propylene, or butylenes.

Alkynyl is understood as meaning unsaturated, linear or branched hydrocarbons, which may be unsubstituted or substituted once or several times. It encompasses groups like e.g. $\text{-C}\equiv\text{C-CH}_3$ (1-propynyl). Preferably alkynyl in the context of this invention is C_{2-10} -alkynyl or C_{2-8} -alkynyl like ethyne, propyne, butyne, pentyne, 5 hexyne, heptyne, or octyne; or is C_{2-6} -alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; or is C_{2-4} -alkynyl like ethyne, propyne, butyne, pentyne, or hexyne.

In the context of this invention cycloalkyl is understood as meaning saturated and unsaturated (but not aromatic) cyclic hydrocarbons (without a heteroatom in the ring), which can be unsubstituted or once or several times substituted. Furthermore, C_{3-4} -cycloalkyl represents C_3 - or C_4 -cycloalkyl, C_{3-5} -cycloalkyl represents C_3 -, C_4 - or C_5 -cycloalkyl, C_{3-6} -cycloalkyl represents C_3 -, C_4 -, C_5 - or C_6 -cycloalkyl, C_{3-7} -cycloalkyl represents C_3 -, C_4 -, C_5 -, C_6 - or C_7 -cycloalkyl, C_{3-8} -cycloalkyl represents C_3 -, C_4 -, C_5 -, C_6 -, C_7 - or C_8 -cycloalkyl, C_{4-5} -cycloalkyl represents C_4 - or C_5 -cycloalkyl, C_{4-6} -cycloalkyl represents C_4 -, C_5 - or C_6 -cycloalkyl, C_{4-7} -cycloalkyl represents C_4 -, C_5 -, C_6 - or C_7 -cycloalkyl, C_{5-6} -cycloalkyl represents C_5 - or C_6 -cycloalkyl and C_{5-7} -cycloalkyl represents C_5 -, C_6 - or C_7 -cycloalkyl. Examples are cyclopropyl, 2-methylcyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cycloheptyl, cyclooctyl, and also adamantly. Preferably in the context of this invention cycloalkyl is C_{3-8} -cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, 20 cyclohexyl, cycloheptyl, or cyclooctyl; or is C_{3-7} -cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; or is C_{3-6} -cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, especially cyclopentyl or cyclohexyl.

In connection with alkyl (also in alkylaryl, alkylheterocyclyl or alkylcycloalkyl), alkenyl, alkynyl and O-alkyl - unless defined otherwise - the term substituted in the context of this invention is understood as meaning replacement of at least one hydrogen radical on a carbon atom by F, Cl, Br, I, NH_2 , SH or OH, -C(O)OH , or $\text{-OC}_{1-4}\text{alkyl}$ being unsubstituted or substituted by one or more of OH or halogen (F, Cl, I, Br). More than one replacement on the same molecule and also on the same carbon atom is possible with the same or different substituents. This includes for example 3 30 hydrogens being replaced on the same C atom, as in the case of CF_3 , or at different places of the same molecule, as in the case of e.g. $\text{-CH(OH)-CH=CH-CHCl}_2$.

More than one replacement on the same molecule and also on the same carbon atom is possible with the same or different substituents. This includes for example 3

hydrogens being replaced on the same C atom, as in the case of CF_3 , or at different places of the same molecule, as in the case of e.g. $-\text{CH}(\text{OH})-\text{CH}=\text{CH}-\text{CHCl}_2$.

In the context of this invention haloalkyl is understood as meaning an alkyl being substituted once or several times by a halogen (selected from F, Cl, Br, I). It encompasses e.g. $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{F}$, $-\text{CHCl}_2$, $-\text{CHF}_2$, $-\text{CCl}_3$, $-\text{CF}_3$ and $-\text{CH}_2-\text{CHCl}_2$. Preferably haloalkyl is understood in the context of this invention as halogen-substituted C_{1-4} -alkyl representing halogen substituted C1-, C2-, C3- or C4-alkyl. The halogen-substituted alkyl radicals are thus preferably methyl, ethyl, propyl, and butyl. Preferred examples include $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{F}$, $-\text{CHCl}_2$, $-\text{CHF}_2$, and $-\text{CF}_3$.

10

In the context of this invention haloalkoxy is understood as meaning an $-\text{O}$ -alkyl being substituted once or several times by a halogen (selected from F, Cl, Br, I). It encompasses e.g. $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{F}$, $-\text{OCHCl}_2$, $-\text{OCHF}_2$, $-\text{OCCl}_3$, $-\text{OCF}_3$ and $-\text{OCH}_2-\text{CHCl}_2$. Preferably haloalkoxy is understood in the context of this invention as halogen-substituted $-\text{OC}_{1-4}$ -alkyl representing halogen substituted C1-, C2-, C3- or C4-alkoxy. The halogen-substituted alkyl radicals are thus preferably O-methyl, O-ethyl, O-propyl, and O-butyl. Preferred examples include $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{F}$, $-\text{OCHCl}_2$, $-\text{OCHF}_2$, and $-\text{OCF}_3$.

15

Most preferably in connection with alkyl (also in alkylaryl, alkylheterocyclyl or alkylcycloalkyl), alkenyl, alkynyl or O-alkyl, substituted is understood in the context of this invention that any alkyl (also in alkylaryl, alkylheterocyclyl or alkylcycloalkyl), alkenyl, alkynyl or O-alkyl which is substituted is substituted by one or more of halogen (F, Cl, I, Br), $-\text{OH}$, $-\text{NH}_2$, $-\text{SH}$, $-\text{C}(\text{O})\text{OH}$, or $-\text{OC}_{1-4}$ alkyl being unsubstituted or substituted by one or more of OH or halogen (F, Cl, I, Br).

20

Aryl is understood as meaning ring systems with at least one aromatic ring but without heteroatoms even in only one of the rings. Examples are phenyl, naphthyl, fluoranthenyl, fluorenyl, tetralinyl or indanyl, in particular 9H-fluorenyl or anthracenyl radicals, which can be unsubstituted or once or several times substituted. Most preferably aryl is understood in the context of this invention as phenyl, naphthyl or anthracenyl, preferably is phenyl.

25

30

In the context of this invention alkylaryl is understood as meaning an aryl group (see above) being connected to another atom through a C_{1-6} -alkyl (see above) which may be branched or linear and is unsubstituted or substituted once or several times. Thus,

in the context of this invention alkylaryl is understood as meaning an aryl group (see above) being connected to another atom through a C₁₋₆-alkyl (see above). The alkyl may be branched or linear and is unsubstituted, while the aryl may be unsubstituted or substituted once or several times. Preferably, alkylaryl is understood as meaning an aryl group (see above) being connected to another atom through 1 to 4 (-CH₂-) groups. Most preferably alkylaryl is benzyl (i.e. -CH₂-phenyl).

In the context of this invention alkylheterocyclyl is understood as meaning a heterocyclyl group being connected to another atom through a C₁₋₆-alkyl (see above) which may be branched or linear and is unsubstituted or substituted once or several times. In the context of this invention alkylheterocyclyl is understood as meaning a heterocyclyl group being connected to another atom through a C₁₋₆-alkyl (see above). The alkyl may be branched or linear and is unsubstituted, while the heterocyclyl may be unsubstituted or substituted once or several times. Preferably alkylheterocyclyl is understood as meaning a heterocyclyl group (see above) being connected to another atom through 1 to 4 (-CH₂-) groups. Most preferably alkylheterocyclyl is -CH₂-pyridine.

In the context of this invention alkylcycloalkyl is understood as meaning a cycloalkyl group being connected to another atom through a C₁₋₆-alkyl (see above) which may be branched or linear and is unsubstituted or substituted once or several times. Thus, in the context of this invention alkylcycloalkyl is understood as meaning a cycloalkyl group being connected to another atom through a C₁₋₆-alkyl (see above). The alkyl may be branched or linear and is unsubstituted, while the cycloalkyl may be unsubstituted or substituted once or several times. Preferably alkylcycloalkyl is understood as meaning a cycloalkyl group (see above) being connected to another atom through 1 to 4 (-CH₂-) groups. Most preferably alkylcycloalkyl is -CH₂-cyclopropyl.

A heterocyclyl radical or group (also called heterocyclyl hereinafter) is understood as meaning heterocyclic ring systems, with at least one saturated or unsaturated ring which contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring. A heterocyclic group can also be substituted once or several times.

Examples include non-aromatic heterocycllys such as tetrahydropyrane, oxazepane, morpholine, piperidine, pyrrolidine as well as heteroaryls such as furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, pyrimidine, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, benzothiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline.

Subgroups inside the heterocycllys as understood herein include heteroaryls and non-aromatic heterocycllys.

- 10 - the heteroaryl (being equivalent to heteroaromatic radicals or aromatic heterocycllys) is an aromatic heterocyclic ring system of one or more rings of which at least one aromatic ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is an aromatic heterocyclic ring system of one or two rings of which at least one aromatic ring contains one or more heteroatoms from the group consisting of
15 nitrogen, oxygen and/or sulfur in the ring, more preferably is selected from furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, pyrimidine, pyrazine, quinoline, isoquinoline, phthalazine, benzothiazole, indole, benzotriazole, carbazole, quinazoline, thiazole, imidazole, pyrazole, oxazole, thiophene and benzimidazole;
- 20 - the non-aromatic heterocycll is a heterocyclic ring system of one or more rings of which at least one ring – with this (or these) ring(s) then not being aromatic - contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two rings of which one or both rings – with this one or two
25 rings then not being aromatic – contain/s one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring, more preferably is selected from oxazepam, pyrrolidine, piperidine, piperazine, indene, 2,3-dihydroindene (indane), tetrahydropyran, morpholine, indoline, oxopyrrolidine, benzodioxane, especially is benzodioxane, morpholine, tetrahydropyran,
30 piperidine, oxopyrrolidine, and pyrrolidine.

Preferably in the context of this invention heterocycll is defined as a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen
35 and/or sulfur in the ring. Preferably it is a heterocyclic ring system of one or two

saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring.

Preferred examples of heterocyclyls include oxazepan, pyrrolidine, imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, piperazine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzodiazole, thiazole, benzothiazole, tetrahydropyran, morpholine, indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, pyrrolo[2,3b]pyridine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, indole, benzotriazole, benzoxazole oxopyrrolidine, pyrimidine, benzodioxolane, benzodioxane, carbazole and quinazoline, especially is pyridine, pyrazine, indazole, benzodioxane, thiazole, benzothiazole, morpholine, tetrahydropyran, pyrazole, imidazole, piperidine, thiophene, indole, benzimidazole, pyrrolo[2,3b]pyridine, benzoxazole, oxopyrrolidine, pyrimidine, oxazepane and pyrrolidine.

In the context of this invention oxopyrrolidine is understood as meaning pyrrolidin-2-one.

In connection with aryl (including alkyl-aryl), cycloalkyl (including alkyl-cycloalkyl) or heterocyclyl (including alkyl-heterocyclyl), substituted is understood - unless defined otherwise - as meaning substitution of the ring-system of the aryl or alkyl-aryl, cycloalkyl or alkyl-cycloalkyl; heterocyclyl or alkyl-heterocyclyl by OH, SH, =O, halogen (F, Cl, Br, I), CN, NO₂, COOH; NR_xR_y, with R_x and R_y independently being either H or a saturated or unsaturated, linear or branched, substituted or unsubstituted C₁₋₆-alkyl; a saturated or unsaturated, linear or branched, substituted or unsubstituted C₁₋₆-alkyl; a saturated or unsaturated, linear or branched, substituted or unsubstituted -O-C₁₋₆-alkyl (alkoxy); a saturated or unsaturated, linear or branched, substituted or unsubstituted -S-C₁₋₆-alkyl; a saturated or unsaturated, linear or branched, substituted or unsubstituted -C(O)-C₁₋₆-alkyl-group; a saturated or unsaturated, linear or branched, substituted or unsubstituted -C(O)-O-C₁₋₆-alkyl-group; a substituted or unsubstituted aryl or alkyl-aryl; a substituted or unsubstituted cycloalkyl or alkyl-cycloalkyl; a substituted or unsubstituted heterocyclyl or alkyl-heterocyclyl.

Most preferably in connection with aryl (including alkyl-aryl), substituted is understood in the context of this invention that any aryl (including alkyl-aryl), which is substituted is substituted by one or more of halogen (F, Cl, I, Br), -OH, -NH₂, -SH, -C(O)OH, -OC₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen (F, Cl, I, Br), -CN, or -C₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen (F, Cl, I, Br).

Most preferably in connection with cycloalkyl (including alkyl-cycloalkyl) or heterocyclyl (including alkyl-heterocyclyl), substituted is understood in the context of this invention that any cycloalkyl and heterocyclyl (also in an alkylcycloalkyl or alkylheterocyclyl) which is substituted is substituted by one or more of halogen (F, Cl, I, Br), -OH, -NH₂, -SH, =O, -C(O)OH, -OC₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen (F, Cl, I, Br), -CN, or -C₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen (F, Cl, I, Br).

Additionally to the above-mentioned substitutions, in connection with cycloalkyl (including alkyl-cycloalkyl), or heterocyclyl (including alkylheterocyclyl) namely non-aromatic heterocyclyl (including non-aromatic alkyl-heterocyclyl), substituted is also understood - unless defined otherwise - as meaning substitution of the ring-system of the cycloalkyl or alkyl-cycloalkyl; non-aromatic heterocyclyl or non aromatic alkyl-

heterocyclyl with  or =O.

The term "leaving group" means a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage. Leaving groups can be anions or neutral molecules. Common anionic leaving groups are halides such as Cl⁻, Br⁻, and I⁻, and sulfonate esters, such as tosylate (TsO⁻).

The term "salt" is to be understood as meaning any form of the active compound used according to the invention in which it assumes an ionic form or is charged and is coupled with a counter-ion (a cation or anion) or is in solution. By this are also to be understood complexes of the active compound with other molecules and ions, in particular complexes which are complexed via ionic interactions.

The term "physiologically acceptable salt" means in the context of this invention any salt that is physiologically tolerated (most of the time meaning not being toxic-

especially not caused by the counter-ion) if used appropriately for a treatment especially if used on or applied to humans and/or mammals.

5 These physiologically acceptable salts can be formed with cations or bases and in the context of this invention is understood as meaning salts of at least one of the compounds used according to the invention - usually a (deprotonated) acid - as an anion with at least one, preferably inorganic, cation which is physiologically tolerated - especially if used on humans and/or mammals. The salts of the alkali metals and alkaline earth metals are particularly preferred, and also those with NH_4 , but in particular (mono)- or (di)sodium, (mono)- or (di)potassium, magnesium or calcium
10 salts.

Physiologically acceptable salts can also be formed with anions or acids and in the context of this invention is understood as meaning salts of at least one of the compounds used according to the invention as the cation with at least one anion
15 which are physiologically tolerated - especially if used on humans and/or mammals. By this is understood in particular, in the context of this invention, the salt formed with a physiologically tolerated acid, that is to say salts of the particular active compound with inorganic or organic acids which are physiologically tolerated - especially if used on humans and/or mammals. Examples of physiologically tolerated salts of particular
20 acids are salts of: hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid or citric acid.

The compounds of the invention may be present in crystalline form or in the form of free compounds like a free base or acid.

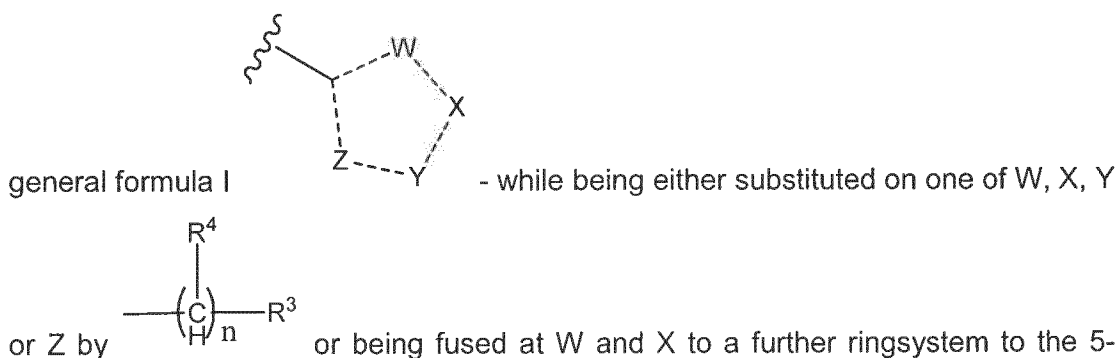
25 Any compound that is a solvate of a compound according to the invention like a compound according to general formula I defined above is understood to be also covered by the scope of the invention. Methods of solvation are generally known within the art. Suitable solvates are pharmaceutically acceptable solvates. The term "solvate" according to this invention is to be understood as meaning any form of the active compound according to the invention in which this compound has attached to it
30 via non-covalent binding another molecule (most likely a polar solvent). Especially preferred examples include hydrates and alcoholates, like methanolates or ethanolates.

Any compound that is a prodrug of a compound according to the invention like a compound according to general formula I defined above is understood to be also covered by the scope of the invention. The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted *in vivo* to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, depending on the functional groups present in the molecule and without limitation, the following derivatives of the present compounds: esters, amino acid esters, phosphate esters, metal salts sulfonate esters, carbamates, and amides. Examples of well known methods of producing a prodrug of a given acting compound are known to those skilled in the art and can be found e.g. in Krogsgaard-Larsen et al. "Textbook of Drug design and Discovery" Taylor & Francis (April 2002).

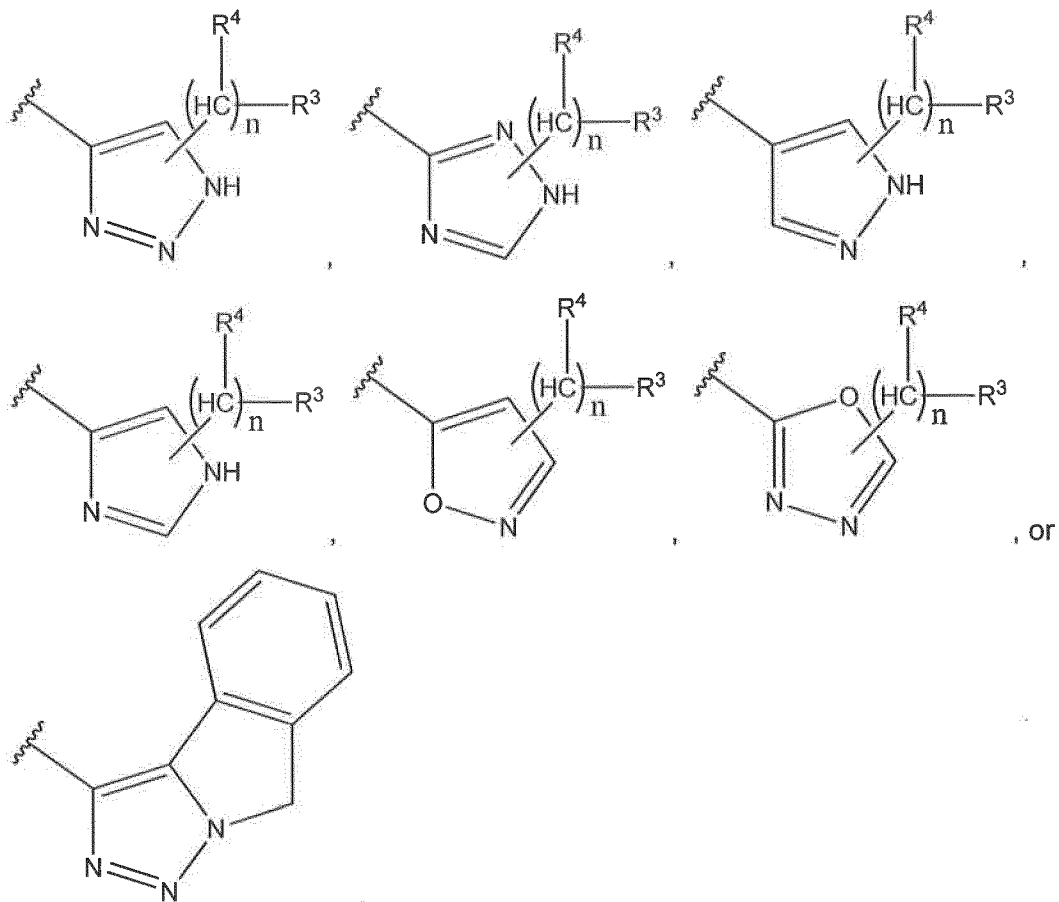
Unless otherwise stated, the compounds of the invention are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C - or ^{14}C -enriched carbon or of a nitrogen by ^{15}N -enriched nitrogen are within the scope of this invention.

The compounds of formula (I) as well as their salts or solvates of the compounds are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. Purity levels for the drug substance are preferably above 50%, more preferably above 70%, most preferably above 90%. In a preferred embodiment it is above 95% of the compound of formula (I) or, or of its salts. This applies also to its solvates or prodrugs.

In a preferred embodiment of the compound according to the invention according to

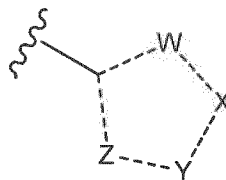


membered heterocyclic ring formed by W-X-Y-Z while being otherwise unsubstituted
- is selected from:



5

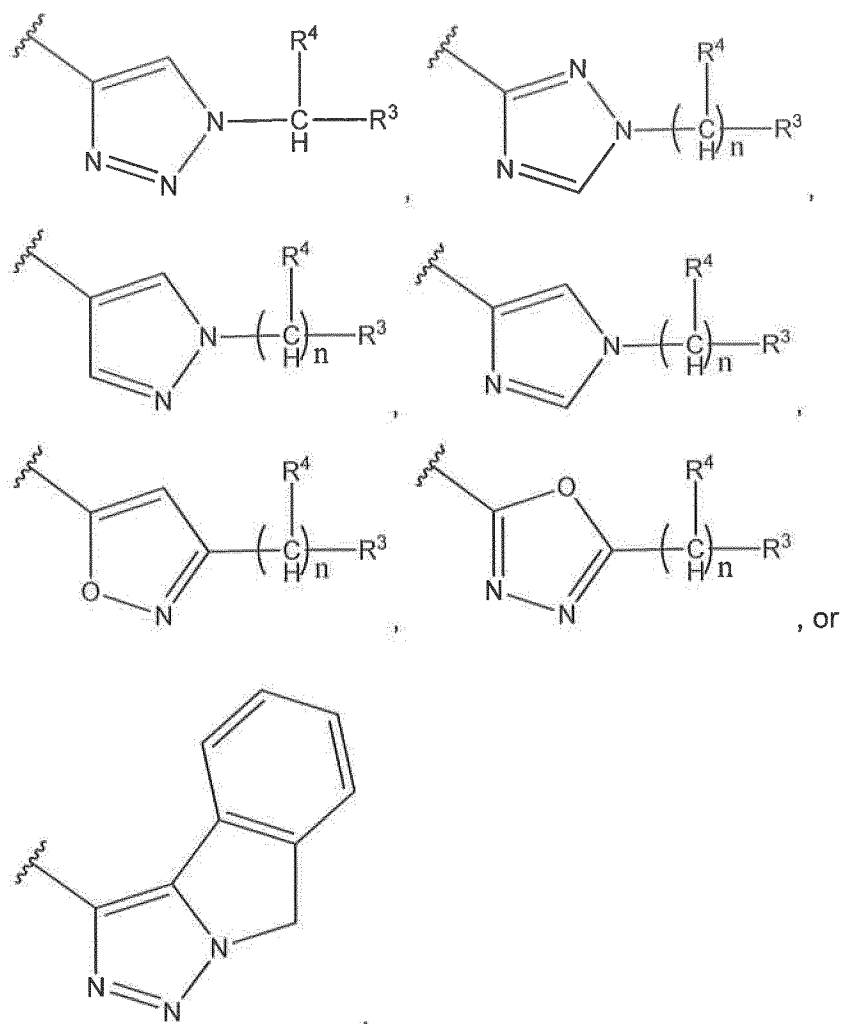
In another preferred embodiment of the compound according to the invention



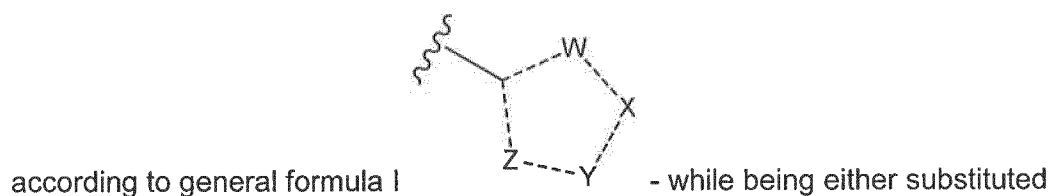
according to general formula I - while being either substituted

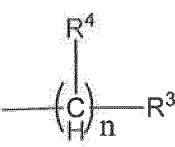
on one of W, X, Y or Z by $(\text{C})_n\text{R}^3$ or being fused at W and X to a further ringsystem to the 5-membered heterocyclic ring formed by W-X-Y-Z while being otherwise unsubstituted - is selected from

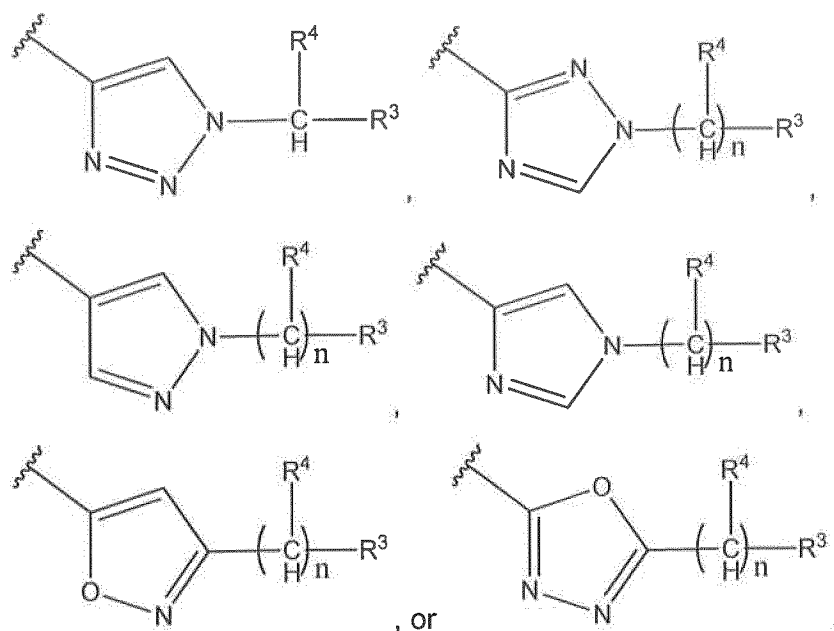
10



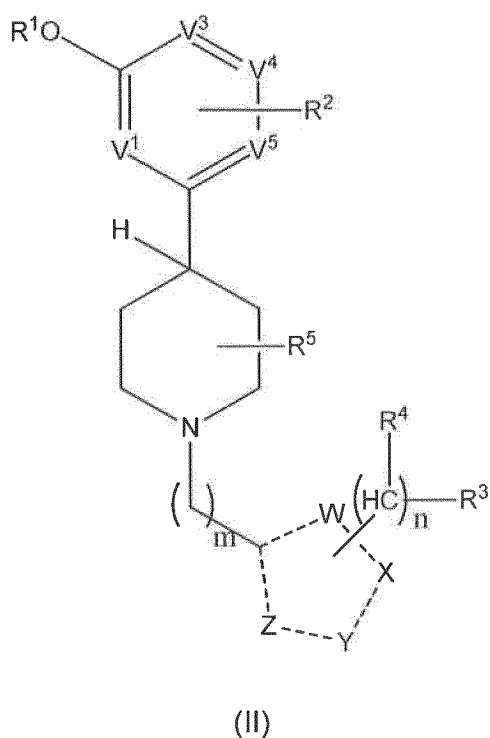
5 In another preferred embodiment of the compound according to the invention



on one of W, X, Y or Z by  or being fused at W and X to a further ringsystem to the 5-membered heterocyclic ring formed by W-X-Y-Z while being otherwise unsubstituted - is selected from



In a further preferred embodiment of the compound according to the invention
 5 according to general formula I the compound is a compound according to Formula II,



wherein

m is 1 or 2;

10

n is 0 or 1;

one of V^1 , V^3 , V^4 and V^5 is selected from nitrogen or carbon while the others are carbon;

5 R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

R^2 is hydrogen, halogen, $-\text{NR}^8\text{R}^9$, $-\text{SR}^7$, $-\text{OR}^7$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

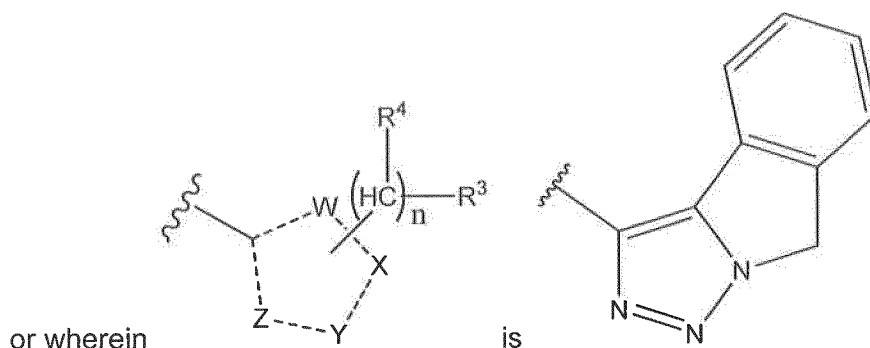
10 R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl; and

15 R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

R^5 is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl;

20 R^6 , R^7 , R^8 and R^9 are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl; or R^6 and R^7 or R^8 and R^9 together with their respective connecting carbon or nitrogen atom
25 may form a cycloalkylic or heterocyclic 4 to 7-membered ring;

and wherein W, X, Y and Z are selected from carbon, nitrogen, or oxygen while W-X-Y-Z are forming together with the bridging C-atom, that is connected to the core scaffold, a 5-membered heterocyclic ring,

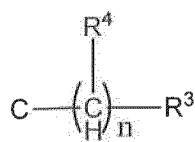


optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof or a corresponding solvate thereof.

In one related and also preferred embodiment of the compound according to the invention according to general formula I wherein the compound is a compound according to Formula II as described, W, X, Y and Z are - while all other radicals remain identically defined – selected from carbon, nitrogen, or oxygen while W-X-Y-Z are forming together with the bridging C-atom, that is connected to the core scaffold, a 5-membered heterocyclic ring.

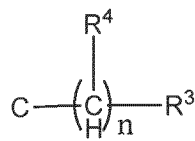
In one embodiment one or more of the following provisos apply:

- with the proviso that if V^1 , V^3 , V^4 and V^5 are carbon and either X or Y is



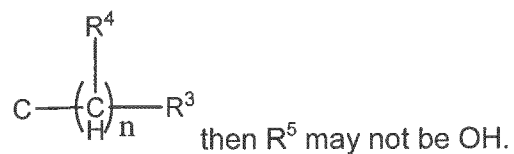
with $n = 0$ and R^3 being CH_3 , then R^1 may not be CH_3 ;

- with the proviso that if V^1 , V^3 , V^4 and V^5 are carbon and either X or Y is

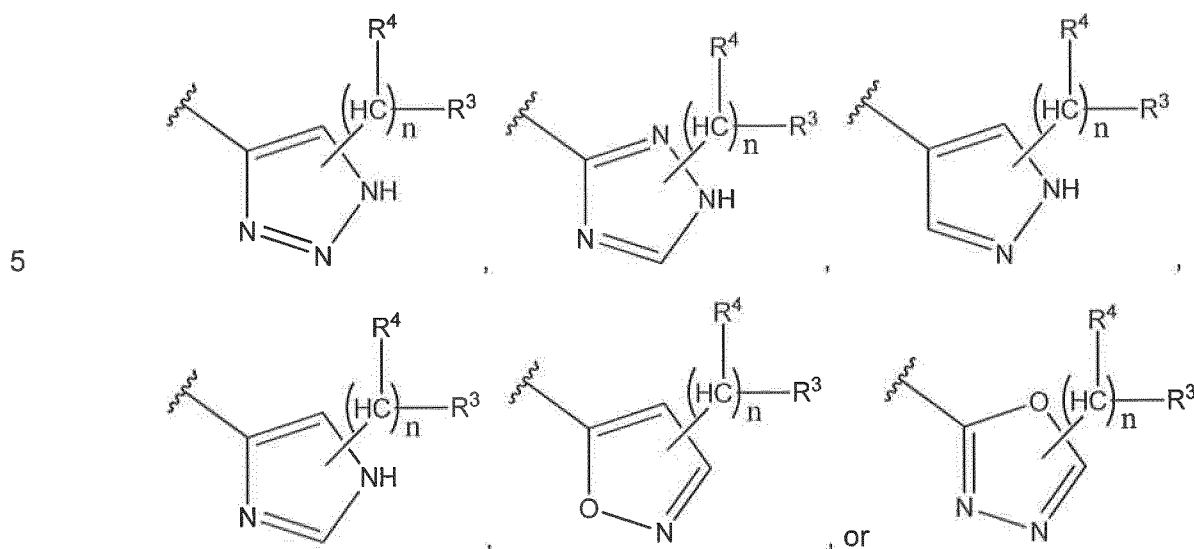
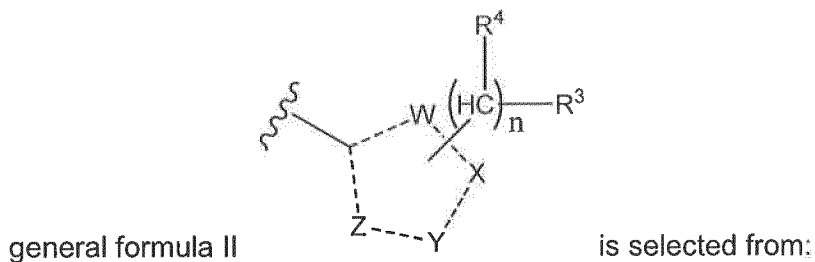


then R^3 may not be alkyl; and/or

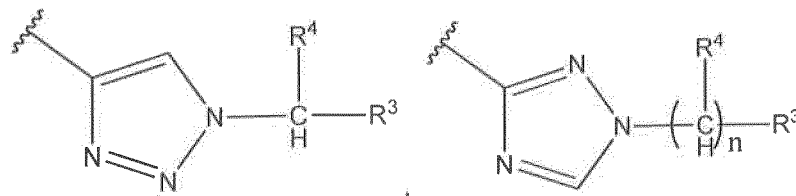
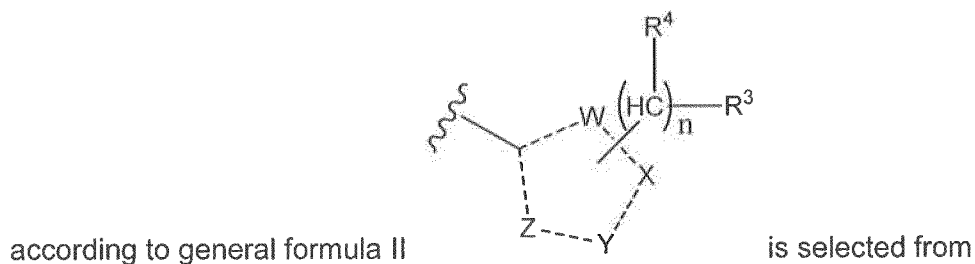
- with the proviso that if V^1 , V^3 , V^4 and V^5 are carbon and either X or Y is

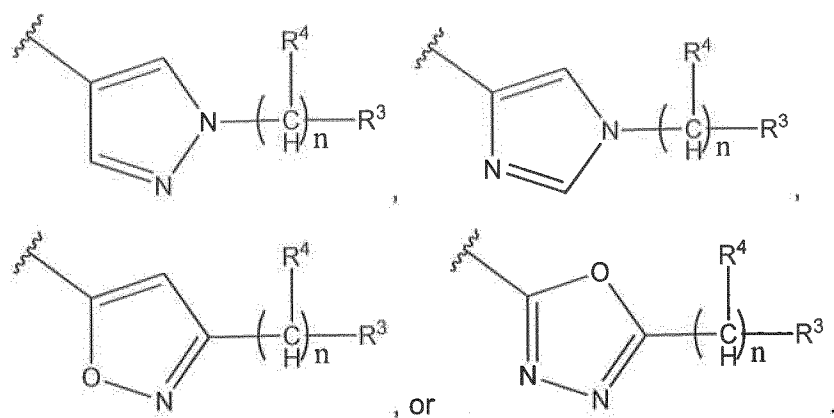


In a preferred embodiment of the compound according to the invention according to

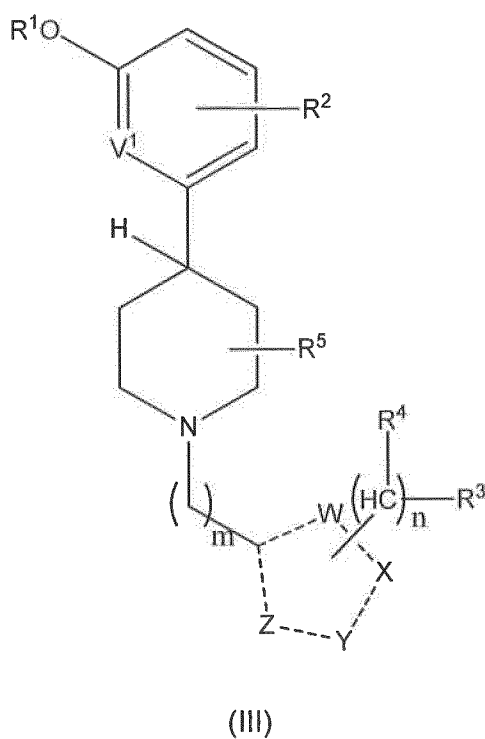


In another preferred embodiment of the compound according to the invention





In another preferred embodiment of the compound according to the invention
 5 according to general formulas I or II the compound is a compound according to Formula III,



wherein

10 m is 1 or 2;

n is 0 or 1;

V^1 is selected from nitrogen or carbon;

R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

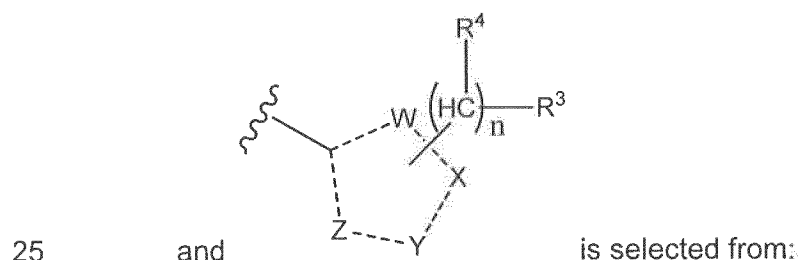
5 R^2 is hydrogen, halogen, $-\text{NR}^8\text{R}^9$, $-\text{SR}^7$, $-\text{OR}^7$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

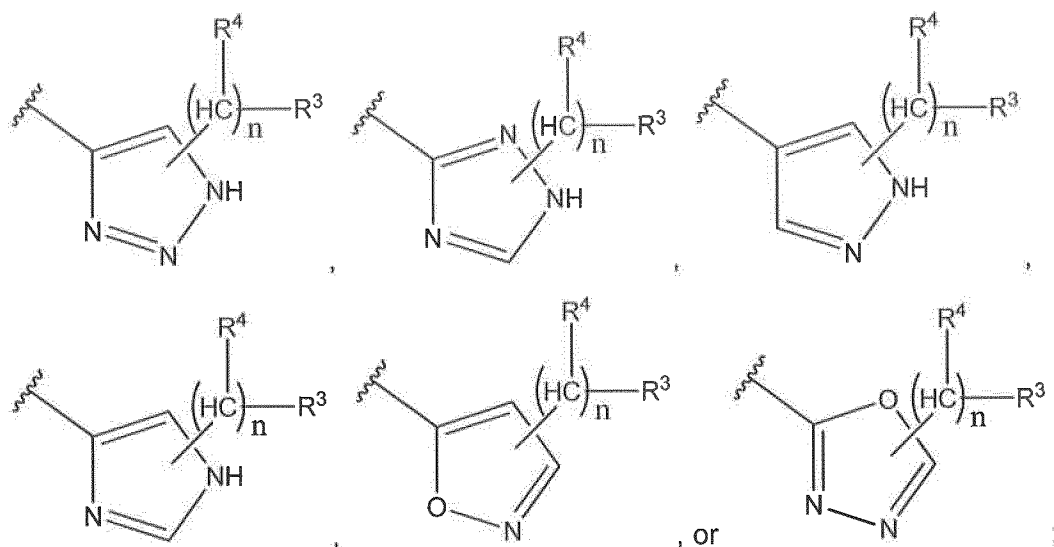
10 R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl; and

15 R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

R^5 is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl;

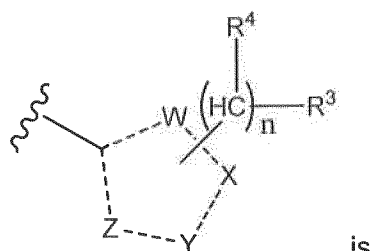
20 R^6 , R^7 , R^8 and R^9 are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl; or R^6 and R^7 or R^8 and R^9 together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring;





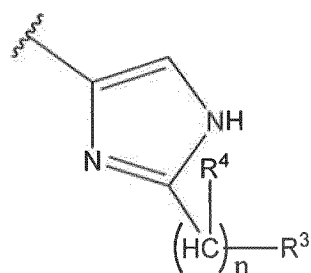
optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof or a corresponding solvate thereof.

In one embodiment one or more of the following provisos apply:

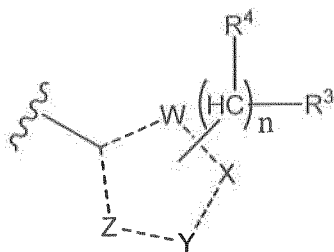


- with the proviso that if V^1 is carbon and

is

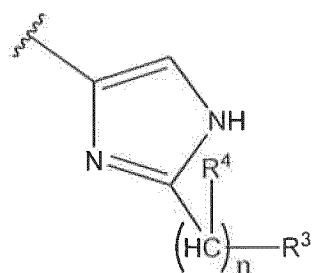


then R^3 may not be alkyl;

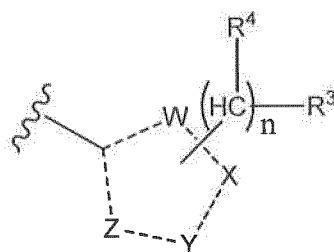


- with the proviso that if V¹ is carbon and

is

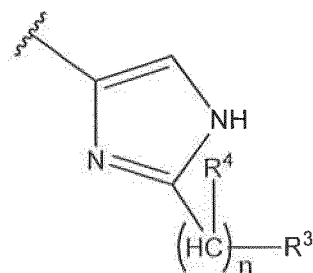


then R⁵ may not be OH; and/or



- with the proviso that if V¹ is carbon and

is



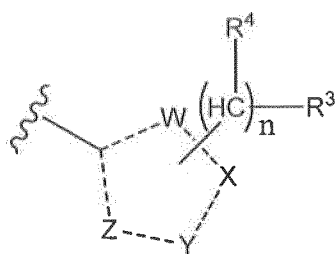
with n = 0 and R³ being CH₃, then R¹ may not be CH₃;

5

and/or

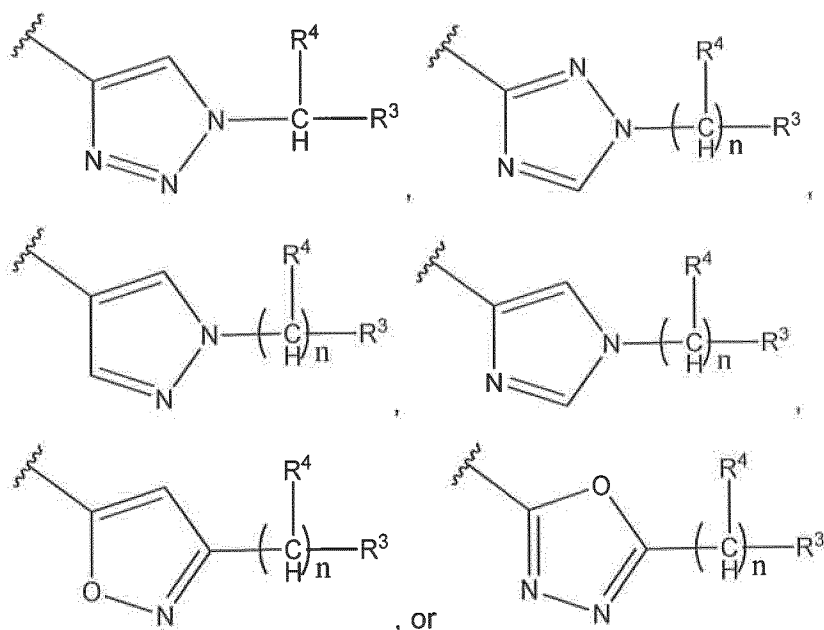
- with the proviso that the compound is not 3-Piperidinol, 4-(3-methoxyphenyl)-1-[(2-methyl-1H-imidazol-5-yl)methyl].

In a preferred embodiment of the compound according to the invention according to



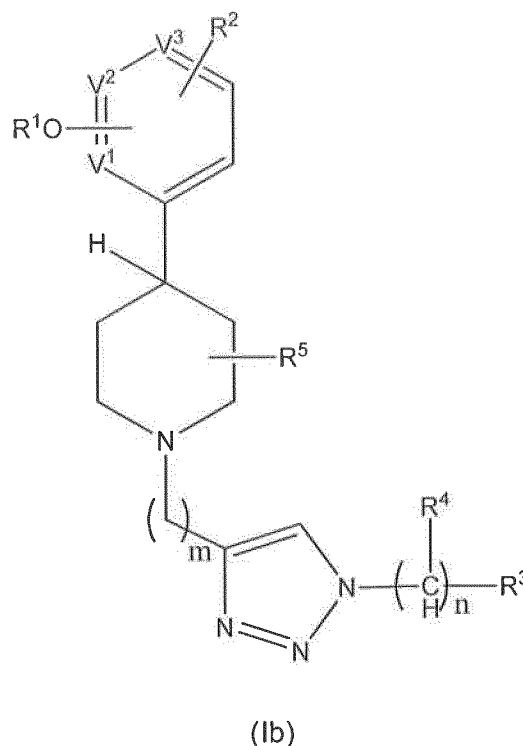
general formula III

is selected from:



5

In another preferred embodiment of the compound according to the invention according to general formulas I or II the compound is a compound according to Formula Ib



, wherein

m is 1 or 2;

5 n is 0 or 1;

one of V¹, V² and V³ is selected from nitrogen or carbon while the others are carbon;

10 R¹ is -COR⁶, -CONR⁸R⁹, -COCR⁶R⁷NR⁸R⁹, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

R² is hydrogen, halogen, -NR⁸R⁹, -SR⁷, -OR⁷, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

15 R³ is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl; and

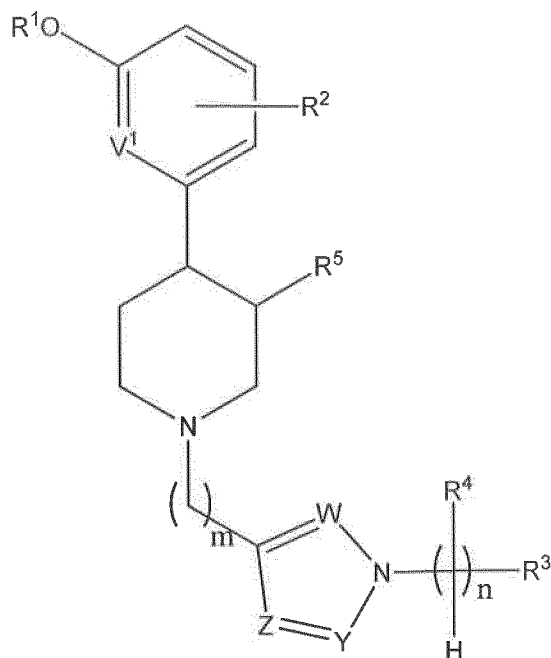
R⁴ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

5 R⁵ is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl; and

10 R⁶, R⁷, R⁸ and R⁹ are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl; or R⁶ and R⁷ or R⁸ and R⁹ together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring;

15 optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof or a corresponding solvate thereof.

20 In another preferred embodiment of the compound according to the invention according to general formulas I or II the compound is a compound according to Formula IV,



(IV)

wherein

m is 1 or 2;

5 n is 0 or 1;

V^1 is selected from nitrogen or carbon;

R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

10 R^2 is hydrogen, halogen, $-\text{NR}^8\text{R}^9$, $-\text{SR}^7$, $-\text{OR}^7$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

15 R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl; and

R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

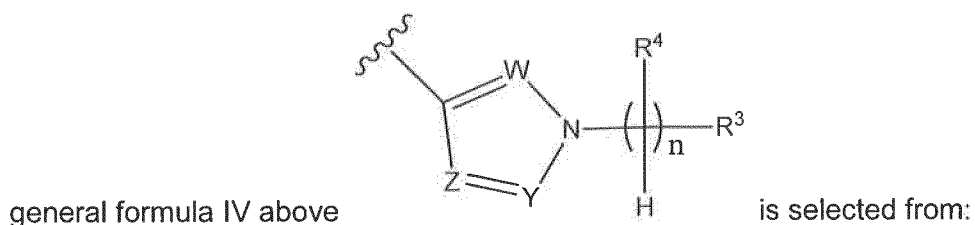
5 R^5 is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl;

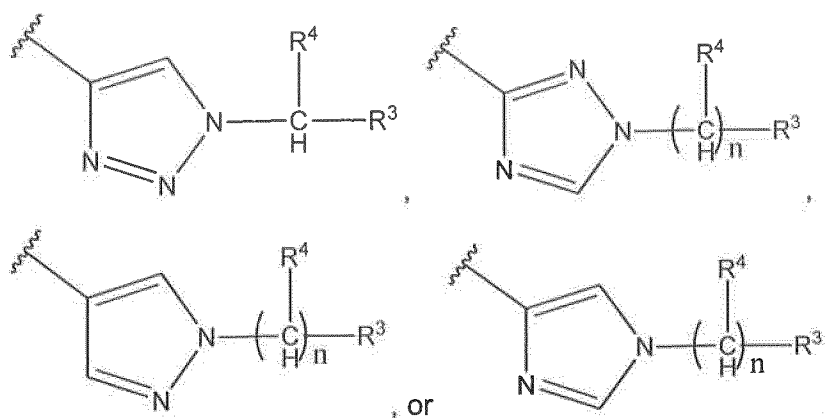
10 R^6 , R^7 , R^8 and R^9 are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl; or R^6 and R^7 or R^8 and R^9 together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring;

15 and W, Y and Z are independently from one another selected from N or CH with only 1 or 2 of them being CH;

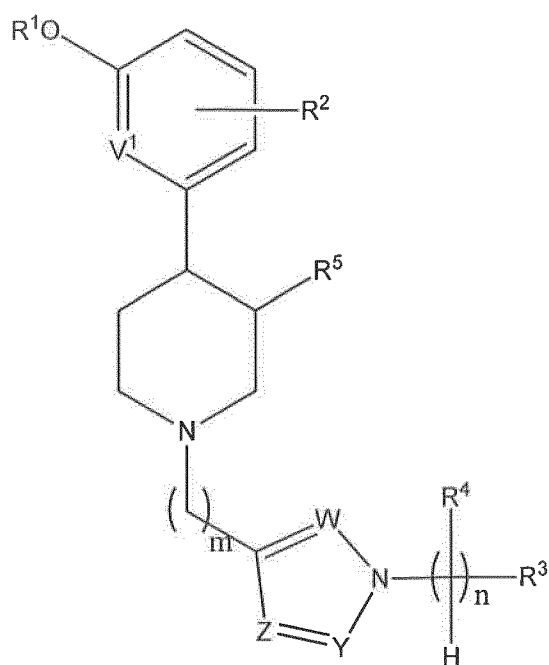
optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

20 In a preferred embodiment of the compound according to the invention according to





In another preferred embodiment of the compound according to the invention according to general formulas I, II, and III the compound is a compound according to Formula IV,



(IV)

wherein

m is 1 or 2;

n is 0 or 1;

V¹ is selected from nitrogen or carbon;

R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

5 R^2 is hydrogen, halogen, $-\text{NR}^8\text{R}^9$, $-\text{SR}^7$, $-\text{OR}^7$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

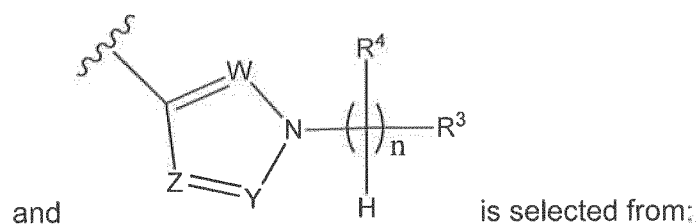
10 R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl; and

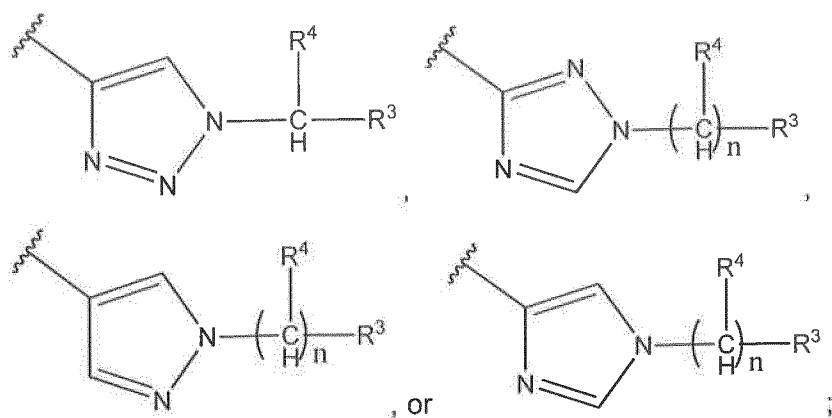
15 R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

R^5 is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl;

20 R^6 , R^7 , R^8 and R^9 are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl; or R^6 and R^7 or R^8 and R^9 together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring;

25





optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

In a preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV

R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein

the aryl is selected from phenyl, naphthyl, or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl; and/or

the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring, more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine,

- benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline;
and/or
the alkyl is selected from C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl; more preferably is C₁₋₄alkyl, like methyl, ethyl, propyl and butyl;
and/or
the cycloalkyl is selected from C₃₋₈cycloalkyl; preferably is C₃₋₇cycloalkyl; more preferably is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;
and/or
most preferably R¹ is -COR⁶, -CONR⁸R⁹, -COCR⁶R⁷NR⁸R⁹, substituted or unsubstituted alkyl like C₁₋₄-alkyl or CH₃, C₂H₄OCH₃, C₃H₆OCH₃,
and/or
R² is hydrogen, halogen, -NR⁸R⁹, -SR⁷, -OR⁷, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein
the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;
and/or
the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine,

- benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline;
and/or
- 5 the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl;
and/or
- 10 the alkenyl is C₂₋₁₀-alkenyl or C₂₋₈-alkenyl like ethylene, propylene, butylene, pentylene, hexylene, heptylene or octylene; preferably is C₁₋₆-alkenyl like ethylene, propylene, butylene, pentylene, or hexylene; more preferably from C₁₋₄-alkenyl, like ethylene, propylene, or butylene;
and/or
- 15 the alkynyl is C₂₋₁₀-alkynyl or C₂₋₈-alkynyl like ethyne, propyne, butyne, pentyne, hexyne, heptyne, or octyne; preferably is C₂₋₆-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne;
and/or
- 20 the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;
and/or
- 25 halogen is any of fluorine, chlorine, iodine or bromine, preferably chlorine or fluorine;
and/or
- most preferably R² is selected from hydrogen, halogen like fluorine, or C₁₋₄alkyl like CH₃ or CF₃;
- 30 and/or

R³ is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein

the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;
and/or

5 the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen
10 and/or sulfur in the ring; more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine,
15 benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline, especially is pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine;
and/or

the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl,
20 heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl or R³ is not alkyl;
and/or

the alkenyl is C₂₋₁₀-alkenyl or C₂₋₈-alkenyl like ethylene, propylene,
25 butylene, pentylene, hexylene, heptylene or octylene; preferably is C₁₋₆-alkenyl like ethylene, propylene, butylene, pentylene, or hexylene;
more preferably from C₁₋₄-alkenyl, like ethylene, propylene, or butylene;
and/or

the alkynyl is C₂₋₁₀-alkynyl or C₂₋₈-alkynyl like ethyne, propyne, butyne,
30 pentyne, hexyne, heptyne, or octyne; preferably is C₂₋₆-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne;
and/or

the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl,
35 cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like

- cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, especially cyclopentyl or cyclohexyl;
and/or
- 5 preferably R³ is not alkyl;
and/or
most preferably R³ is selected from substituted or unsubstituted alkyl like propyl or butyl, from substituted or unsubstituted cycloalkyl like cyclopentyl or cyclohexyl, or from substituted or unsubstituted aryl, like
- 10 phenyl, or from substituted or unsubstituted heterocyclyl, like pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine, or most preferably R³ is selected from substituted or unsubstituted cycloalkyl like cyclopentyl or cyclohexyl, or from substituted or unsubstituted aryl, like phenyl, or from substituted or unsubstituted
- 15 heterocyclyl, like pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine;
and/or
- R⁴ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted
- 20 alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein
- the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;
and/or
- 25 the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one
- 30 or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole,

indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline, especially is pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine; and/or

the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl; and/or

the alkenyl is C₂₋₁₀-alkenyl or C₂₋₈-alkenyl like ethylene, propylene, butylene, pentylene, hexylene, heptylene or octylene; preferably is C₁₋₆-alkenyl like ethylene, propylene, butylene, pentylene, or hexylene; more preferably from C₁₋₄-alkenyl, like ethylene, propylene, or butylene; and/or

the alkynyl is C₂₋₁₀-alkynyl or C₂₋₈-alkynyl like ethyne, propyne, butyne, pentyne, hexyne, heptyne, or octyne; preferably is C₂₋₆-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; and/or

the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, especially cyclopentyl or cyclohexyl; and/or

most preferably R⁴ is selected from hydrogen or from substituted or unsubstituted C₁₋₄alkyl like CH₃ or CH₂OH;

30 and/or

R⁵ is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl, wherein

- the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl;
- 5 and/or
- the O-alkyl is -O-C₁₋₈alkyl like -Omethyl, -O-ethyl, -O-propyl, -O-butyl, -O-pentyl, -O-hexyl, -O-heptyl, or -O-octyl; preferably is -O-C₁₋₆alkyl like -O-methyl, -O-ethyl, -O-propyl, -O-butyl, -O-pentyl, or -O-hexyl; more preferably is -O-C₁₋₄alkyl like -O-methyl, -O-ethyl, -O-propyl or -O-butyl;
- 10 and/or
- halogen is any of fluorine, chlorine, iodine or bromine, preferably chlorine or fluorine;
- and/or
- most preferably R⁵ is selected from hydrogen or hydroxy;
- 15 and/or
- R⁶, R⁷, R⁸ and R⁹ are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or
- 20 unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl, or R⁶ and R⁷ or R⁸ and R⁹ together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring, wherein
- the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;
- 25 and/or
- the alkyl-aryl is C₁₋₄-alkyl-aryl; preferably is benzyl;
- and/or
- the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more
- 30 heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen

- and/or sulfur in the ring; more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, indoline, furan, triazole, isoxazole, pyrazole, thiophene,
- 5 benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline, especially is pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine;
- and/or
- 10 the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl;
- and/or
- 15 the alkenyl is C₂₋₁₀-alkenyl or C₂₋₈-alkenyl like ethylene, propylene, butylene, pentylene, hexylene, heptylene or octylene; preferably is C₁₋₆-alkenyl like ethylene, propylene, butylene, pentylene, or hexylene; more preferably from C₁₋₄-alkenyl, like ethylene, propylene, or butylene;
- and/or
- 20 the alkynyl is C₂₋₁₀-alkynyl or C₂₋₈-alkynyl like ethyne, propyne, butyne, pentyne, hexyne, heptyne, or octyne; preferably is C₂₋₆-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne;
- and/or
- 25 the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, especially cyclopentyl or cyclohexyl;
- 30 and/or
- when R⁶ and R⁷ or R⁸ and R⁹ together with their respective connecting carbon or nitrogen atom form a cycloalkylic or heterocyclic ring this ring is 5 or 6 membered, preferably R⁶ and R⁷ together with their respective connecting carbon atom form a saturated cycloalkylic ring of 5 or 6

members, more preferably R^6 and R^7 together with their respective connecting carbon atom form saturated, unsubstituted cyclohexyl; and/or

most preferably R^6 , R^7 , R^8 and R^9 are independently from each other selected from hydrogen, from substituted or unsubstituted C_{1-4} alkyl like methyl, ethyl, propyl or butyl, from substituted or unsubstituted aryl like phenyl, from substituted or unsubstituted heterocyclyl like pyrrolidine, or from substituted or unsubstituted alkyl-aryl like benzyl, or R^6 and R^7 together with their connecting carbon atom form a cycloalkylic 5 or 6-membered ring like cyclohexyl.

In a preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV R^1 is $-COR^6$, $-CONR^8R^9$, $-COCR^6R^7NR^8R^9$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein

the aryl is selected from phenyl, naphthyl, or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl; and/or

the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring, more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline; and/or

the alkyl is selected from C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl; more preferably is C₁₋₄alkyl, like methyl, ethyl, propyl and butyl;

5

and/or

the cycloalkyl is selected from C₃₋₈cycloalkyl; preferably is C₃₋₇cycloalkyl; more preferably is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

10 In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV R¹ is -COR⁶, -CONR⁸R⁹, -COCR⁶R⁷NR⁸R⁹, substituted or unsubstituted alkyl like C₁₋₄-alkyl or CH₃, C₂H₄OCH₃, C₃H₆OCH₃,

15 In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV R² is hydrogen, halogen, -NR⁸R⁹, -SR⁷, -OR⁷, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein

20 the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;

20

and/or

the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, 25 indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline;

30

and/or

the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl;

5 and/or

the alkenyl is C₂₋₁₀-alkenyl or C₂₋₈-alkenyl like ethylene, propylene, butylene, pentylene, hexylene, heptylene or octylene; preferably is C₁₋₆-alkenyl like ethylene, propylene, butylene, pentylene, or hexylene; more preferably from C₁₋₄-alkenyl, like ethylene, propylene, or butylene;

10 and/or

the alkynyl is C₂₋₁₀-alkynyl or C₂₋₈-alkynyl like ethyne, propyne, butyne, pentyne, hexyne, heptyne, or octyne; preferably is C₂₋₆-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne;

15 and/or

the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

20 and/or

halogen is any of fluorine, chlorine, iodine or bromine, preferably chlorine or fluorine.

In another preferred embodiment of the compound according to the invention

25 according to general formulas I, II, III or IV R² is selected from hydrogen, halogen like fluorine, or C₁₋₄alkyl like CH₃ or CF₃,

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV R³ is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl,

30 substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein

the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;

and/or

the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline, especially is pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine; and/or

the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl or R³ is not alkyl; and/or

the alkenyl is C₂₋₁₀-alkenyl or C₂₋₈-alkenyl like ethylene, propylene, butylene, pentylene, hexylene, heptylene or octylene; preferably is C₁₋₆-alkenyl like ethylene, propylene, butylene, pentylene, or hexylene; more preferably from C₁₋₄-alkenyl, like ethylene, propylene, or butylene; and/or

the alkynyl is C₂₋₁₀-alkynyl or C₂₋₈-alkynyl like ethyne, propyne, butyne, pentyne, hexyne, heptyne, or octyne; preferably is C₂₋₆-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; and/or

the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, especially cyclopentyl or cyclohexyl.

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV R^3 is selected from substituted or unsubstituted alkyl like propyl or butyl, from substituted or unsubstituted cycloalkyl like cyclopentyl or cyclohexyl, or from substituted or unsubstituted aryl, like phenyl, or from substituted or unsubstituted heterocyclyl, like pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine.

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV R^3 is not alkyl. In such a preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV R^3 is selected from substituted or unsubstituted cycloalkyl like cyclopentyl or cyclohexyl, or from substituted or unsubstituted aryl, like phenyl, or from substituted or unsubstituted heterocyclyl, like pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine.

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein

the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;
and/or

the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole,

indoline, furan, triazole, isoxazole, pyrazole, thiophene,
 benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine,
 benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane,
 benzodioxane, carbazole and quinazoline, especially is pyridine,
 5 imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine;
 and/or
 the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl,
 heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl,
 pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or
 10 butyl;
 and/or
 the alkenyl is C₂₋₁₀-alkenyl or C₂₋₈-alkenyl like ethylene, propylene,
 butylene, pentylene, hexylene, heptylene or octylene; preferably is C₁₋₆-
 alkenyl like ethylene, propylene, butylene, pentylene, or hexylene;
 15 more preferably from C₁₋₄-alkenyl, like ethylene, propylene, or butylene;
 and/or
 the alkynyl is C₂₋₁₀-alkynyl or C₂₋₈-alkynyl like ethyne, propyne, butyne,
 pentyne, hexyne, heptyne, or octyne; preferably is C₂₋₆-alkynyl like
 ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-
 20 alkynyl like ethyne, propyne, butyne, pentyne, or hexyne;
 and/or
 the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl,
 cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like
 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more
 25 preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl
 or cyclohexyl, especially cyclopentyl or cyclohexyl.

In another preferred embodiment of the compound according to the invention
 according to general formulas I, II, III or IV R⁴ is selected from hydrogen or from
 30 substituted or unsubstituted C₁₋₄alkyl like CH₃ or CH₂OH.

In another preferred embodiment of the compound according to the invention
 according to general formulas I, II, III or IV R⁵ is hydrogen, halogen, hydroxy,
 substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl, wherein

the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl;
5 and/or
the O-alkyl is -O-C₁₋₈alkyl like -Omethyl, -O-ethyl, -O-propyl, -O-butyl, -O-pentyl, -O-hexyl, -O-heptyl, or -O-octyl; preferably is -O-C₁₋₆alkyl like -O-methyl, -O-ethyl, -O-propyl, -O-butyl, -O-pentyl, or -O-hexyl; more preferably is -O-C₁₋₄alkyl like -O-methyl, -O-ethyl, -O-propyl or -O-butyl;
10 and/or
halogen is any of fluorine, chlorine, iodine or bromine, preferably chlorine or fluorine.

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV R⁵ is selected from hydrogen or hydroxyl.

15

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV R⁶, R⁷, R⁸ and R⁹ are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or
20 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl, or R⁶ and R⁷ or R⁸ and R⁹ together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring, wherein

25 the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;

and/or

the alkyl-aryl is C₁₋₄-alkyl-aryl; preferably is benzyl;

and/or

30 the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two

saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline, especially is pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine; and/or

the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl; and/or

the alkenyl is C₂₋₁₀-alkenyl or C₂₋₈-alkenyl like ethylene, propylene, butylene, pentylene, hexylene, heptylene or octylene; preferably is C₁₋₆-alkenyl like ethylene, propylene, butylene, pentylene, or hexylene; more preferably from C₁₋₄-alkenyl, like ethylene, propylene, or butylene; and/or

the alkynyl is C₂₋₁₀-alkynyl or C₂₋₈-alkynyl like ethyne, propyne, butyne, pentyne, hexyne, heptyne, or octyne; preferably is C₂₋₆-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; and/or

the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, especially cyclopentyl or cyclohexyl; and/or

when R⁶ and R⁷ or R⁸ and R⁹ together with their respective connecting carbon or nitrogen atom form a cycloalkylic or heterocyclic ring this ring is 5 or 6 membered, preferably R⁶ and R⁷ together with their respective

connecting carbon atom form a saturated cycloalkylic ring of 5 or 6 members, more preferably R^6 and R^7 together with their respective connecting carbon atom form saturated, unsubstituted cyclohexyl;

- 5 In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV R^6 , R^7 , R^8 and R^9 are independently from each other selected from hydrogen, from substituted or unsubstituted C_{1-4} alkyl like methyl, ethyl, propyl or butyl, from substituted or unsubstituted aryl like phenyl, from substituted or unsubstituted heterocyclyl like pyrrolidine, or from substituted or
- 10 unsubstituted alkyl-aryl like benzyl, or R^6 and R^7 together with their connecting carbon atom form a cycloalkylic 5 or 6-membered ring like cyclohexyl.

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV

- 15 V^1 is selected from nitrogen or carbon;
 m is 1 or 2;
 n is 0 or 1;
 R^1 is $-COR^6$, $-CONR^8R^9$, $-COCR^6R^7NR^8R^9$, substituted or unsubstituted alkyl like C_{1-4} -alkyl or CH_3 , $C_2H_4OCH_3$, $C_3H_6OCH_3$;
- 20 R^2 is selected from hydrogen, halogen like fluorine, or C_{1-4} alkyl like CH_3 or CF_3 ;
- R^3 is selected from substituted or unsubstituted alkyl like propyl or butyl, from substituted or unsubstituted cycloalkyl like cyclopentyl or cyclohexyl, or from substituted or unsubstituted aryl, like phenyl, or from substituted or unsubstituted heterocyclyl, like pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran,
- 25 pyrimidine;
- R^4 is selected from hydrogen or from substituted or unsubstituted C_{1-4} alkyl like CH_3 or CH_2OH ;
- R^5 is selected from hydrogen or hydroxy; and

5 R^6 , R^7 , R^8 and R^9 are independently from each other selected from hydrogen, from substituted or unsubstituted C_{1-4} alkyl like methyl, ethyl, propyl or butyl, from substituted or unsubstituted aryl like phenyl, from substituted or unsubstituted heterocyclyl like pyrrolidine, or from substituted or unsubstituted alkyl-aryl like benzyl,

or R^6 and R^7 together with their connecting carbon atom may form a cycloalkylic 5 or 6-membered ring like unsubstituted cyclohexyl;

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV (wherein R^3 is not alkyl)

10 V^1 is selected from nitrogen or carbon;

m is 1 or 2;

n is 0 or 1;

R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl like C_{1-4} -alkyl or CH_3 , $\text{C}_2\text{H}_4\text{OCH}_3$, $\text{C}_3\text{H}_6\text{OCH}_3$;

15 R^2 is selected from hydrogen, halogen like fluorine, or C_{1-4} alkyl like CH_3 or CF_3 ;

R^3 is selected from substituted or unsubstituted cycloalkyl like cyclopentyl or cyclohexyl, or from substituted or unsubstituted aryl, like phenyl, or from substituted or unsubstituted heterocyclyl, like pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine;

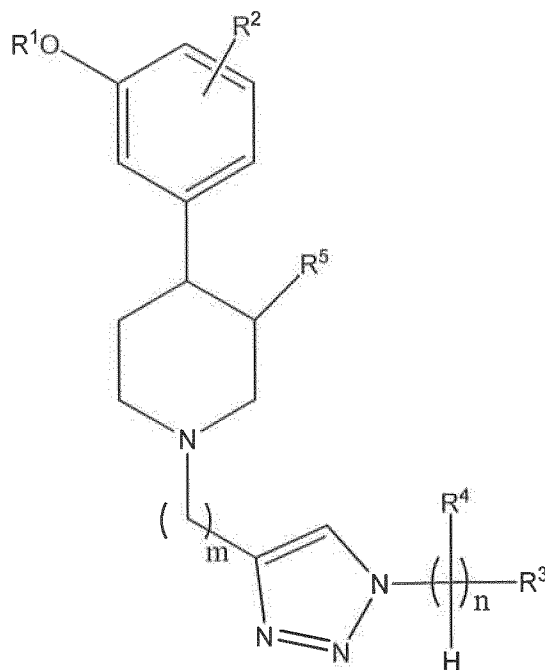
20 R^4 is selected from hydrogen or from substituted or unsubstituted C_{1-4} alkyl like CH_3 or CH_2OH ;

R^5 is selected from hydrogen or hydroxy; and

25 R^6 , R^7 , R^8 and R^9 are independently from each other selected from hydrogen, from substituted or unsubstituted C_{1-4} alkyl like methyl, ethyl, propyl or butyl, from substituted or unsubstituted aryl like phenyl, from substituted or unsubstituted heterocyclyl like pyrrolidine, or from substituted or unsubstituted alkyl-aryl like benzyl,

or R^6 and R^7 together with their connecting carbon atom may form a cycloalkylic 5 or 6-membered ring like unsubstituted cyclohexyl.

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV the compound is having a general formula V,



(V)

wherein

m is 1 or 2, preferably is 1;

n is 0 or 1;

R¹ is -COR⁶, -CONR⁸R⁹, -COCR⁶R⁷NR⁸R⁹, substituted or unsubstituted C₁₋₄alkyl, preferably is -COR⁶, -CONR⁸R⁹, -COCR⁶R⁷NR⁸R⁹, -CH₃, -C₂H₄OCH₃, or -C₃H₆OCH₃;

R² is hydrogen, halogen, substituted or unsubstituted C₁₋₄alkyl, preferably is hydrogen;

R³ is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl, preferably is substituted or unsubstituted phenyl or substituted or unsubstituted pyridine;

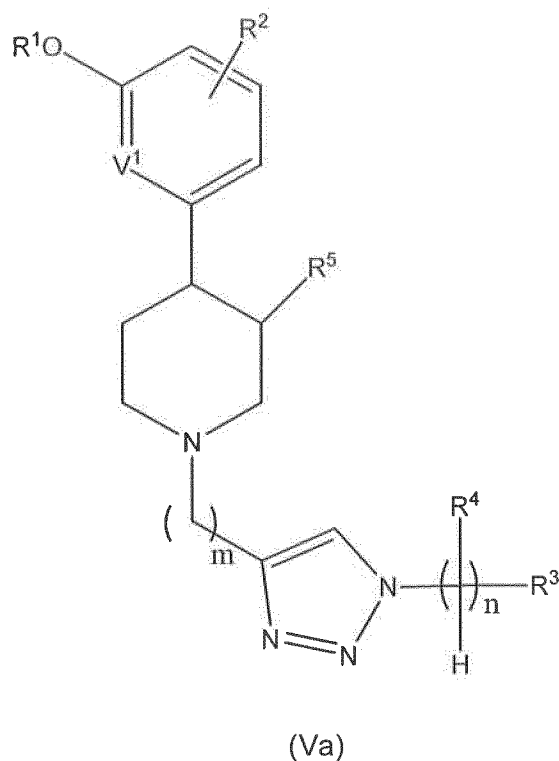
R⁴ is hydrogen, substituted or unsubstituted C₁₋₄alkyl, preferably is hydrogen or -CH₂OH;

R⁵ is hydrogen, halogen or hydroxyl, preferably is hydrogen;

5 R⁶, R⁷, R⁸ and R⁹ are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted C₁₋₄alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted benzyl, or R⁶ and R⁷ together with their connecting atom might form an unsubstituted 5- or 6-membered saturated cycloalkylic ring; preferably R⁶, R⁷,
10 R⁸ and R⁹ are independent from each other selected from hydrogen, -CH₃, -CHCOOH, -C₂H₅, -C₃H₇, -CH(NH₂)C₃H₇, -CH(COOH)C₃H₇, substituted phenyl, unsubstituted pyrrolidine, unsubstituted benzyl, or R⁶ and R⁷ together with their connecting carbon atom form an unsubstituted cyclohexyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the
15 stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

In a parallel preferred embodiment of the compound according to the invention according to general formulas I, II, III or IV the compound is having a general formula
20 Va (which only differs from formula V by allowing V1 being also nitrogen),



wherein

V^1 is selected from nitrogen or carbon, preferably is carbon;

5 m is 1 or 2, preferably is 1;

n is 0 or 1;

R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted C_{1-4} alkyl, preferably is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, $-\text{CH}_3$, $-\text{C}_2\text{H}_4\text{OCH}_3$, or $-\text{C}_3\text{H}_6\text{OCH}_3$;

10 R^2 is hydrogen, halogen, substituted or unsubstituted C_{1-4} alkyl, preferably is hydrogen;

R^3 is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl, preferably is substituted or unsubstituted phenyl or substituted or unsubstituted pyridine;

15 R^4 is hydrogen, substituted or unsubstituted C_{1-4} alkyl, preferably is hydrogen or $-\text{CH}_2\text{OH}$;

R^5 is hydrogen, halogen or hydroxyl, preferably is hydrogen;

5 R^6 , R^7 , R^8 and R^9 are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted benzyl, or R^6 and R^7 together with their connecting atom might form an unsubstituted 5- or 6-membered saturated cycloalkylic ring; preferably R^6 , R^7 , R^8 and R^9 are independent from each other selected from hydrogen, $-CH_3$, $-CHCOOH$, $-C_2H_5$, $-C_3H_7$, $-CH(NH_2)C_3H_7$, $-CH(COOH)C_3H_7$, substituted phenyl, unsubstituted pyrrolidine, unsubstituted benzyl, or R^6 and R^7 together with their connecting carbon atom form an unsubstituted cyclohexyl;

10 optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

15 In a preferred embodiment of a compound of general formula V (but also for formula Va with V^1 being selected from nitrogen or carbon) above

m is 1;

and/or

n is 0 or 1;

and/or

20 R^1 is $-COR^6$, $-CONR^8R^9$, $-COCR^6R^7NR^8R^9$, $-CH_3$, $-C_2H_4OCH_3$, or $-C_3H_6OCH_3$;

and/or

R^2 is hydrogen;

and/or

R^3 is substituted or unsubstituted phenyl or substituted or unsubstituted pyridine;

25 and/or

R^4 is hydrogen or $-CH_2OH$;

and/or

R⁵ is hydrogen;

and/or

- 5 R⁶, R⁷, R⁸ and R⁹ are independent from each other selected from hydrogen, -CH₃, -CHCOOH, -C₂H₅, -C₃H₇, -CH(NH₂)C₃H₇, -CH(COOH)C₃H₇, substituted phenyl, unsubstituted pyrrolidine, unsubstituted benzyl, or R⁶ and R⁷ together with their connecting carbon atom form an unsubstituted cyclohexyl.

In another preferred embodiment of a compound of general formula V above

m is 1;

n is 0 or 1;

- 10 R¹ is -COR⁶, -CONR⁸R⁹, -COCR⁶R⁷NR⁸R⁹, -CH₃, -C₂H₄OCH₃, or -C₃H₆OCH₃;

R² is hydrogen;

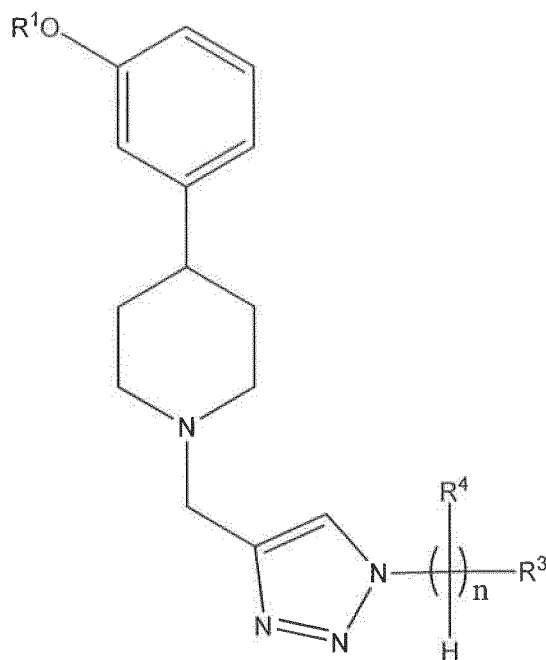
R³ is substituted or unsubstituted phenyl or substituted or unsubstituted pyridine;

R⁴ is hydrogen or -CH₂OH;

R⁵ is hydrogen; and

- 15 R⁶, R⁷, R⁸ and R⁹ are independent from each other selected from hydrogen, -CH₃, -CHCOOH, -C₂H₅, -C₃H₇, -CH(NH₂)C₃H₇, -CH(COOH)C₃H₇, substituted phenyl, unsubstituted pyrrolidine, unsubstituted benzyl, or R⁶ and R⁷ together with their connecting carbon atom form an unsubstituted cyclohexyl.

In both these embodiment general formula V can be written as formula Va:



(Va).

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III, IV and V (thus then applying to all definitions of all radicals R¹ to R⁹ of the compounds of general formulas I, II, III, IV and V)

- 5 any aryl which is substituted is substituted by one or more of halogen (F, Cl, I, Br), -OH, -NH₂, -SH, -C(O)OH, -OC₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen (F, Cl, I, Br), -CN, or -C₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen (F, Cl, I, Br),
- 10 any cycloalkyl or heterocyclyl which is substituted is substituted by one or more of halogen (F, Cl, I, Br), -OH, -NH₂, -SH, =O, -C(O)OH, -OC₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen (F, Cl, I, Br), -CN, or -C₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen (F, Cl, I, Br), and
- 15 any alkyl, alkenyl, alkynyl or O-alkyl which is substituted is substituted by one or more of halogen (F, Cl, I, Br), -OH, -NH₂, -SH, -C(O)OH, or -OC₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen (F, Cl, I, Br).

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III, IV or V the compound is selected from

- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl ethylcarbamate,
- 1-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(3-methoxyphenyl)piperidine,
- 5 • 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
- 4-((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonylamino)benzoic acid,
- 10 • 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl isobutyrate,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-methylbutanoate,
- 4-(3-methoxyphenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 15 • 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl dimethylcarbamate,
- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
- 4-(3-(2-methoxyethoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 20 • 4-(3-(3-methoxypropoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine,
- (S)-3-methyl-2-((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonylamino)butanoic acid,
- 25 • 2-((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonylamino)acetic acid,
- 30 • 3-fluoro-2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine,
- 5-fluoro-2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine,
- 2-(4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-2-phenylethanol,
- 35 • (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl pyrrolidine-2-carboxylate,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-phenylpropanoate, and

- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 1-aminocyclohexanecarboxylate;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III, IV or V the compound is selected from

- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl ethylcarbamate,
- 1-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(3-methoxyphenyl)piperidine,
- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
- 4-((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonylamino)benzoic acid,
- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl isobutyrate,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-methylbutanoate,
- 4-(3-methoxyphenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl dimethylcarbamate,
- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
- 4-(3-(2-methoxyethoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 4-(3-(3-methoxypropoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine,
- 3-fluoro-2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine,
- 5-fluoro-2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine,
- 2-(4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-2-phenylethanol,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl pyrrolidine-2-carboxylate,

- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-phenylpropanoate, and
- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 1-aminocyclohexanecarboxylate;

5

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

10

In another very preferred embodiment of the compound according to the invention according to general formulas I, II, III, IV or V the compound is selected from

15

- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl ethylcarbamate,
- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
- 4-((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonylamino)benzoic acid,
- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl isobutyrate,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-methylbutanoate,
- 4-(3-methoxyphenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl dimethylcarbamate,
- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
- 4-(3-(2-methoxyethoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 4-(3-(3-methoxypropoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl pyrrolidine-2-carboxylate,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-phenylpropanoate, and
- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 1-aminocyclohexanecarboxylate;

30

35

40

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers,

preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

In another preferred embodiment of the compound according to the invention according to general formulas I, II, III, IV or V the compound is selected from

- 5
 - 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl ethylcarbamate,
 - 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
- 10
 - 4-((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonylamino)benzoic acid,
 - 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl isobutyrate,
- 15
 - (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-methylbutanoate,
 - 4-(3-methoxyphenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
 - 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl dimethylcarbamate,
- 20
 - 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
 - 4-(3-(2-methoxyethoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
 - 4-(3-(3-methoxypropoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

In another highly preferred embodiment of the compound according to the invention according to general formulas I, II, III, IV or V the compound is selected from

- 35
 - 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate, and
 - 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

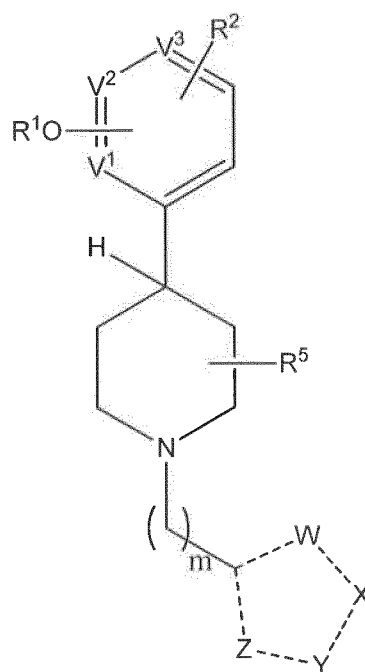
As this invention is aimed at providing a compound or a chemically related series of compounds which act as dual ligands of the σ_1 receptor and the μ -opioid receptor it is a very preferred embodiment in which the compounds are selected which act as dual ligands of the σ_1 receptor and the μ -opioid receptor and especially compounds which have a binding expressed as K_i which is < 100 nm for both receptors.

In the following the phrase "compound of the invention" is used. This is to be understood as any compound according to the invention as described above according to general formulas I, II, III, IV, or V.

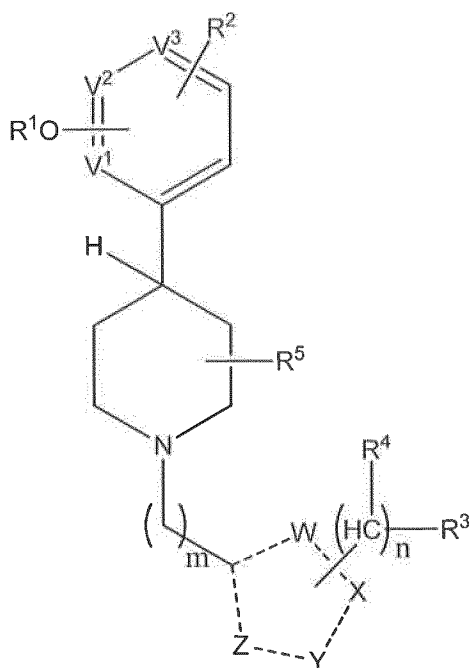
The compounds of the invention represented by the above described formula (I) may include enantiomers depending on the presence of chiral centres or isomers depending on the presence of multiple bonds (e.g. Z, E). The single isomers, enantiomers or diastereoisomers and mixtures thereof fall within the scope of the present invention.

In general the processes are described below in the experimental part. The starting materials are commercially available or can be prepared by conventional methods.

A preferred aspect of the invention is also a process for the production of a compound according to formula I,



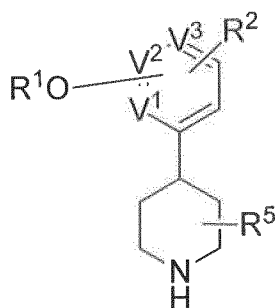
wherein R^1 , R^2 , R^5 , V^1 , V^2 , V^3 , W , X , Y , Z and m are as defined for formula (I) or for a compound according to formula Ia (below)



(Ia)

- 5 wherein R^1 , R^2 , R^3 , R^4 , R^5 , V^1 , V^2 , V^3 , W , X , Y , Z , n and m are as defined for formula I,

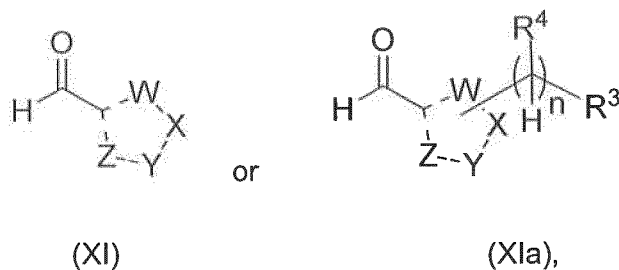
wherein a compound of formula X or its suitable salt like the hydrochloride



(X),

- 10 wherein R^1 , R^2 , R^5 , V^1 , V^2 , and V^3 are as defined for formula I, is reacted with a compound according to formula XI (for a compound according to formula I) or

according to formula XIa (for a compound according to formula Ia) under the conditions of Step 1

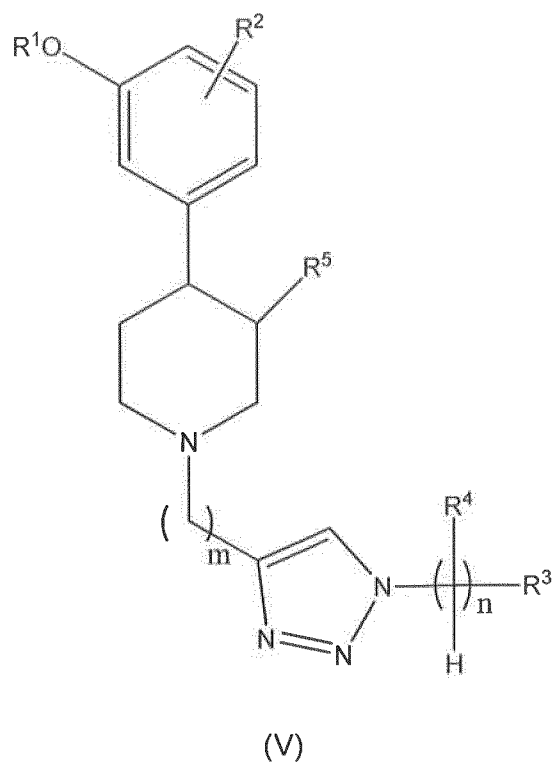


5 wherein R³, R⁴, W, X, Y, Z and n are as defined for formula I, leading to a compound according to formula (I) or formula (Ia) respectively,

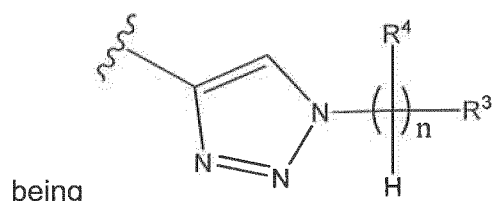
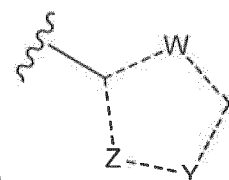
wherein the reductive amination reaction of the compounds of formula (X) and (XI or XIa) of Step 1 is carried out with a reductive reagent in an aprotic solvent in the presence of an organic base.

10 Preferably in the reaction of Step 1 above the reductive reagent is sodium triacetoxyborohydride, the aprotic solvent is dichloroethane and/or the organic base is diisopropylethylamine.

Another preferred aspect of the invention is a process for the production of a compound according to the invention, wherein a the compound is a compound of formula V

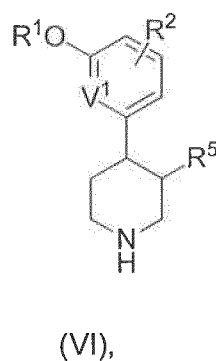


or a compound according to claim 1 according to formula I with



being , wherein R^1 , R^2 , R^3 , R^4 , R^5 , V^1 , V^2 , V^3 , W , X , Y ,
 5 Z , n and m are as defined for formula V or formula I, respectively,

wherein a compound of formula VI or its suitable salt like the hydrochloride



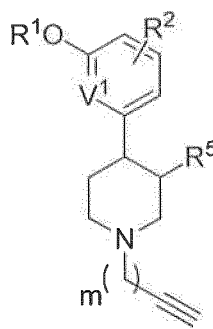
wherein R^1 , R^2 , R^5 and V^1 are as defined for formula V or formula I, respectively,
is reacted with a compound according to formula VIII under the conditions of Step
2



5

(VIII),

wherein m is as defined for formula V or formula I, leading to a compound
according to formula VII,

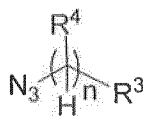


(VII)

10

wherein R^1 , R^2 , R^5 , V^1 and m are as defined for formula V or formula I,
respectively.

Preferably this is followed by reacting said compound according to formula VII
with a compound according to formula IX under the conditions of Step 3



15

(IX)

wherein R^3 , R^4 and n are as defined for formula V or formula I, respectively,
under the conditions of Step 3, leading to a compound according to formula (V),

wherein X is a leaving group like a halogen or sulphate like chlorine,

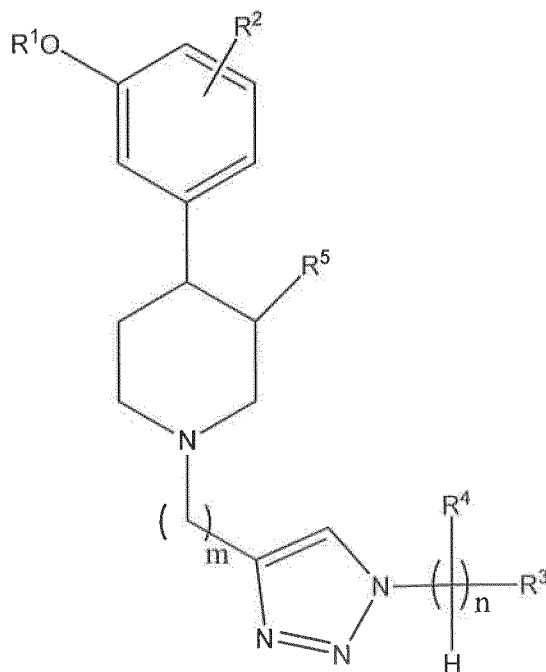
wherein the reaction of Step 2 of said compounds of general formula (VI) with said compounds of formula (VIII) is carried out in the presence of a base in an aprotic solvent;

5 wherein the reaction of Step 3 of said compounds of general formula (VII) with said compounds of formula (IX) is carried out in the presence of a copper salt and sodium ascorbate in a mixture of protic organic solvent and water.

10 Preferably in the reaction of Step 2 above the base is Et_3N , the aprotic solvent is tetrahydrofuran (THF) and/or the reaction is preferably carried out at a temperature range of 25-75 °C. The temperature may be raised by conventional methods or by use of microwave.

Preferably in the reaction of Step 3 above the copper salt is $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and the mixture of protic organic solvent and water is a mixture of $t\text{-BuOH}:\text{H}_2\text{O}$ 1:1 and/or the reaction is preferably carried out at room temperature.

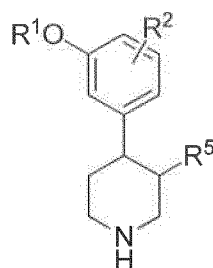
15 Another preferred aspect of the invention is a process for the production of a compound according to the invention, wherein the compound is a compound of formula V



(V),

wherein R^1 , R^2 , R^3 , R^4 , R^5 , n and m are as defined for formula V above,

wherein a compound of formula VI or its suitable salt like the hydrochloride



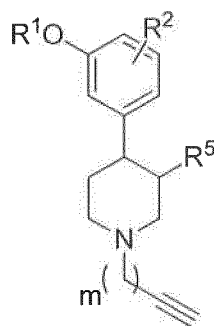
(VI),

5 wherein R^1 , R^2 , and R^5 are as defined for formula V above, is reacted with a compound according to formula VIII under the conditions of Step 2



(VIII),

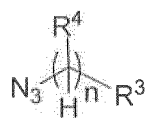
10 wherein m is as defined for formula V above, leading to a compound according to formula VII,



(VII)

wherein R^1 , R^2 , R^5 and m are as defined for formula V above.

15 Preferably this is followed by reacting said compound according to formula VII with a compound according to formula IX under the conditions of Step 3



(IX)

wherein R^3 , R^4 and n are as defined for formula V above, under the conditions of Step 3, leading to a compound according to formula (V),

5 wherein X is a leaving group like a halogen or sulphate like chlorine,

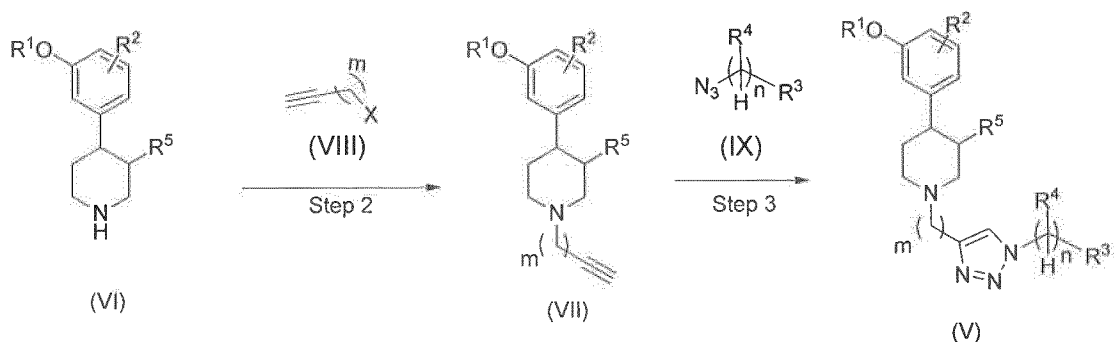
wherein the reaction of Step 2 of said compounds of general formula (VI) with said compounds of formula (VIII) is carried out in the presence of a base in an aprotic solvent;

10 wherein the reaction of Step 3 of said compounds of general formula (VII) with said compounds of formula (IX) is carried out in the presence of a copper salt and sodium ascorbate in a mixture of protic organic solvent and water.

15 Preferably in the reaction of Step 2 above the base is Et_3N , the aprotic solvent is tetrahydrofuran (THF) and/or the reaction is preferably carried out at a temperature range of 25-75 °C. The temperature may be raised by conventional methods or by use of microwave.

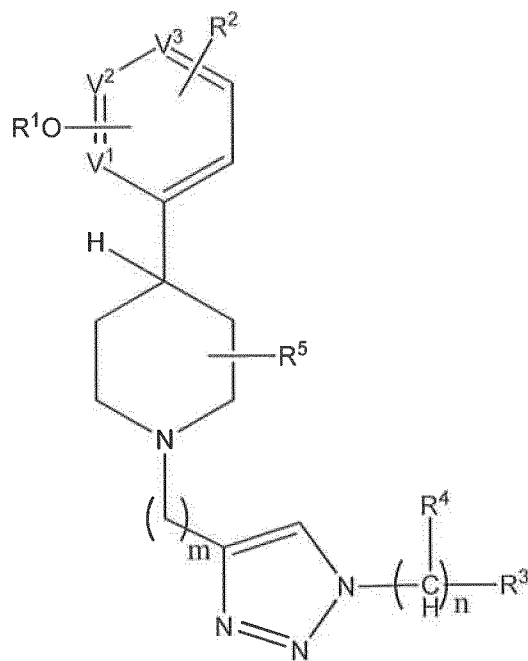
Preferably in the reaction of Step 3 above the copper salt is $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and the mixture of protic organic solvent and water is a mixture of $t\text{-BuOH}:\text{H}_2\text{O}$ 1:1 and/or the reaction is preferably carried out at room temperature.

In summary, this gives the following Scheme:



20

Another preferred aspect of the invention is a process for the production of a compound according to the invention, wherein the compound is a compound of formula Ib

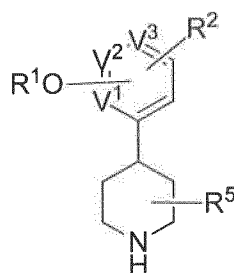


5

(Ib),

wherein R^1 , R^2 , R^3 , R^4 , R^5 , V^1 , V^2 , V^3 , n and m are as defined for formula Ib,

wherein a compound of formula VIa or its suitable salt like the hydrochloride



(VIa),

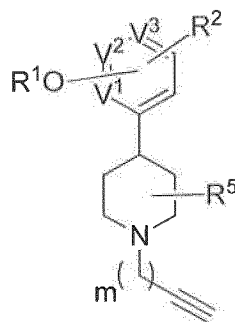
10

wherein R^1 , R^2 , R^5 , V^1 , V^2 and V^3 are as defined for formula Ib, is reacted with a compound according to formula VIII under the conditions of Step 2



(VIII),

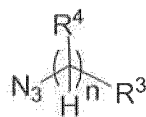
wherein m is 1 or 2, leading to a compound according to formula VIIa,



(VIIa)

wherein R¹, R², R⁵, V¹, V², V³ and m are as defined for formula Ib.

Preferably this is followed by reacting said compound according to formula VIIa with a compound according to formula IX under the conditions of Step 3



(IX)

wherein R³, R⁴ and n are as defined as for formula Ib, under the conditions of Step 3, leading to a compound according to formula Ib,

wherein X is a leaving group like a halogen or sulphate like chlorine,

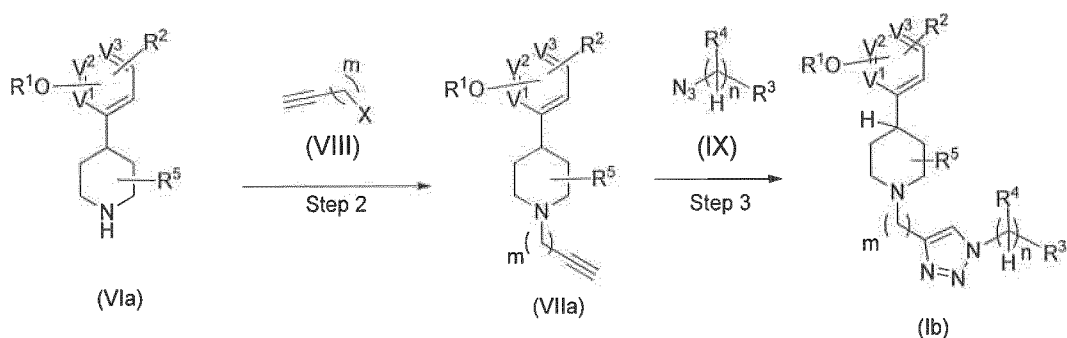
wherein the reaction of Step 2 of said compounds of general formula (VIa) with said compounds of formula (VIII) is carried out in the presence of a base in an aprotic solvent;

wherein the reaction of Step 3 of said compounds of general formula (VIIa) with said compounds of formula (IX) is carried out in the presence of a copper salt and sodium ascorbate in a mixture of protic organic solvent and water.

Preferably in the reaction of Step 2 above the base is Et_3N , the aprotic solvent is tetrahydrofuran (THF) and/or the reaction is preferably carried out at a temperature range of 25-75 °C. The temperature may be raised by conventional methods or by use of microwave.

- 5 Preferably in the reaction of Step 3 above the copper salt is $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and the mixture of protic organic solvent and water is a mixture of $t\text{-BuOH}:\text{H}_2\text{O}$ 1:1 and/or the reaction is preferably carried out at room temperature.

In summary, this gives the following Scheme:



- 10 The obtained reaction products may, if desired, be purified by conventional methods, such as crystallisation and chromatography. Where the above described processes for the preparation of compounds of the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. If there are chiral centers the compounds may be prepared in racemic form, or individual enantiomers may be prepared either by
- 15 prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution.

- One preferred pharmaceutically acceptable form of a compound of the invention is the crystalline form, including such form in pharmaceutical composition. In the case of salts and also solvates of the compounds of the invention the additional ionic and solvent moieties must also be non-toxic. The compounds of the invention may present different polymorphic forms, it is intended that the invention encompasses all such forms.
- 20

- Another aspect of the invention refers to a pharmaceutical composition which comprises a compound according to the invention as described above according to general formulas I, II, III, IV, or V or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier, adjuvant or vehicle. The present
- 25

invention thus provides pharmaceutical compositions comprising a compound of this invention, or a pharmaceutically acceptable salt or stereoisomers thereof together with a pharmaceutically acceptable carrier, adjuvant, or vehicle, for administration to a patient.

- 5 Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules etc.) or liquid (solutions, suspensions or emulsions) composition for oral, topical or parenteral administration.

10 In a preferred embodiment the pharmaceutical compositions are in oral form, either solid or liquid. Suitable dose forms for oral administration may be tablets, capsules, syrups or solutions and may contain conventional excipients known in the art such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycolate or
15 microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulfate.

20 The solid oral compositions may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are conventional in the art. The tablets may for example be prepared by wet or dry granulation and optionally coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

25 The pharmaceutical compositions may also be adapted for parenteral administration, such as sterile solutions, suspensions or lyophilized products in the appropriate unit dosage form. Adequate excipients can be used, such as bulking agents, buffering agents or surfactants.

30 The mentioned formulations will be prepared using standard methods such as those described or referred to in the Spanish and US Pharmacopoeias and similar reference texts.

Administration of the compounds or compositions of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, and

intraperitoneal and intravenous administration. Oral administration is preferred because of the convenience for the patient and the chronic character of the diseases to be treated.

5 Generally an effective administered amount of a compound of the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the weight of the sufferer. However, active compounds will typically be administered once or more times a day for example 1, 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 1000 mg/kg/day.

10 The compounds and compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or at different time.

15 Another aspect of the invention refers to the use of a compound of the invention or a pharmaceutically acceptable salt or isomer thereof in the manufacture of a medicament.

Another aspect of the invention refers to a compound of the invention according as described above according to general formulas I, II, III, IV, or V or a pharmaceutically acceptable salt or isomer thereof, for use as a medicament for the treatment of pain. Preferably the pain is medium to severe pain, visceral pain, chronic pain, cancer pain,
20 migraine, inflammatory pain, acute pain or neuropathic pain, allodynia or hyperalgesia. This may include mechanical allodynia or thermal hyperalgesia.

Another aspect of the invention refers to the use of a compound of the invention in the manufacture of a medicament for the treatment or prophylaxis of pain.

25 In a preferred embodiment the pain is selected from medium to severe pain, visceral pain, chronic pain, cancer pain, migraine, inflammatory pain, acute pain or neuropathic pain, allodynia or hyperalgesia, also preferably including mechanical allodynia or thermal hyperalgesia.

Another aspect of this invention relates to a method of treating or preventing pain which method comprises administering to a patient in need of such a treatment a
30 therapeutically effective amount of a compound as above defined or a pharmaceutical composition thereof. Among the pain syndromes that can be treated are medium to

severe pain, visceral pain, chronic pain, cancer pain, migraine, inflammatory pain, acute pain or neuropathic pain, allodynia or hyperalgesia, whereas this could also include mechanical allodynia or thermal hyperalgesia.

- 5 The present invention is illustrated below with the aid of examples. These illustrations are given solely by way of example and do not limit the general spirit of the present invention.

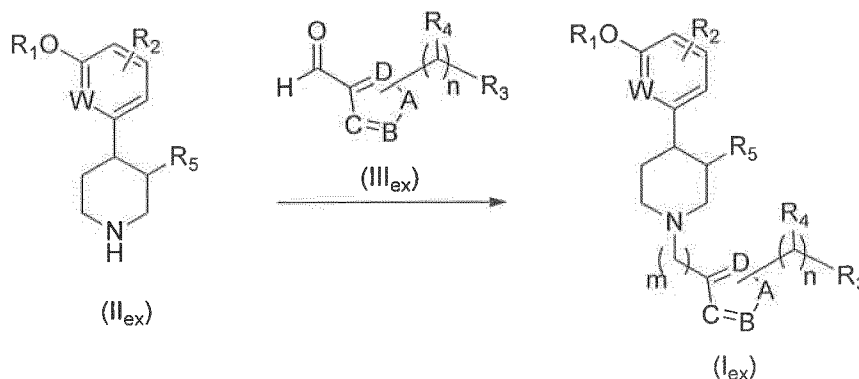
EXAMPLES:**General Experimental Part (Methods and Equipment of the synthesis and analysis)**

All solvents used for synthesis were p. a. quality.

5 METHOD I

A process is described for the preparation of compounds of general formula (I_{ex}) where R₁, R₂, R₃, R₄, R₅, A, B, C, D, W, n and m have the meanings as defined above (with "A", "B", "C", and "D" being "X", "Y", "Z", "W" in the above description, respectively, and "W" being "V¹" in the above description), comprising the reaction of
 10 compound of formula (II_{ex}), or its suitable salt, such as hydrochloride, with a compound of general formula (III_{ex}) as described in scheme 1:

Scheme 1:



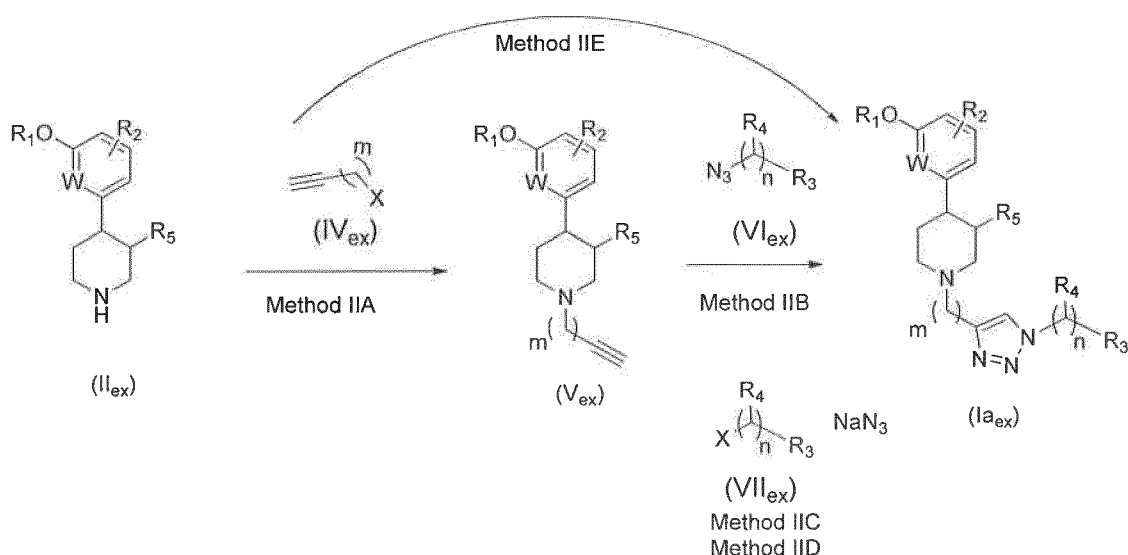
15 The reductive amination reaction of compounds of formula (II_{ex}) and (III_{ex}) is preferably carried out with a reductive reagent, preferably sodium triacetoxyborohydride, in an aprotic solvent, preferably dichloroethane, in the presence of an organic base, preferably diisopropylethylamine.

20 METHOD II

A process is described for the preparation of compounds of general formula (Ia_{ex} and Ib_{ex}) where R₁, R₂, R₃, R₄, R₅, W, n and m have the meanings as defined above (with

“W” being “V¹” in the above description), comprising the reaction of a compound of formula (II_{ex}) with a compound of formula (IV_{ex}), where X is a suitable leaving group such as a halogen or sulfonate, and the reaction of the resulting intermediate (V_{ex}) with convenient reagents such as (VI_{ex}), (VII_{ex}) or (VIII_{ex}) to give the triazoles (Ia_{ex}) and (Ib_{ex}). As indicated in Scheme 2 different methods can be used in the practical realization of these two reactions. In some cases, the intermediate (V_{ex}) can be isolated but in other cases the two steps may be carried out one-pot. The compounds of formula (IV_{ex}) and the reagents of formula (VI_{ex}), (VII_{ex}) or (VIII_{ex}) are either commercially available or can be prepared following conventional methods reported in the literature. Alternately, some of the azides can be prepared *in situ*.

Scheme 2:



- 15 In Method IIA the reaction of compounds of general formula (II_{ex}) with compounds of formula (IV_{ex}) where X is a suitable leaving group, such as halogen or sulfonate, is carried out in the presence of a base, preferably Et₃N, in an aprotic solvent such as tetrahydrofuran (THF) at a temperature range of 25-75 °C, using conventional heating or a microwave reactor.
- 20 In Method IIB the reaction of compounds of formula (V_{ex}) with azides of general formula (VI_{ex}) is carried out in the presence of a copper salt, preferably CuSO₄·5H₂O

and sodium ascorbate, in a mixture of protic organic solvent and water, preferably a mixture of t-BuOH:H₂O 1:1 at room temperature.

5 In Method IIC the azide is generated in situ. The precursor of the azide (VII_{ex}), where X is a suitable leaving group such as halogen or sulfonate, is treated with sodium azide and a copper salt, preferably CuI, in an organic solvent, preferably dimethylformamide, at 100 °C using microwave irradiation. Alternatively, some additives such as N₁,N₂-dimethylethane-1,2-diamine (DMEDA) and sodium ascorbate can be added to the reaction mixture.

10 In Method IID the precursor of the azide of general formula (VII_{ex}) is treated with sodium azide in a mixture of a protic organic solvent and water, preferably a mixture of t-BuOH:H₂O 1:1, at 100 °C using microwave irradiation for a suitable time, such as 1h or until completed reaction. The in situ formed azide is then treated with compounds of general formula (V_{ex}) in the presence of a copper salt, preferably CuSO₄·5H₂O and sodium ascorbate at room temperature.

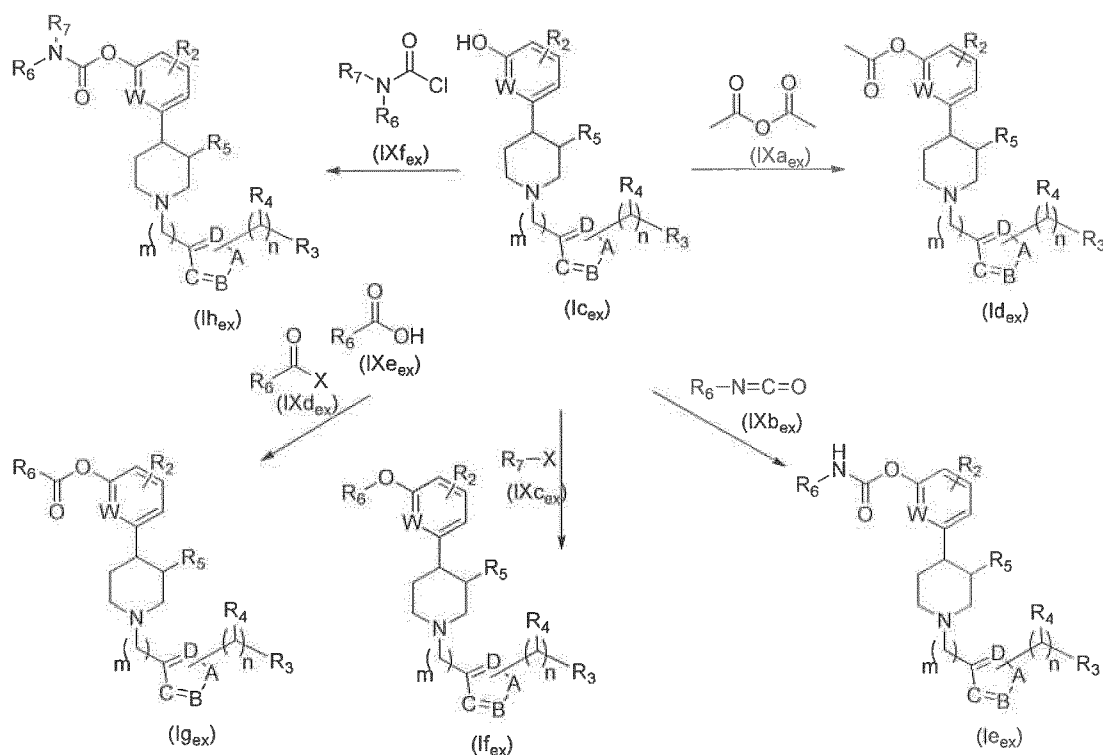
15 In Method IIE the intermediates of general formula (Ia_{ex}) are prepared in a one-pot procedure comprising the reaction of compounds of general formula (II_{ex}) and propargyl bromide in the presence of a base, preferably Et₃N, in water at room temperature for 1h or until completed reaction, after which compounds of general formula (VI_{ex}) are added in the presence of a copper salt, preferably CuI, at room temperature (*Tetrahedron* 2005, 61, 9331-9337).

20 If desired, racemic intermediates of general formula (II_{ex}) or final compounds of general formula (I_{ex}) may be resolved into their enantiomers by conventional resolution methods as for example, chiral chromatography, crystallization of the diastereomeric salts, etc.

25 Thus, the obtained reaction products may, if desired, be purified by conventional methods, such as crystallisation and chromatography. Where the above described processes for the preparation of compounds of the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. If there are chiral centers the compounds may be prepared in racemic form, or individual enantiomers may be prepared either by
30 enantiospecific synthesis or by resolution.

Method III

Scheme 3:



5

10

The process for the preparation of intermediates of formula (I_{d_{ex}}-I_{h_{ex}}) where R₂, R₃, R₄, R₅, R₆, R₇, A, B, C, D, W, m and n have the meanings as defined above (with "A", "B", "C", and "D" being "X", "Y", "Z", "W" in the above description, respectively, and "W" being "V¹" in the above description), according to scheme 3, which comprises the reaction of compounds of formula (Ic_{ex}) with a compound of formula (IXa_{ex}-IXd_{ex}), where X is a suitable leaving group such as halogen, in the presence of a base, preferably pyridine, Et₃N, NaH, K₂CO₃ or Cs₂CO₃, alternatively in the presence of 4-N,N-dimethylaminopyridine, at a range of temperature of 0 to 120 °C, in the presence of a

suitable solvent, such as dichloromethane, acetone, acetonitrile or THF; alternatively, the reactions can be carried out in a microwave reactor.

Alternatively, compounds ($I_{g_{ex}}$) can be prepared by reaction of compounds ($I_{c_{ex}}$) with a carboxylic acid of formula ($I_{X_{ex}}$) in the presence of an activating agent, preferably
5 N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC-HCl), and 4-dimethylaminopyridine as additive, in an organic solvent, preferably dichloromethane.

In some cases, an additional final deprotection step was needed to obtain compounds of formula ($I_{e_{ex}}$) and ($I_{g_{ex}}$), preferably in an acidic medium, preferably HCl in an organic solvent, preferably 1,4-dioxane, or trifluoroacetic acid.

10

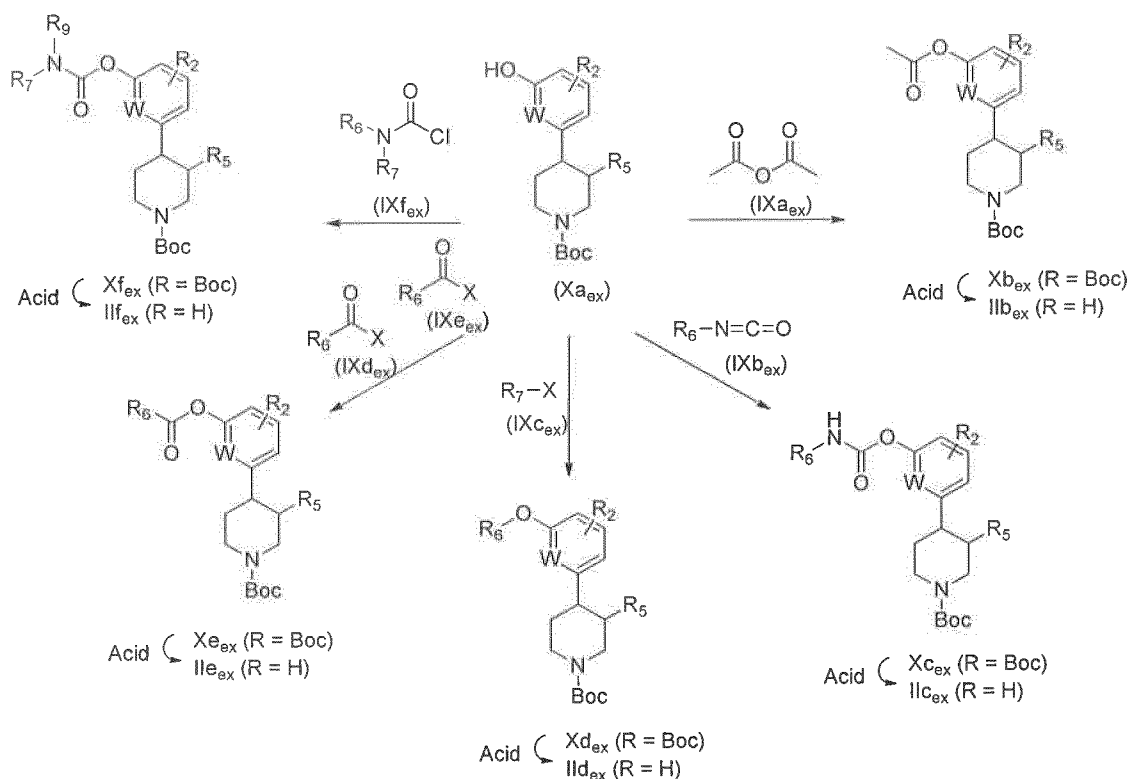
Synthesis of intermediates of general formula (II_{ex})

In some cases, compounds of formula (II_{ex}) are commercially available or they can be obtained by conventional methods. Alternatively compound of formula (II_{ex}) can be obtained following different methods:

15

Method IV

Scheme 4



5 The process for the preparation of intermediates of general formula (IIf_{ex}-f_{ex}) where W, R₂, R₅, R₆, R₇, have the meanings as defined above (with "A", "B", "C", and "D" being "X", "Y", "Z", "W" in the above description, respectively, and "W" being "V¹" in the above description), according to the reaction sequence shown in scheme 4, which comprises:

- 10 a) The reaction of compounds of formula (Xa_{ex}) with a compound of formula (IXa_{ex}-d_{ex} and f_{ex}), where X is a suitable leaving group, such as halogen, in the presence of a base, preferably pyridine, Et₃N, NaH, K₂CO₃ or Cs₂CO₃, alternatively in the presence of 4-N,N-dimethylaminopyridine, at a range of temperature of 0 to 120 °C, in the presence of a suitable solvent, such as
- 15 dichloromethane, toluene, acetone, acetonitrile, THF or DMF; alternatively, the reactions can be carried out in a microwave reactor. Alternatively, compounds (IIf_{ex}) can be prepared by reaction of compounds (Xa_{ex}) with a carboxylic acid of formula (IXe_{ex}) in the presence of an activating agent, preferably N-Ethyl-N'-(3-

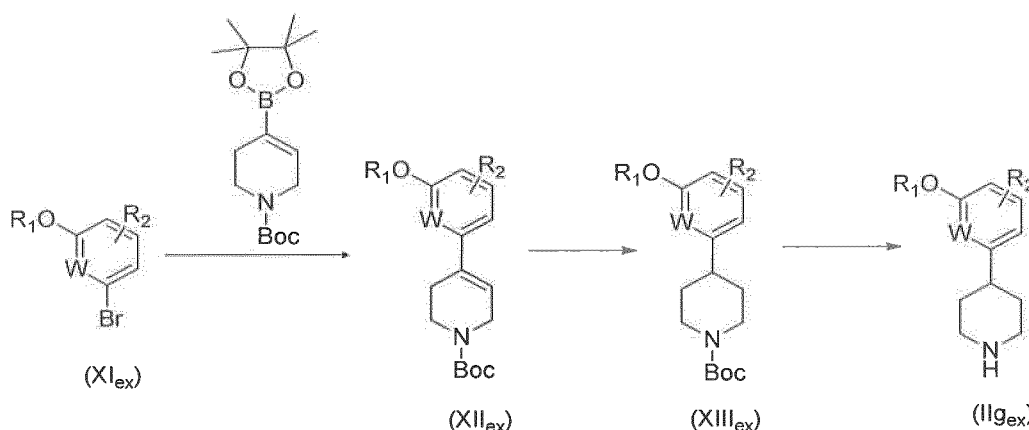
dimethylaminopropyl)carbodiimide hydrochloride (EDAC-HCl), and 4-dimethylaminopyridine as additive, in an organic solvent, preferably dichloromethane

b) The deprotection of the resulting compounds ($X_{b_{ex}-f_{ex}}$) in an acidic medium, preferably HCl in an organic solvent, preferably 1,4-dioxane.

5

Method V

Scheme 5



The process for the preparation of intermediates of general formula ($II_{g_{ex}}$) where W, R_1 and R_2 have the meanings as defined above (with W being V^1 above), according to the reaction sequence shown in scheme 5 and comprises:

a) The coupling reaction of an aromatic bromide of general formula (XI_{ex}) with 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid pinacol ester in the presence of a palladium catalyst, such as $Pd(PPh_3)_4$ and an inorganic base, preferably K_2CO_3 or Na_2CO_3 in a mixture of organic solvents and water, preferably a mixture of dimethoxyethane/ethanol/water or dioxane/ethanol/water at a temperature range of 90-160 °C. Alternatively, the reaction can be carried out in a microwave reactor. The bromides of general formula (XI_{ex}) are commercially available or can be prepared by conventional methods.

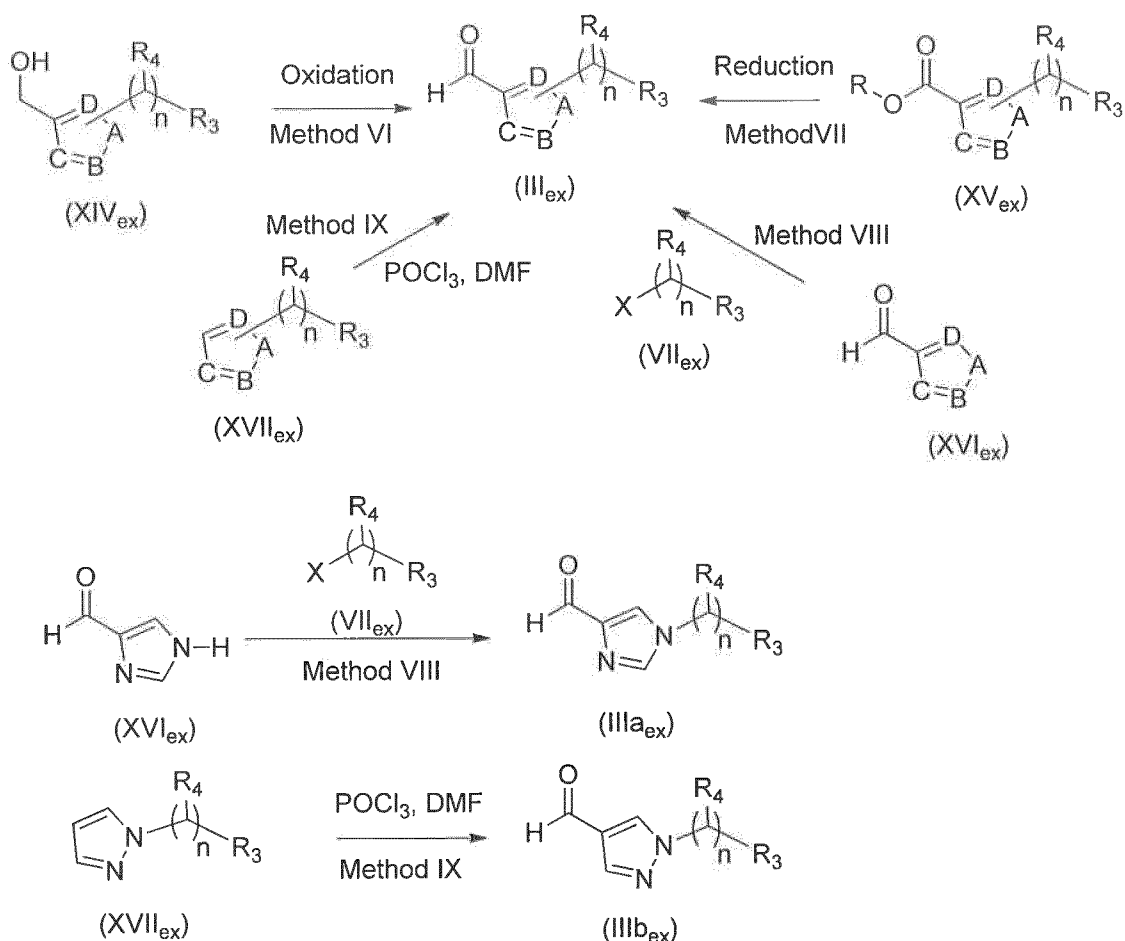
b) The reduction of compounds of formula (XII_{ex}), by any suitable method such as hydrogenation using a palladium catalyst, preferably $Pd(OH)_2$, in a protic solvent preferably MeOH.

c) The deprotection of the resulting compounds of formula (XIII_{ex}) in an acidic medium, preferably HCl in an organic solvent preferably 1,4-dioxane.

Synthesis of intermediates of general formula III_{ex}

5 The aldehydes of general formula (III_{ex}) where R₃, R₄, A, B, C, D and n have the meanings as defined above (with "A", "B", "C", and "D" being "X", "Y", "Z", "W" in the above description, respectively), are commercially available or can be prepared by methods described in the bibliography (for example, WO2010046780 A2, WO2008157844 A1) or by the methods described below and summarized in Scheme
10 6.

Scheme 6



Method VI involves the oxidation of compounds of general formula (XIV_{ex}), using a suitable oxidizing reagent, such as MnO₂, in an aprotic solvent such as dichloromethane.

Method VII involves the reduction of compounds of general formula (XV_{ex}) with a suitable reducing agent such as DIBAL-H at -78 °C in an aprotic solvent, preferably dichloromethane.

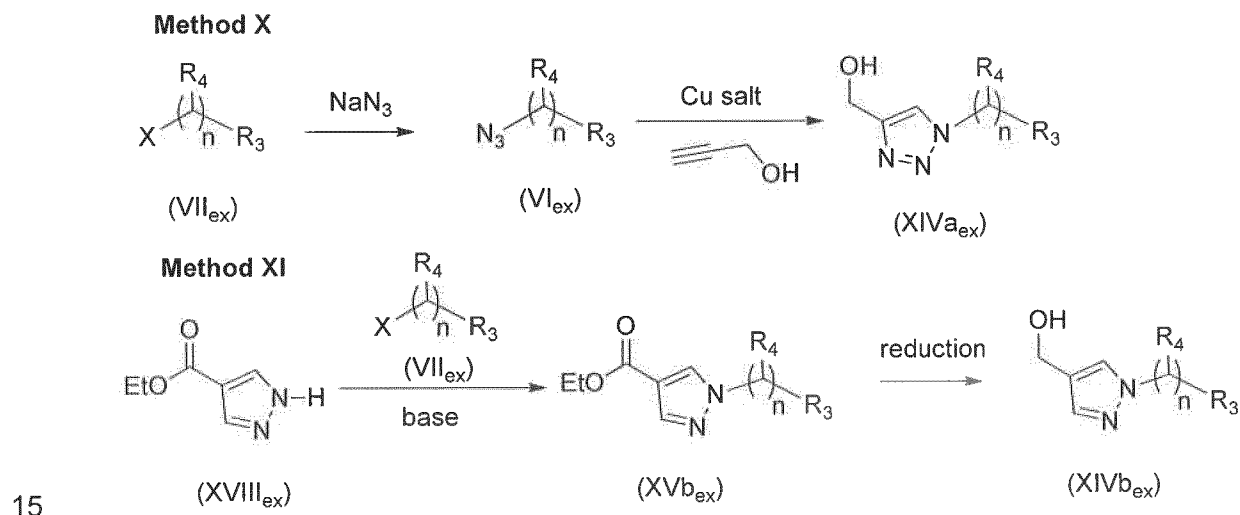
Method VIII, which is exemplified for the preparation of compounds of formula (III_{a_ex}), comprises the reaction between compounds of formula (XVI_{ex}) with compounds of general formula (VII_{ex}) where X is a suitable leaving group as halogen or sulfonate, in the presence of an inorganic base, preferably an aqueous solution of NaOH and a phase transfer catalyst, preferably tetra-n-butylammonium bromide, in an aprotic solvent preferably toluene at room temperature.

Method IX, which is exemplified for the preparation of compounds of formula (IIIb_{ex}), comprises the reaction between the compounds of general formula (XVII_{ex}) with POCl₃ in DMF as solvent at 90-110 °C.

5 Synthesis of intermediates of general formula XIV_{ex}

The alcohols of general formula (XIV_{ex}) where R₃, R₄, A, B, C, D and n have the meanings as defined above, are commercially available or can be prepared by methods described in the bibliography (for example *J. Org. Chem.* 2010, 75, 6540-6548, WO2010080864, *Org. Lett.* 2009, 21, 4954-4957, *J. Med. Chem.* 2011, 54, 5988-5999). In particular, alcohols of formula XIVa_{ex} and XIVb_{ex} can be prepared by the methods outlined in Scheme 7.

Scheme 7



Method X comprises the cycloaddition reaction of an azide of general formula (VI_{ex}) with propargyl alcohol in the presence of a copper salt as catalysts. The azides of general formula (VI_{ex}) are commercially available or may be prepared following conventional methods reported in the literature; alternately, some of the azides can be prepared *in situ*. The reaction is performed in the presence of a copper salt,

preferably $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and sodium ascorbate in a mixture of protic organic solvent and water, preferably a mixture of $\text{t-BuOH}:\text{H}_2\text{O}$ 1:1 at room temperature Alternatively, CuI can be used as copper salt in a polar solvent as dimethylformamide at 100 °C using microwave irradiation or $\text{Cu}(\text{OAc})_2$ can be used as copper salt in a polar solvent, such as methanol at room temperature. The reaction can also be effected using a one-pot procedure, in which case it is performed with sodium azide in a mixture of protic organic solvent and water, preferably a mixture of $\text{t-BuOH}:\text{H}_2\text{O}$ 1:1, heating at 100 °C using microwave irradiation for 1h or until completed reaction, followed by the reaction with propargyl alcohol in the presence of a copper salt, preferably $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and sodium ascorbate at room temperature. Alternatively, CuI is used as copper salt in a polar solvent, such as dimethylformamide and at 90 °C using microwave irradiation.

Compounds of general formula (XIVb_{ex}), where R_3 , R_4 , and n have the meanings as defined above can be prepared using Method XI. This process comprises:

- a) The reaction between compound of formula (XVIII_{ex}) with a compound of general formula (VII_{ex}) where X is a suitable leaving group such as halogen or sulfonate, in the presence of a base, preferably K_2CO_3 , in a polar solvent, preferably acetone at 60° C.
- b) The reduction of the resulting compound (XVb_{ex}) with a suitable hydride reagent, preferably LiAlH_4 at 0 °C, in an aprotic solvent, preferably THF.

Synthesis of intermediates of general formula XV_{ex}

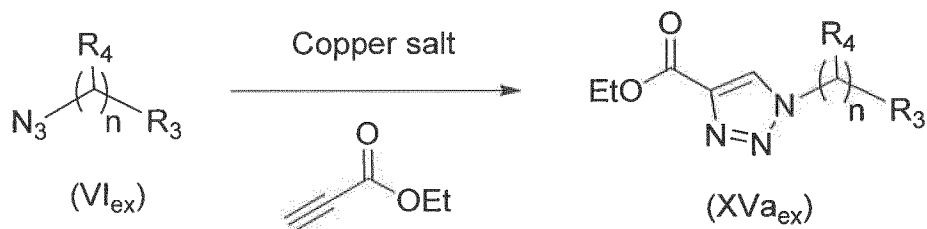
The esters of general formula (XV_{ex}), where R_3 , R_4 , A , B , C , D and n have the meanings as defined above, are commercially available or can be prepared by methods described in the bibliography (*Synthesis*, 1975, 9, 609-610; WO2011098904; *Org. Lett.* 2010, 12, 9, 2166-2169)

The esters of general formula (XVa_{ex}), where R_3 , R_4 , and n have the meanings as defined above, can be prepared by Method XII, which involves the cycloaddition reaction of an azide of general formula (VI_{ex}) with ethyl propiolate in the presence of a

copper salt as catalyst, preferably $\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6$ in an aprotic solvent, preferably toluene, at 70-100 °C (Scheme 8).

Method XII

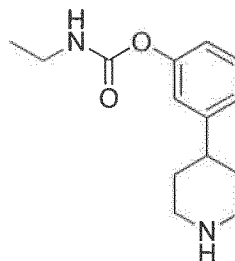
5 Scheme 8



Synthesis of intermediates

10 Example of preparation of an intermediate of formula (IIc_{ex}), Method IV

Synthesis of 3-(piperidin-4-yl)phenyl ethylcarbamate



tert-Butyl 4-(3-((ethylcarbamoyl)oxy)phenyl)piperidine-1-carboxylate: To a solution of *tert*-butyl 4-(3-hydroxyphenyl)piperidine-1-carboxylate (60 mg, 0.21 mmol) in toluene (4 mL), ethylisocyanate (34 μL , 0.43 mmol) and pyridine (7 μL , 0.087 mmol) were added. The mixture was heated at 110 °C overnight. The reaction mixture was cooled, ethyl acetate was added and the reaction mixture was washed with water, brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography, silica gel, gradient hexane to ethyl acetate to afford the title compound (47 mg, 62% yield). $^1\text{H-NMR}$ (300MHz, CDCl_3), δ ppm: 7.29 (t, J = 8 Hz,

15

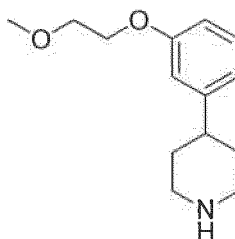
20

1H), 7.04 (t, J = 8 Hz, 1H), 6.98 (m, 2H), 5.04 (bs, 1H), 3.33 (m, 2H), 2.79 (m, 2H), 2.65 (tt J = 12, 3.5 Hz, 1H), 1.84 (m, 2H), 1.63 (m, 4H), 1.49 (s, 9H), 1.23 (t, J = 7 Hz, 3H).

5 **3-(Piperidin-4-yl)phenyl ethylcarbamate:** To a solution of *tert*-butyl 4-(3-((ethylcarbamoyl)oxy)phenyl)piperidine-1-carboxylate (47 mg, 0.13 mmol) in dioxane (0.5 mL), a solution of 4M HCl in dioxane (0.5 mL, 2.02 mmol) was added and the mixture was stirred at rt overnight. The solution was concentrated to dryness to afford the title compound (38 mg, 99% yield) as hydrochloride. ¹H-NMR (500MHz, MeOD), δ ppm: 7.35 (t, J = 8 Hz, 1H), 7.14 (t, J = 8 Hz, 1H), 7.04 (s, 1H), 6.99 (d, J = 8 Hz, 1H),
10 3.68 (m, 1H), 3.50 (m, 2H), 3.22 (q, J = 7 Hz, 2H), 3.14 (m, 2H), 2.93 (m, 1H), 2.07 (m, 2H), 1.94 (m, 2H), 1.19 (t, J = 7 Hz, 3H).

Example of preparation of an intermediate of formula (IId_{ex}), Method IV

Synthesis of 4-(3-(2-methoxyethoxy)phenyl)piperidine



15

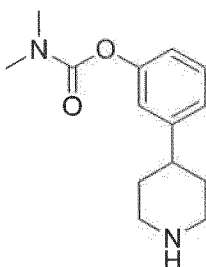
***tert*-Butyl 4-(3-(2-methoxyethoxy)phenyl)piperidine-1-carboxylate:** In a microwave vial, to a solution of *tert*-butyl 4-(3-hydroxyphenyl)piperidine-1-carboxylate (80 mg, 0.28 mmol) and Cs₂CO₃ (188 mg, 0.57 mmol) in acetonitrile (3 mL), 1-bromo-2-methoxyethane (80 mg, 0.57 mmol) was added and the mixture was irradiated with
20 microwaves at 100 °C for 30 min. Water was added and the product was extracted with ethyl acetate, the organic phase was washed with brine, dried Na₂SO₄, filtered and concentrated under vacuum to afford the title product (80 mg, 83% yield). ¹H-NMR (400MHz, CDCl₃), δ ppm: 7.23 (t, J = 8 Hz, 1H), 6.81 (m, 3H), 4.24 (m, 2H), 4.13 (m, 2H), 3.77 (m, 2H), 3.47 (s, 3H), 2.80 (m, 2H), 2.62 (tt J = 12, 3.5 Hz, 1H), 1.83 (m,
25 2H), 1.63 (m, 2H), 1.50 (s, 9H).

4-(3-(2-Methoxyethoxy)phenyl)piperidine: To a solution of *tert*-Butyl 4-(3-(2-methoxyethoxy)phenyl)piperidine-1-carboxylate (80 mg, 0.23 mmol) in dioxane (0.5

mL), a solution of 4M HCl in dioxane (0.89 mL, 3.5 mmol) was added and stirred at rt overnight. The mixture was concentrated to dryness to afford the titled compound (60 mg, 95% yield) as hydrochloride that was used directly in the next step.

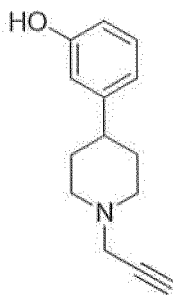
Example of preparation of an intermediate of formula (Ilf_{ex}), Method IV

5 **Synthesis of 3-(piperidin-4-yl)phenyl dimethylcarbamate**

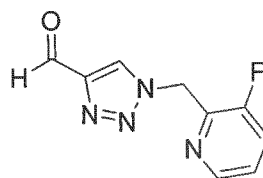


***tert*-Butyl 4-(3-((dimethylcarbamoyl)oxy)phenyl)piperidine-1-carboxylate:** To a suspension of NaH in DMF at 0 °C under inert atmosphere, a solution of *tert*-butyl 4-(3-hydroxyphenyl)piperidine-1-carboxylate (65 mg, 0.23 mmol) was added. The reaction mixture was warmed at rt and stirred for 30 min; then, dimethylcarbamic chloride (30 mg, 0.28 mmol) was added and the mixture was stirred at rt for 2 h. Ethyl acetate was added, washed with water, brine, dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by flash chromatography, silica gel, gradient hexane to ethyl acetate afforded the title product (80 mg, 98% yield). ¹H-NMR (400MHz, CDCl₃), δ ppm: 7.29 (m, 1H), 7.04 (m, 1H), 4.24 (m, 2H), 3.11 (s, 3H), 3.03 (s, 3H), 2.79 (m, 2H), 2.66 (tt J = 12, 3.5 Hz, 1H), 1.85 (m, 2H), 1.64 (m, 2H), 1.49 (s, 9H).

3-(Piperidin-4-yl)phenyl dimethylcarbamate: To a solution of 4-(3-((dimethylcarbamoyl)oxy)phenyl)piperidine-1-carboxylate (80 mg, 0.23 mmol) in dioxane (0.5 mL), a solution of 4M HCl in dioxane (0.86 mL, 3.44 mmol) was added, and the mixture was stirred at rt overnight. The solution was concentrated to dryness to afford the title compound (65 mg, 99% yield) as hydrochloride. ¹H-NMR (500MHz, MeOD) δ ppm: 7.37 (t, J = 8 Hz, 1H), 7.17 (d, J = 8 Hz, 1H), 7.04 (m, 1H), 7.00 (m, 1H), 3.51 (m, 2H), 3.15 (m, 2H), 3.14 (s, 3H), 3.01 (s, 3H), 2.95 (tt J = 12, 3.5 Hz, 1H), 2.11 (m, 2H), 1.92 (m, 2H).

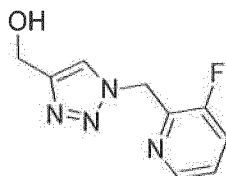
Example of preparation of an intermediate of formula (V_{ex}), Method IIA**Synthesis of 3-(1-(prop-2-yn-1-yl)piperidin-4-yl)phenol**

- 5 A suspension of 4-(3-hydroxyphenyl)piperidine (403 mg, 2.23 mmol), Et₃N (404 μ L, 2.90 mmol) and propargyl bromide (273 μ L, 80% wt in toluene, 2.45 mmol) in THF (20 mL) was irradiated with microwaves at 75 °C for 1h. The reaction mixture was cooled and the solvent evaporated. Purification by flash chromatography, silica gel, gradient hexane to ethyl acetate afforded the desired product (352 mg, 73% yield). ¹H-NMR (400MHz, CDCl₃), δ ppm: 7.16 (t, J = 8 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 6.77 (m, 2H),
 10 3.37 (d, J = 2 Hz, 2H), 3.02 (d, J = 11 Hz, 2H), 2.46 (m, 1H), 2.36 (td, J = 11, 3 Hz, 2H), 2.28 (t, J = 2 Hz, 1H), 1.84 (m, 4H).

Example of preparation of an intermediate of formula (III_{ex}), Method VI**Synthesis of 1-(3-fluoropyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carbaldehyde**

15

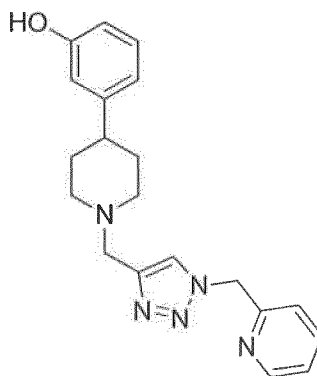
- To a solution of (1-((3-fluoropyridin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methanol (408 mg, 1.96 mmol) in dry dichloromethane (19 mL), MnO₂ (1.74 g, 17.6 mmol) was added and the mixture was stirred at rt overnight. The reaction mixture was filtered on Celite and the solvent was removed under vacuum. Purification by flash
 20 chromatography, silica gel, gradient hexane to ethyl acetate, afforded the title product (297 mg, 73% yield). ¹H-NMR (400MHz, CDCl₃), δ ppm: 10.16 (s, 1H), 8.43 (dt, J = 4.7, 1.4 Hz, 1H), 8.36 (s, 1H), 7.51 (m, 1H), 7.39 (m, 1H), 5.83 (d, J = 2 Hz, 2H).

Example of preparation of an intermediate of formula (XIVa_{ex}), Method X**Synthesis of 1-((3-fluoropyridin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methanol**

- 5 To a solution of 2-(azidomethyl)-3-fluoropyridine (529 mg, 3.48 mmol), in MeOH (7.7 mL), propargyl alcohol (390 mg, 6.96 mmol) and a solution of Cu(OAc)₂ (44 mg, 0.24 mmol) in water (4 mL) were added and the mixture was stirred at rt overnight. The reaction mixture was filtered through alumina, washed with ethyl acetate and MeOH and the combined filtrates concentrated under vacuum. Purification was carried out
- 10 by flash chromatography, silica gel, gradient dichloromethane to dichloromethane:methanol 8:2 to afford the title product (408 mg, 56% yield). ¹H-NMR (400MHz, CDCl₃), δ ppm: 8.41 (bs, 1H), 7.80 (bs, 1H), 7.44 (t, J = 8 Hz, 1H), 7.34 (m, 1H), 5.72 (s, 2H), 4.77 (bs, 2H).

Example of preparation of an intermediate of formula (Ic_{ex}), Method IIB

- 15 **Synthesis of 3-(1-((1-Pyridin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenol**



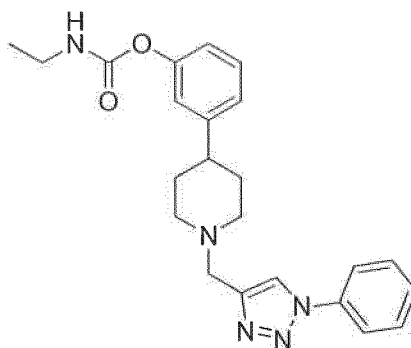
- A mixture of 3-(1-(prop-2-yn-1-yl)piperidin-4-yl)phenol (416 mg, 1.32 mmol), 2-(azidomethyl)pyridine (337 mg, 2.51 mmol), CuSO₄·5H₂O (48 mg, 0.19 mmol) and
- 20 sodium ascorbate (77 mg, 0.38 mmol) in t-BuOH:H₂O 1:1 (32 mL) was stirred at rt for 16 h. Water and saturated NH₄Cl aqueous solution were added and the mixture

extracted with EtOAc. The organic phases were combined, dried over Na_2SO_4 and concentrated. Purification was carried out by flash chromatography, silica gel, gradient hexane to acetone to afford the title product (525 mg, 78% yield). ^1H -NMR (300MHz, CDCl_3), δ ppm: 8.60 (m, 1H), 7.70 (td, $J = 7.6, 1.8$ Hz, 1H), 7.68 (s, 1H), 7.28 (m, 1H), 7.20 (d, $J = 8$ Hz, 1H), 7.13 (t, $J = 7.6$ Hz, 1H), 6.74 (d, $J = 7.6$ Hz, 1H), 6.66 (m, 2H), 5.65 (s, 2H), 3.73 (s, 2H), 3.06 (m, 2H), 2.44 (tt, $J = 11, 4$ Hz, 1H), 2.17 (m, 2H), 1.78 (m, 4H).

Synthesis of Examples

Preparation of compounds of general formula (I_{ex}), Method I

Example 1: 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl ethylcarbamate

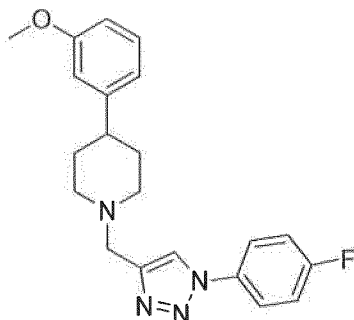


To a suspension of 3-(piperidin-4-yl)phenyl dimethylcarbamate hydrochloride (38 mg, 0.13 mmol) in dichloroethane (3 mL), DIPEA (163 μL , 0.93 mmol) was added and the mixture was stirred at rt for 5 min. Then, 1-phenyl-1H-1,2,3-triazole-4-carbaldehyde (30 mg, 0.17 mmol) and $\text{NaBH}(\text{OAc})_3$ (45 mg, 0.21 mmol) were added and the reaction mixture was stirred at rt overnight. Dichloromethane was added and washed with NaHCO_3 sat solution and brine, dried over Na_2SO_4 , filtered and concentrated. Purification by flash chromatography, silica gel, gradient dichloromethane to dichloromethane: methanol 90:10 afforded the title product (40 mg, 73% yield). HPLC retention time: 5.62 min; HRMS: 406.2227 ($\text{M}+\text{H}$).

This method was used for the preparation of examples 1, 8, 10, 11, 12, 15, 16, 17.

Preparation of compounds of general formula (I_{ex}), Method IIF

Example 2: 1-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)4-(3-methoxyphenyl)piperidine



5

A mixture of 4-(3-methoxyphenyl)piperidine (61 mg, 0.32 mmol), Et₃N (178 μ L, 1.27 mmol) and propargyl bromide (36 μ L, 0.32 mmol, 80% solution in toluene) in water (1.2 mL) was vigorously stirred at rt for 1 h. Then, 4-fluorophenylazide (670 μ L, 0.5M solution in tert-butylmethylether, 0.33 mmol) and CuI (6 mg, 0.03 mmol) were added. The mixture was stirred at rt overnight. NH₄Cl saturated solution was added and the mixture was extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography, silica gel, gradient from hexane to hexane:ethyl acetate (1:1) afforded the titled product (70 mg, 60% yield). HPLC retention time: 5.91 min; HRMS: 367.1946 (M+H).

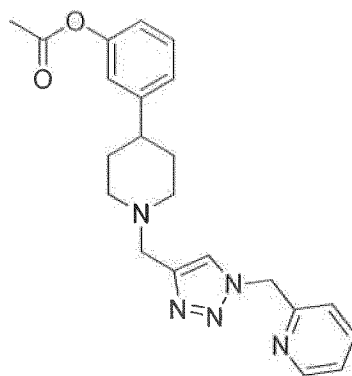
15

This method was used for the preparation of the examples of formula (I) 2, 7.

Preparation of compounds of general formula (Id_{ex}), Method III

Example 3: 3-(1-((1-(pyridine-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate

20

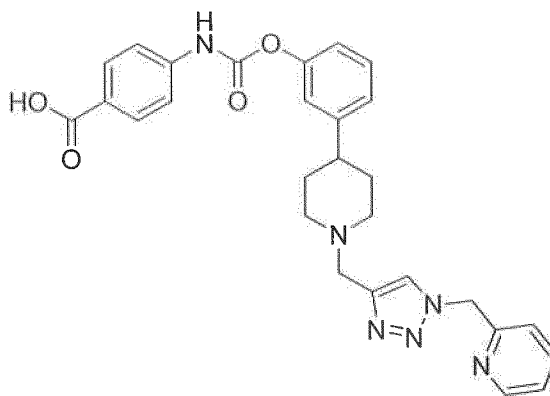


To a solution of 3-(1-((1-pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenol (130 mg, 0.37 mmol) in DCM (6 mL), Et₃N (156 μL, 1.12 mmol) and 4-DMAP (9 mg, 0.07 mmol) were added. The reaction mixture was cooled at 0 °C and acetic anhydride (42 mL, 0.44 mmol) was added. The reaction mixture was warmed at rt and stirred overnight, NaHCO₃ saturated solution was added and extracted with DCM, washed with brine, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography silica gel, gradient from DCM to DCM:MeOH (95:5) afforded the title product (130 mg, 89% yield). HPLC retention time: 4.97 min; HRMS: 392.2079 (M+H).

This method was used for the preparation of examples of formula (I) 3, 9.

Preparation of compounds of general formula (Ie_{ex}), Method III

Example 4: 4-(((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonyl)amino)benzoic acid



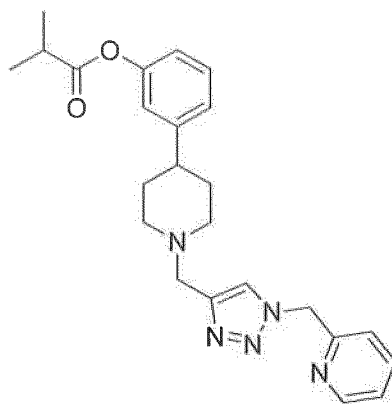
tert-Butyl 4-(((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonyl)amino)benzoate: A mixture of 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenol (340 mg, 0.397 mmol) and *tert*-butyl-4-isocyanatobenzoate (300 mg, 1.36 mmol) in THF (10 mL) under inert atmosphere, was heated at 70 °C in a sealed tube for 16 h. The reaction mixture was cooled down to rt and concentrated under vacuum. Purification by flash chromatography silica gel, gradient from DCM to DCM:MeOH (90:10) afforded the title product (350 mg, 63% yield). ¹H-NMR (400MHz, MeOD), δ ppm: 8.62 (m, 1H), 8.11 (s, 1H), 7.98 (d AB system, 2H), 7.92 (td, J = 7.5, 1.8 Hz, 1H), 7.65 (d AB system, 2H), 7.45 (m, 1H), 7.40 (t, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 1H), 7.15 (t, J = 2 Hz, 1H), 7.10 (m, 1H), 5.80 (s, 2H), 3.82 (s, 2H), 3.15 (m, 2H), 2.65 (tt, J = 12, 4 Hz, 1H), 2.33 (m, 2H), 1.89 (m, 4H), 1.66 (s, 9H).

4-(((3-(1-((1-(Pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonyl)amino)benzoic acid: To a suspension of *tert*-butyl 4-(((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonyl)amino)benzoate (175 mg, 0.31 mmol) in dioxane (1 mL), a solution of 4M HCl in dioxane (1 mL, 4 mmol) was added and the mixture was stirred at rt for 6 h. The solid was isolated by filtration to afford the titled product (151 mg, 79% yield) as hydrochloride. HPLC retention time: 5.13 min; HRMS: 511.2104 (M-H).

This method was used for the preparation of examples of formula (I) 4, 13, 14.

Preparation of compounds of general formula (I_{ex}), Method III

Example 5: 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl isobutyrate

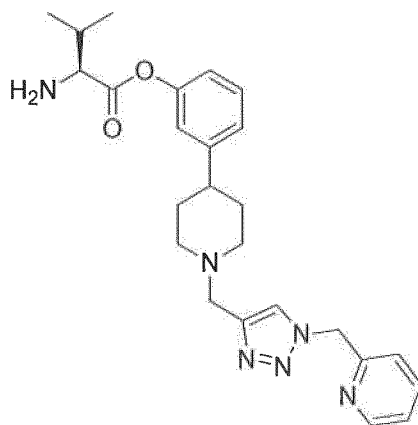


To a solution of 3-(1-((1-pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenol (200 mg, 0.57 mmol) in anhydrous THF (10 mL) at 0 °C, Et₃N (160 μl, 1.15 mmol) and isobutyryl chloride (91 mg, 0.86 mmol) were added. The reaction mixture was stirred at 0 °C for 10 min and then at rt for 4 h. The reaction mixture was cooled again at 0 °C and additional amount of isobutyryl chloride (45 mg, 0.43 mmol) was added and stirred at rt for 2 h until completed reaction. NaHCO₃ saturated solution was added and extracted with DCM, washed with brine, dried over Na₂SO₄, filtered and concentrated to afforded the title product (209 mg, 87% yield). HPLC retention time: 5.67 min; HRMS: 420.2395 (M+H).

This method was used for the preparation of examples of formula (I) 5.

Preparation of compounds of general formula (I_{ex}), Method III

Example 6: (S)-3-(1-((1-(4-(2-amino-3-methylbutanoate)phenyl)piperidin-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)pyridin-2-ylmethyl)phenol



(S)-3-(1-((1-Pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-((tert-butoxycarbonyl)amino-3-methylbutanoate: To a solution of 3-(1-((1-pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenol (300 mg, 0.86 mmol) and Boc-(L)-Val-OH (261 mg, 1.20 mmol) in anhydrous DCM (20 mL) under inert atmosphere, EDAC-HCl (247 mg, 1.28 mmol) and 4-DMAP (52 mg, 0.43 mmol) were added. The reaction mixture was stirred at rt for 16 h. DCM was added and washed with water and brine, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography, silica gel, gradient from DCM to DCM:MeOH (90:10) afforded the title product (440 mg, 93% yield). ¹H-NMR (400MHz, MeOD), δ ppm: 8.61 (m, 1H), 7.69 (td, J = 7.5, 1.8 Hz, 1H), 7.67 (s, 1H), 7.29 (m, 2H), 7.20 (d, J = 8 Hz, 1H), 7.09 (d, J = 8 Hz, 1H), 6.92 (m, 2H), 5.66 (s, 2H), 5.10 (d, J = 9 Hz, 1H), 4.45 (m, 1H), 3.72 (s, 2H), 3.07 (m, 2H), 2.50 (tt, J = 12, 4 Hz, 1H), 2.32 (m, 1H), 2.17 (td, J = 12, 2 Hz, 2H), 1.79 (m, 4H), 1.47 (s, 9H), 1.08 (d, J 6.8 Hz, 3H), 1.02 (d, J 6.8 Hz, 3H).

(S)-3-(1-((1-Pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-methylbutanoate: To a solution of (S)-3-(1-((1-pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-((tert-butoxycarbonyl)amino-3-methylbutanoate (540 mg, 0.98 mmol) in dioxane (3 mL), a solution of 4M HCl in dioxane (3.7 mL, 14.7 mmol) was added and the mixture was stirred at rt for 2 h. The reaction mixture was concentrated to dryness to afford the title product (455 mg, 89% yield) as hydrochloride. HPLC retention time: 4.28 min; MS: 471.3 (M+Na).

This method was used for the preparation of examples of formula (I) 6, 18, 19, 20.

Table of Examples with results of HRMS and binding to the μ -opioid Receptor and the σ 1-Receptor:

HPLC:

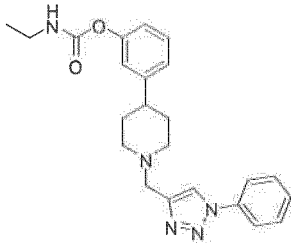
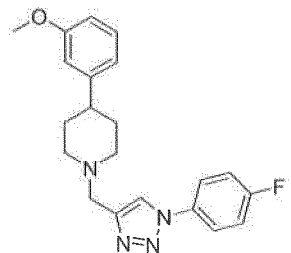
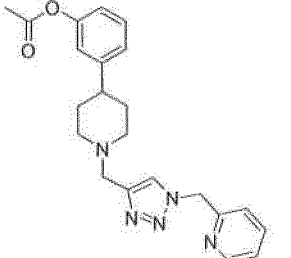
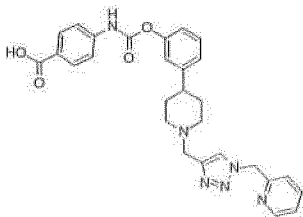
column: Agilent Eclipse XDB-C18, 4.6x150mm, 5 mm, flux: 1ml/min.

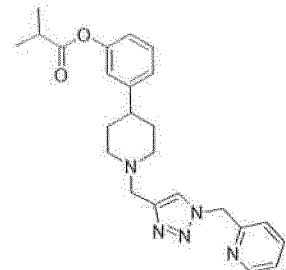
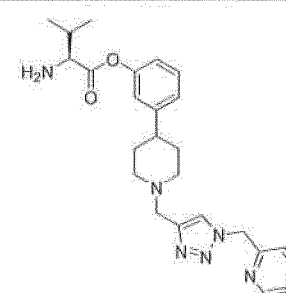
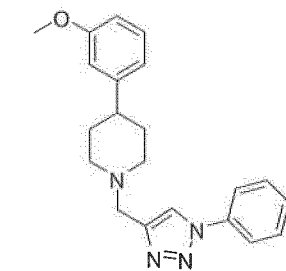
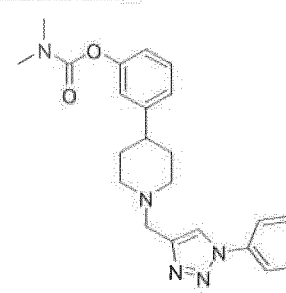
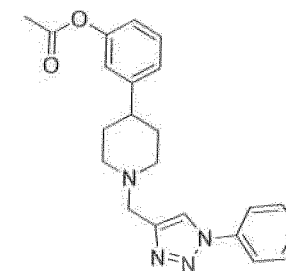
A:H₂O(0.05%TFA), B:ACN.

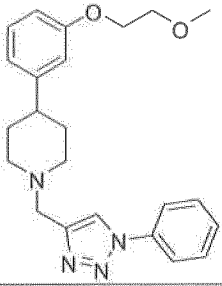
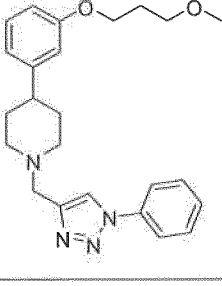
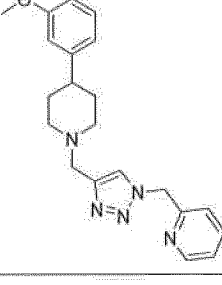
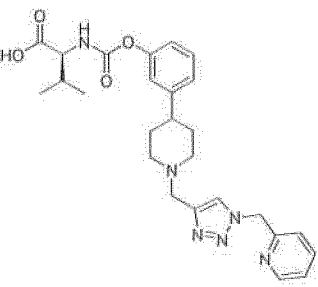
Conditions: 1° gradient 5% to 95%B in 7 min. 2° isocratic 95%B 5 min.

HRMS:

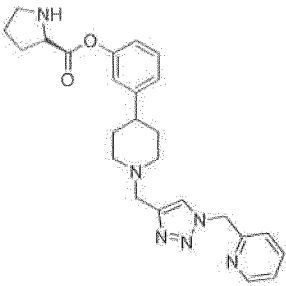
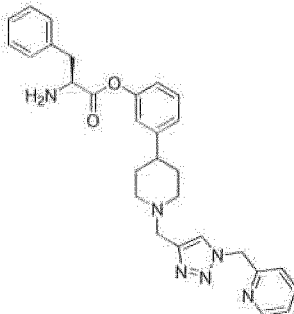
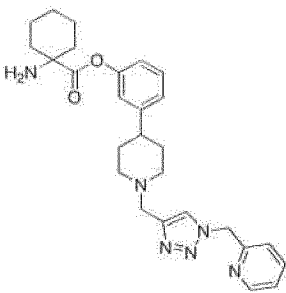
Source type: ESI; Ion Polarity: Positive or Negative

EX	Structure	Chemical name	Ret time (min)	HRMS
1		3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl ethylcarbamate	5.62	406.22 27 (M+H)
2		1-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(3-methoxyphenyl)piperidine	5.91	367.19 46(M+H)
3		3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate	4.97	392.20 79 (M+H)
4		4-((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonyl amino)benzoic acid	5.13	511.21 04 (M-H)

5		3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl isobutyrate	5.67	420.23 95 (M+H)
6		(S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-methylbutanoate	4.28	471.3 (M+Na)
7		4-(3-methoxyphenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine	5.84	349.20 36 (M+H)
8		3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl dimethylcarbamate	5.65	406.22 55(M+H)
9		3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate	5.70	377.19 74(M+H)

10		4-(3-(2-methoxyethoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine	5.75	393.2309 (M+H)
11		4-(3-(3-methoxypropoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine	5.87	407.2457 (M+H)
12		2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine	5.06	364.2128 (M+H)
13		(S)-3-methyl-2-((3-((1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonyl amino)butanoic acid	5.05	491.2424 (M-H)

14		2-((3-((1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonyl amino)acetic acid	4.45	449.19 44 (M-H)
15		3-fluoro-2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine	5.33	382.20 41 (M+H)
16		5-fluoro-2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine	5.36	382.20 40 (M+H)
17		2-(4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-2-phenylethanol	5.58	393.22 92 (M+H)

18		(S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl pyrrolidine-2-carboxylate	4.12	469.3 (M+Na)
19		(S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-phenylpropanoate	4.70	519.3 (M+Na)
20		3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 1-aminocyclohexanecarboxylate		

BIOLOGICAL ACTIVITY

Pharmacological study

5 Human σ_1 receptor radioligand assay

To investigate binding properties of σ_1 receptor ligands to human σ_1 receptor, transfected HEK-293 membranes and [3 H](+)-pentazocine (Perkin Elmer, NET-1056), as the radioligand, were used. The assay was carried out with 7 μ g of membrane suspension, 5 nM of [3 H](+)-pentazocine in either absence or presence of either buffer or 10 μ M Haloperidol for total and non-specific binding, respectively. Binding

10 buffer contained Tris-HCl 50 mM at pH 8. Plates were incubated at 37 °C for 120 minutes. After the incubation period, the reaction mix was then transferred to MultiScreen HTS, FC plates (Millipore), filtered and plates were washed 3 times with ice-cold 10 mM Tris-HCL (pH7.4). Filters were dried and counted at approximately

40% efficiency in a MicroBeta scintillation counter (Perkin-Elmer) using EcoScint liquid scintillation cocktail

Human μ -opioid receptor radioligand assay

- 5 To investigate binding properties of μ -opioid receptor ligands to human μ -opioid receptor, transfected CHO-K1 cell membranes and [3 H]-DAMGO (Perkin Elmer, ES-542-C), as the radioligand, were used. The assay was carried out with 20 μ g of membrane suspension, 1 nM of [3 H]-DAMGO in either absence or presence of either buffer or 10 μ M Naloxone for total and non-specific binding, respectively. Binding
- 10 buffer contained Tris-HCl 50 mM, MgCl₂ 5 mM at pH 7.4. Plates were incubated at 27°C for 60 minutes. After the incubation period, the reaction mix was then transferred to MultiScreen HTS, FC plates (Millipore), filtered and plates were washed 3 times with ice-cold 10 mM Tris-HCL (pH 7.4). Filters were dried and counted at approximately 40% efficiency in a MicroBeta scintillation counter (Perkin-Elmer) using
- 15 EcoScint liquid scintillation cocktail.

Results:

As this invention is aimed at providing a compound or a chemically related series of compounds which act as dual ligands of the σ_1 receptor and the μ -opioid receptor it is a very preferred embodiment in which the compounds are selected which act as dual
 5 ligands of the σ_1 receptor and the μ -opioid receptor and especially compounds which have a binding expressed as K_i which is preferably < 1000 nM for both receptors, more preferably < 500 nM, even more preferably < 100 nM.

The following scale as been adopted for representing the binding to the the σ_1
 10 receptor and the μ -opioid receptor expressed as K_i :

- + Both K_i - μ and K_i - $\sigma_1 \geq 500$ nM
- ++ One $K_i < 500$ nM while the other K_i is ≥ 500 nM
- +++ Both K_i - μ and K_i - $\sigma_1 < 500$ nM
- ++++ Both K_i - μ and K_i - $\sigma_1 < 100$ nM

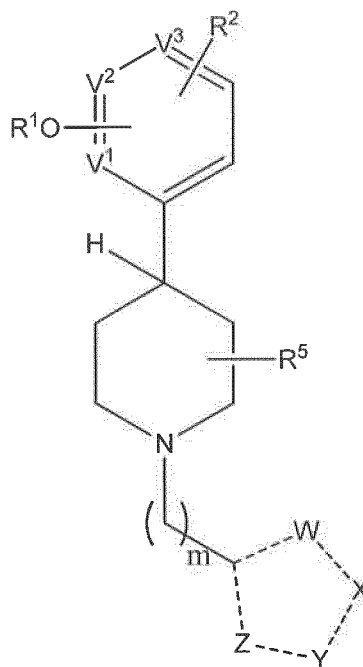
15 All compounds prepared in the present application exhibit binding to the σ_1 receptor and the μ -opioid receptor, in particular the following binding results are shown:

EX	μ and σ_1 dual binding
1	+++
2	++
3	++
4	+++
5	+++
6	+++
7	+++
8	+++
9	++++
10	+++
11	+++
12	++
13	+

14	+
15	++
16	++
17	++
18	+++
19	+++
20	+

CLAIMS:

1. A Compound of general formula (I),



(I)

5 wherein

m is 1 or 2;

one of V¹, V² and V³ is selected from nitrogen or carbon while the others are carbon;

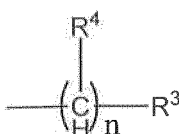
10 R¹ is -COR⁶, -CONR⁸R⁹, -COCR⁶R⁷NR⁸R⁹, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

15 R² is hydrogen, halogen, -NR⁸R⁹, -SR⁷, -OR⁷, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

R⁵ is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl;

R^6 , R^7 , R^8 and R^9 are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl; or R^6 and R^7 or R^8 and R^9 together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring;

and wherein W, X, Y and Z are selected from carbon, nitrogen, or oxygen while W-X-Y-Z are forming together with the bridging C-atom, that is connected to the core scaffold, a 5-membered heterocyclic ring, which is either substituted on one

of W, X, Y or Z by  or in which this said 5-membered heterocyclic ring - being otherwise unsubstituted - is fused at W and X to a further ringsystem;

wherein

n is 0 or 1;

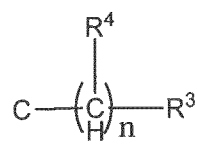
R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl; and

R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof;

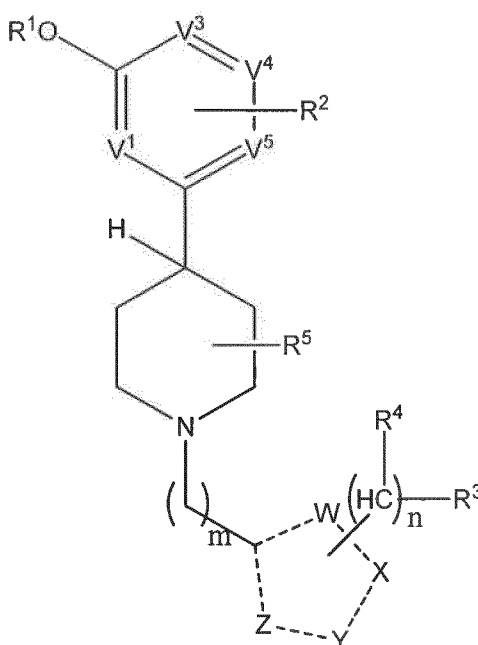
with the following proviso applying:

- with the proviso that if V^1 , V^2 and V^3 are carbon and either X or Y is



with $n = 0$ and R^3 being CH_3 , then OR^1 may not be $-\text{OCH}_3$ in meta position.

2. Compound according to claim 1, wherein the compound is a compound according to Formula II,



(II)

wherein

m is 1 or 2;

n is 0 or 1;

one of V^1 , V^3 , V^4 and V^5 is selected from nitrogen or carbon while the others are carbon;

R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycl;

R² is hydrogen, halogen, -NR⁸R⁹, -SR⁷, -OR⁷, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

5 R³ is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl; and

10 R⁴ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

R⁵ is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl;

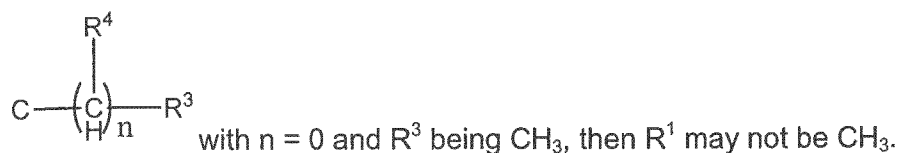
15 R⁶, R⁷, R⁸ and R⁹ are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl; or R⁶ and
20 R⁷ or R⁸ and R⁹ together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring;

and wherein W, X, Y and Z are selected from carbon, nitrogen, or oxygen while W-X-Y-Z are forming together with the bridging C-atom, that is connected to the core scaffold, a 5-membered heterocyclic ring,

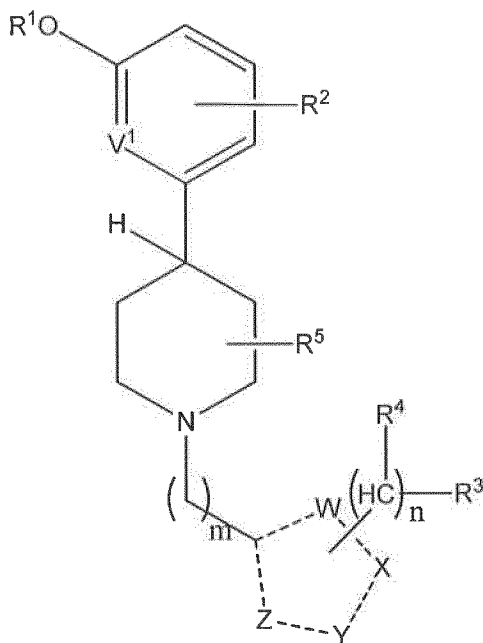
25 optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof;

with the following proviso applying:

- with the proviso that if V^1 , V^3 , V^4 and V^5 are carbon and either X or Y is



3. Compound according to any one of claims 1 or 2, wherein the compound is compound according to Formula III,



(III)

wherein

m is 1 or 2;

n is 0 or 1;

V^1 is selected from nitrogen or carbon;

R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

R^2 is hydrogen, halogen, $-\text{NR}^8\text{R}^9$, $-\text{SR}^7$, $-\text{OR}^7$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl,

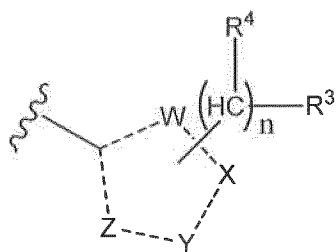
substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl; and

R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

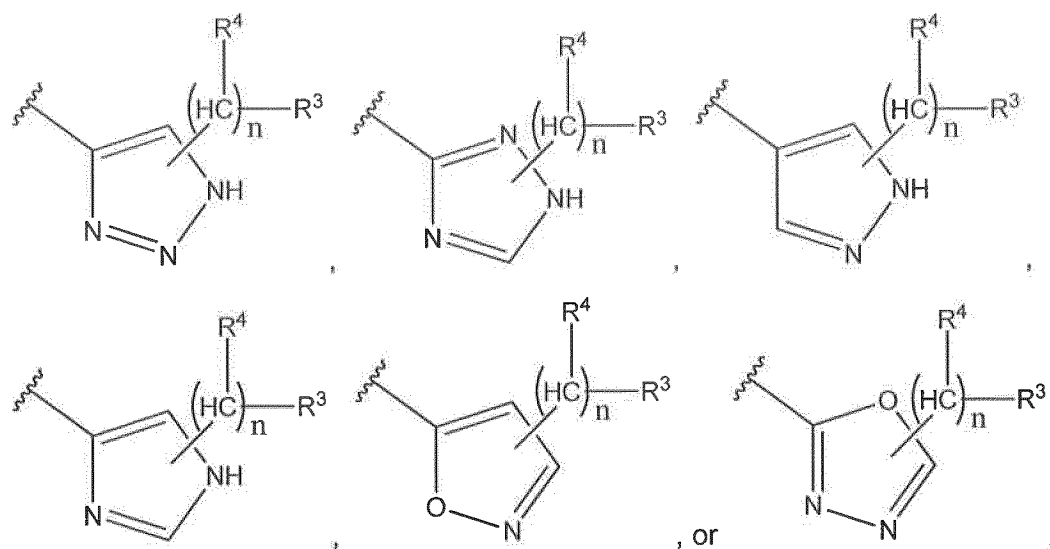
R^5 is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl;

R^6 , R^7 , R^8 and R^9 are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl; or R^6 and R^7 or R^8 and R^9 together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring;



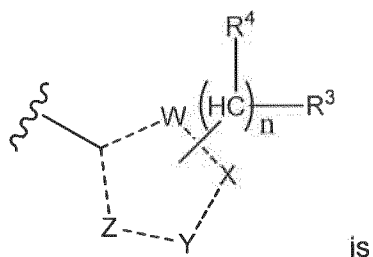
and

is selected from:



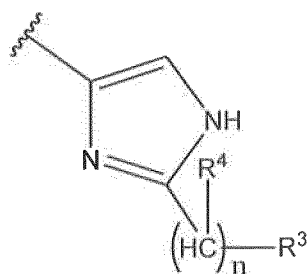
- optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof;
- 5

with the following proviso applying:

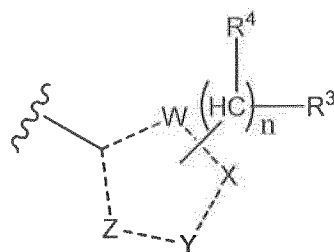


- with the proviso that if V^1 is carbon and

is

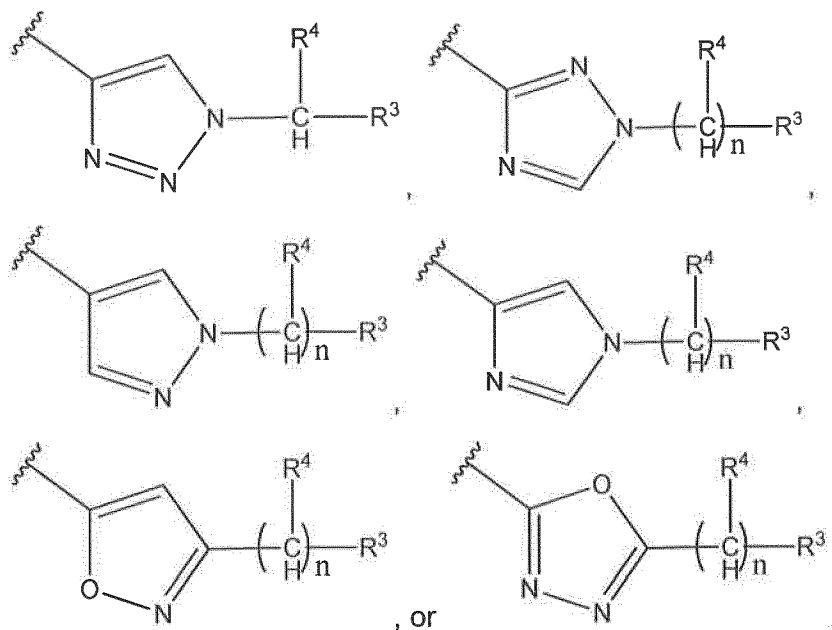


with $n = 0$ and R^3 being CH_3 , then R^1 may not be CH_3 .



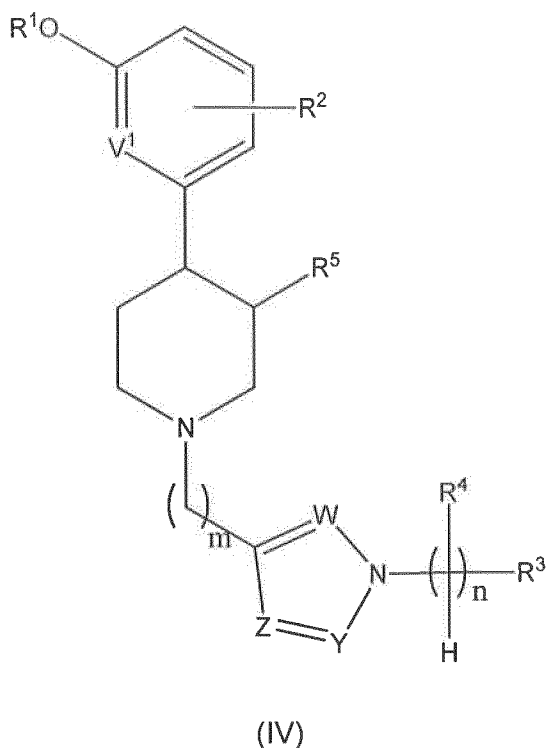
4. Compound according to claim 3, wherein
from:

is selected



5

5. Compound according to any one of claims 1 or 2, wherein the compound is
compound according to Formula IV,



wherein

m is 1 or 2;

5 n is 0 or 1;

V¹ is selected from nitrogen or carbon;

R¹ is -COR⁶, -CONR⁸R⁹, -COCR⁶R⁷NR⁸R⁹, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

10 R² is hydrogen, halogen, -NR⁸R⁹, -SR⁷, -OR⁷, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

15 R³ is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl; and

R⁴ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

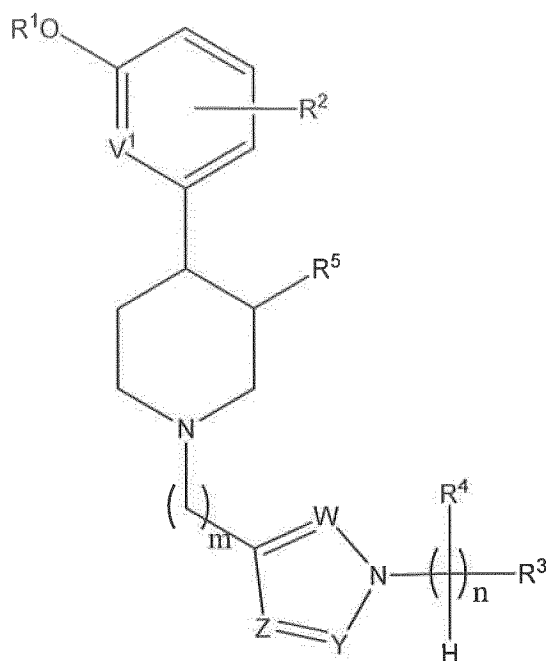
- 5 R⁵ is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl;

- 10 R⁶, R⁷, R⁸ and R⁹ are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl; or R⁶ and R⁷ or R⁸ and R⁹ together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring;

- 15 and W, Y and Z are independently from one another selected from N or CH with only 1 or 2 of them being CH;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

- 20 6. Compound according to any one of claims 1 to 5, wherein the compound is compound according to Formula IV,



(IV)

wherein

m is 1 or 2;

5 n is 0 or 1;

V^1 is selected from nitrogen or carbon;

R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

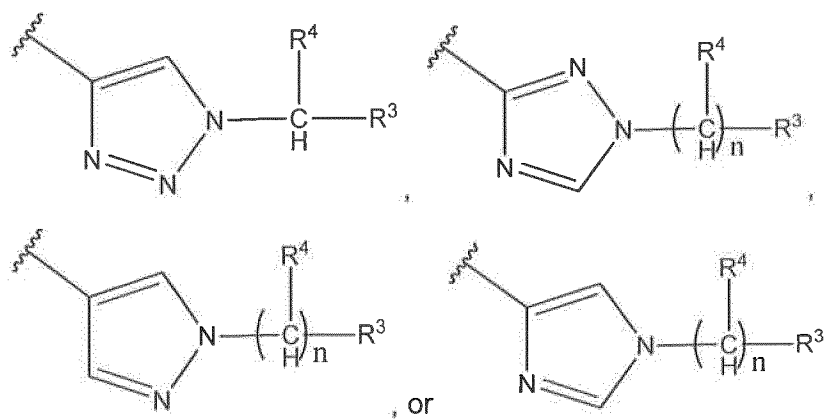
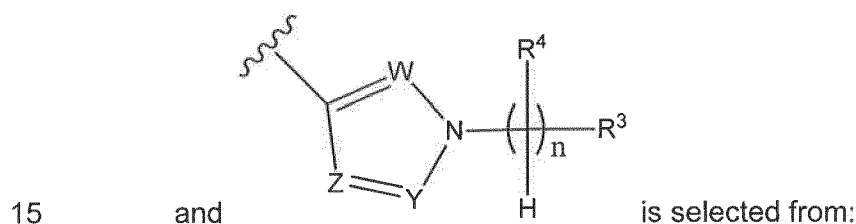
10 R^2 is hydrogen, halogen, $-\text{NR}^8\text{R}^9$, $-\text{SR}^7$, $-\text{OR}^7$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

15 R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl; and

R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl;

5 R^5 is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl;

R^6 , R^7 , R^8 and R^9 are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl; or R^6 and R^7 or R^8 and R^9 together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring;



optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

7. Compound according to any one of claims 1 to 6, wherein

R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein

5 the aryl is selected from phenyl, naphthyl, or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;
and/or

10 the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring, more preferably is selected from imidazole, 15 oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, 20 benzodioxane, carbazole and quinazoline;
and/or

25 the alkyl is selected from C_{1-8} alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl; preferably is C_{1-6} alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl; more preferably is C_{1-4} alkyl, like methyl, ethyl, propyl and butyl;
and/or

30 the cycloalkyl is selected from C_{3-8} cycloalkyl; preferably is C_3 - C_7 cycloalkyl; more preferably is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;
and/or

most preferably R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted alkyl like C_{1-4} -alkyl or CH_3 , $\text{C}_2\text{H}_4\text{OCH}_3$, $\text{C}_3\text{H}_6\text{OCH}_3$,

and/or

R^2 is hydrogen, halogen, $-NR^8R^9$, $-SR^7$, $-OR^7$, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein

- 5 the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;
and/or
the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more
- 10 heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; more preferably is selected from imidazole,
- 15 oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane,
- 20 benzodioxane, carbazole and quinazoline;
and/or
the alkyl is C_{1-8} alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C_{1-6} alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C_{1-4} alkyl like methyl, ethyl, propyl or
- 25 butyl;
and/or
the alkenyl is C_{2-10} -alkenyl or C_{2-8} -alkenyl like ethylene, propylene, butylene, pentylene, hexylene, heptylene or octylene; preferably is C_{1-6} -alkenyl like ethylene, propylene, butylene, pentylene, or hexylene;
- 30 more preferably from C_{1-4} -alkenyl, like ethylene, propylene, or butylene;
and/or
the alkynyl is C_{2-10} -alkynyl or C_{2-8} -alkynyl like ethyne, propyne, butyne, pentyne, hexyne, heptyne, or octyne; preferably is C_{2-6} -alkynyl like

- ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne;
and/or
the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;
and/or
halogen is any of fluorine, chlorine, iodine or bromine, preferably chlorine or fluorine;
and/or
most preferably R² is selected from hydrogen, halogen like fluorine, or C₁₋₄alkyl like CH₃ or CF₃;
and/or
R³ is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein
the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;
and/or
the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine,

- benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline, especially is pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine; and/or
- 5 the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl or R³ is not alkyl; and/or
- 10 the alkenyl is C₂₋₁₀-alkenyl or C₂₋₈-alkenyl like ethylene, propylene, butylene, pentylene, hexylene, heptylene or octylene; preferably id C₁₋₆-alkenyl like ethylene, propylene, butylene, pentylene, or hexylene; more preferably from C₁₋₄-alkenyl, like ethylene, propylene, or butylene; and/or
- 15 the alkynyl is C₂₋₁₀-alkynyl or C₂₋₈-alkynyl like ethyne, propyne, butyne, pentyne, hexyne, heptyne, or octyne; preferably is C₂₋₆-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; and/or
- 20 the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, especially cyclopentyl or cyclohexyl;
- 25 and/or preferably R³ is not alkyl; and/or
- 30 most preferably R³ is selected from substituted or unsubstituted alkyl like propyl or butyl, from substituted or unsubstituted cycloalkyl like cyclopentyl or cyclohexyl, or from substituted or unsubstituted aryl, like phenyl, or from substituted or unsubstituted heterocyclyl, like pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine, or most preferably R³ is selected from substituted or unsubstituted cycloalkyl like cyclopentyl or cyclohexyl, or from substituted or
- 35 unsubstituted aryl, like phenyl, or from substituted or unsubstituted

heterocyclyl, like pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine;

and/or

5 R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocyclyl, wherein

the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;

10 and/or

the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, 15 indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline, especially is pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine;

25 and/or

the alkyl is C_{1-8} alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C_{1-6} alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C_{1-4} alkyl like methyl, ethyl, propyl or butyl;

30 and/or

the alkenyl is C_{2-10} -alkenyl or C_{2-8} -alkenyl like ethylene, propylene, butylene, pentylene, hexylene, heptylene or octylene; preferably is C_{1-}

₆-alkenyl like ethylene, propylene, butylene, pentylene, or hexylene;
more preferably from C₁₋₄-alkenyl, like ethylene, propylene, or butylene;
and/or

5 the alkynyl is C₂₋₁₀-alkynyl or C₂₋₈-alkynyl like ethyne, propyne, butyne, pentyne, hexyne, heptyne, or octyne; preferably is C₂₋₆-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne;
and/or

10 the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, especially cyclopentyl or cyclohexyl;
and/or

15 most preferably R⁴ is selected from hydrogen or from substituted or unsubstituted C₁₋₄alkyl like CH₃ or CH₂OH;

and/or

R⁵ is hydrogen, halogen, hydroxy, substituted or unsubstituted O-alkyl, substituted or unsubstituted alkyl, wherein

20 the alkyl is C₁₋₈alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C₁₋₆alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C₁₋₄alkyl like methyl, ethyl, propyl or butyl;
and/or

25 the O-alkyl is -O-C₁₋₈alkyl like -O-methyl, -O-ethyl, -O-propyl, -O-butyl, -O-pentyl, -O-hexyl, -O-heptyl, or -O-octyl; preferably is -O-C₁₋₆alkyl like -O-methyl, -O-ethyl, -O-propyl, -O-butyl, -O-pentyl, or -O-hexyl; more preferably is -O-C₁₋₄alkyl like -O-methyl, -O-ethyl, -O-propyl or -O-butyl;
and/or

30 halogen is any of fluorine, chlorine, iodine or bromine, preferably chlorine or fluorine;
and/or

most preferably R⁵ is selected from hydrogen or hydroxy;

and/or

R^6 , R^7 , R^8 and R^9 are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted alkyl-aryl, or R^6 and R^7 or R^8 and R^9 together with their respective connecting carbon or nitrogen atom may form a cycloalkylic or heterocyclic 4 to 7-membered ring, wherein

the aryl is phenyl, naphthyl or anthracene; preferably is naphthyl and phenyl; more preferably is phenyl;

and/or

the alkyl-aryl is C_{1-4} -alkyl-aryl; preferably is benzyl;

and/or

the heterocyclyl is a heterocyclic ring system of one or more saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; preferably is a heterocyclic ring system of one or two saturated or unsaturated rings of which at least one ring contains one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur in the ring; more preferably is selected from imidazole, oxadiazole, tetrazole, pyridine, pyrimidine, piperidine, indene, 2,3-dihydroindene, benzofuran, benzimidazole, indazole, benzothiazole, indoline, furan, triazole, isoxazole, pyrazole, thiophene, benzothiophene, pyrrole, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline, especially is pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine;

and/or

the alkyl is C_{1-8} alkyl like methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; preferably is C_{1-6} alkyl like methyl, ethyl, propyl, butyl, pentyl, or hexyl; more preferably is C_{1-4} alkyl like methyl, ethyl, propyl or butyl;

and/or

the alkenyl is C₂₋₁₀-alkenyl or C₂₋₈-alkenyl like ethylene, propylene, butylene, pentylene, hexylene, heptylene or octylene; preferably is C₁₋₆-alkenyl like ethylene, propylene, butylene, pentylene, or hexylene; more preferably from C₁₋₄-alkenyl, like ethylene, propylene, or butylene;
 5 and/or
 the alkynyl is C₂₋₁₀-alkynyl or C₂₋₈-alkynyl like ethyne, propyne, butyne, pentyne, hexyne, heptyne, or octyne; preferably is C₂₋₆-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne; more preferably is C₂₋₄-alkynyl like ethyne, propyne, butyne, pentyne, or hexyne;
 10 and/or
 the cycloalkyl is C₃₋₈cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; preferably is C₃₋₇cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; more preferably from C₃₋₆cycloalkyl like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, especially cyclopentyl or cyclohexyl;
 15 and/or
 when R⁶ and R⁷ or R⁸ and R⁹ together with their respective connecting carbon or nitrogen atom form a cycloalkylic or heterocyclic ring this ring is 5 or 6 membered, preferably R⁶ and R⁷ together with their respective
 20 connecting carbon atom form a saturated cycloalkylic ring of 5 or 6 members, more preferably R⁶ and R⁷ together with their respective connecting carbon atom form saturated, unsubstituted cyclohexyl;
 and/or
 most preferably R⁶, R⁷, R⁸ and R⁹ are independently from each other
 25 selected from hydrogen, from substituted or unsubstituted C₁₋₄alkyl like methyl, ethyl, propyl or butyl, from substituted or unsubstituted aryl like phenyl, from substituted or unsubstituted heterocyclyl like pyrrolidine, or from substituted or unsubstituted alkyl-aryl like benzyl, or R⁶ and R⁷
 30 together with their connecting carbon atom form a cycloalkylic 5 or 6-membered ring like cyclohexyl.

8. Compound according to any one of claims 1 to 7, wherein

V¹ is selected from nitrogen or carbon;

m is 1 or 2;

n is 0 or 1;

V¹ is selected from nitrogen or carbon;

R¹ is -COR⁶, -CONR⁸R⁹, -COCR⁶R⁷NR⁸R⁹, substituted or unsubstituted alkyl like C₁₋₄-alkyl or CH₃, C₂H₄OCH₃, C₃H₆OCH₃;

5 R² is selected from hydrogen, halogen like fluorine, or C₁₋₄alkyl like CH₃ or CF₃;

10 R³ is selected from substituted or unsubstituted alkyl like propyl or butyl, from substituted or unsubstituted cycloalkyl like cyclopentyl or cyclohexyl, or from substituted or unsubstituted aryl, like phenyl, or from substituted or unsubstituted heterocyclyl, like pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine;

R⁴ is selected from hydrogen or from substituted or unsubstituted C₁₋₄alkyl like CH₃ or CH₂OH;

R⁵ is selected from hydrogen or hydroxy; and

15 R⁶, R⁷, R⁸ and R⁹ are independently from each other selected from hydrogen, from substituted or unsubstituted C₁₋₄alkyl like methyl, ethyl, propyl or butyl, from substituted or unsubstituted aryl like phenyl, from substituted or unsubstituted heterocyclyl like pyrrolidine, or from substituted or unsubstituted alkyl-aryl like benzyl,

20 or R⁶ and R⁷ together with their connecting carbon atom may form a cycloalkylic 5 or 6-membered ring like unsubstituted cyclohexyl;

or

wherein

V¹ is selected from nitrogen or carbon;

m is 1 or 2;

25 n is 0 or 1;

R¹ is -COR⁶, -CONR⁸R⁹, -COCR⁶R⁷NR⁸R⁹, substituted or unsubstituted alkyl like C₁₋₄-alkyl or CH₃, C₂H₄OCH₃, C₃H₆OCH₃;

R^2 is selected from hydrogen, halogen like fluorine, or C_{1-4} alkyl like CH_3 or CF_3 ;

R^3 is selected from substituted or unsubstituted cycloalkyl like cyclopentyl or cyclohexyl, or from substituted or unsubstituted aryl, like phenyl, or from substituted or unsubstituted heterocyclyl, like pyridine, imidazole, indene, 2,3-dihydroindene, benzofuran, pyrimidine;

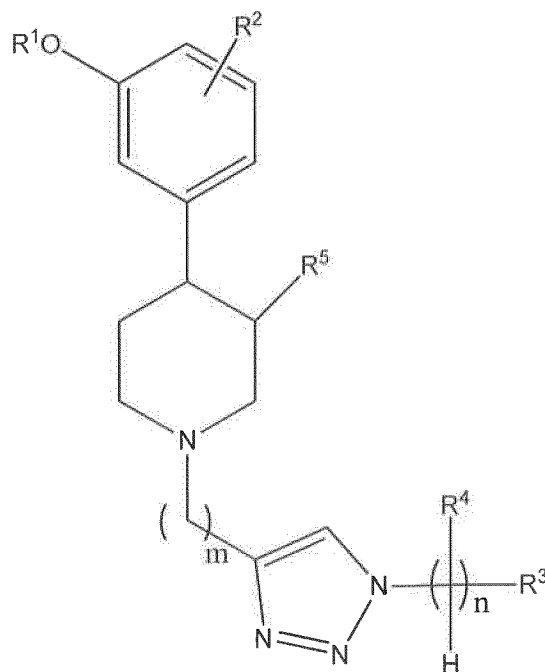
R^4 is selected from hydrogen or from substituted or unsubstituted C_{1-4} alkyl like CH_3 or CH_2OH ;

R^5 is selected from hydrogen or hydroxy; and

R^6 , R^7 , R^8 and R^9 are independently from each other selected from hydrogen, from substituted or unsubstituted C_{1-4} alkyl like methyl, ethyl, propyl or butyl, from substituted or unsubstituted aryl like phenyl, from substituted or unsubstituted heterocyclyl like pyrrolidine, or from substituted or unsubstituted alkyl-aryl like benzyl,

or R^6 and R^7 together with their connecting carbon atom may form a cycloalkylic 5 or 6-membered ring like unsubstituted cyclohexyl.

9. Compound according to claims 1 to 8, having a general formula V,



(V)

wherein

m is 1 or 2, preferably is 1;

n is 0 or 1;

5 R^1 is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, substituted or unsubstituted C_{1-4} alkyl, preferably is $-\text{COR}^6$, $-\text{CONR}^8\text{R}^9$, $-\text{COCR}^6\text{R}^7\text{NR}^8\text{R}^9$, $-\text{CH}_3$, $-\text{C}_2\text{H}_4\text{OCH}_3$, or $-\text{C}_3\text{H}_6\text{OCH}_3$;

R^2 is hydrogen, halogen, substituted or unsubstituted C_{1-4} alkyl, preferably is hydrogen;

10 R^3 is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl, preferably is substituted or unsubstituted phenyl or substituted or unsubstituted pyridine;

R^4 is hydrogen, substituted or unsubstituted C_{1-4} alkyl, preferably is hydrogen or $-\text{CH}_2\text{OH}$;

15 R^5 is hydrogen, halogen or hydroxyl, preferably is hydrogen;

R^6 , R^7 , R^8 and R^9 are independent from each other and selected from the group formed by hydrogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted benzyl, or R^6 and R^7 together with their connecting atom might form
20 an unsubstituted 5- or 6-membered saturated cycloalkylic ring; preferably R^6 , R^7 , R^8 and R^9 are independent from each other selected from hydrogen, $-\text{CH}_3$, $-\text{CHCOOH}$, $-\text{C}_2\text{H}_5$, $-\text{C}_3\text{H}_7$, $-\text{CH}(\text{NH}_2)\text{C}_3\text{H}_7$, $-\text{CH}(\text{COOH})\text{C}_3\text{H}_7$, substituted phenyl, unsubstituted pyrrolidine, unsubstituted benzyl, or R^6 and R^7 together with their connecting carbon atom form an unsubstituted cyclohexyl;

25 optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding salt thereof, or a corresponding solvate thereof.

10. Compound according to claims 1 to 9, wherein

any aryl which is substituted is substituted by one or more of halogen, -OH, -NH₂, -SH, -C(O)OH, -OC₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen, -CN, or -C₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen,

any cycloalkyl or heterocyclyl which is substituted is substituted by one or more of halogen, -OH, -NH₂, -SH, =O, -C(O)OH, -OC₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen, -CN, or -C₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen, and

any alkyl, alkenyl, alkynyl or O-alkyl which is substituted is substituted by one or more of halogen, -OH, -NH₂, -SH, -C(O)OH, or -OC₁₋₄alkyl being unsubstituted or substituted by one or more of OH or halogen.

11. Compound according to any one of claims 1 to 10, characterized in that the compound is selected from

- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl ethylcarbamate,
- 1-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(3-methoxyphenyl)piperidine,
- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
- 4-((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonylamino)benzoic acid,
- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl isobutyrate,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-methylbutanoate,
- 4-(3-methoxyphenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl dimethylcarbamate,
- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
- 4-(3-(2-methoxyethoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 4-(3-(3-methoxypropoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,

- 2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine,
- (S)-3-methyl-2-((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonylamino)butanoic acid,
- 2-((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonylamino)acetic acid,
- 3-fluoro-2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine,
- 5-fluoro-2-((4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)pyridine,
- 2-(4-((4-(3-methoxyphenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-2-phenylethanol,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl pyrrolidine-2-carboxylate,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-phenylpropanoate, and
- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 1-aminocyclohexanecarboxylate;

preferably selected from

- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl ethylcarbamate,
- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
- 4-((3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenylpyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenoxy)carbonylamino)benzoic acid,
- 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl isobutyrate,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-methylbutanoate,
- 4-(3-methoxyphenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl dimethylcarbamate,
- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate,
- 4-(3-(2-methoxyethoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,
- 4-(3-(3-methoxypropoxy)phenyl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidine,

- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl pyrrolidine-2-carboxylate,
- (S)-3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 2-amino-3-phenylpropanoate, and
- 5 • 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl 1-aminocyclohexanecarboxylate;

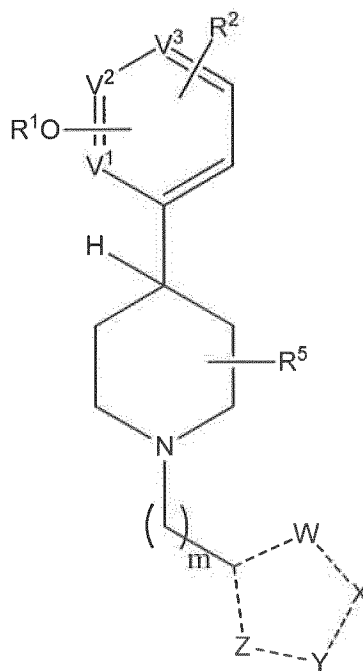
most preferably

- 3-(1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate, and
- 10 • 3-(1-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)phenyl acetate;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio,

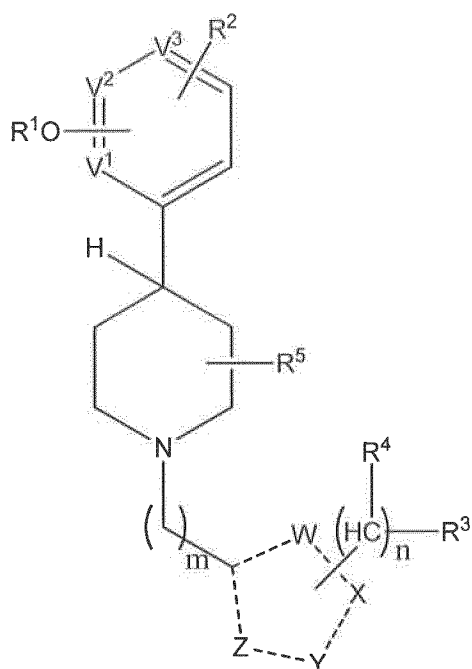
15 or a corresponding salt thereof, or a corresponding solvate thereof.

12. Process for the production of a compound according to claim 1 according to formula I,



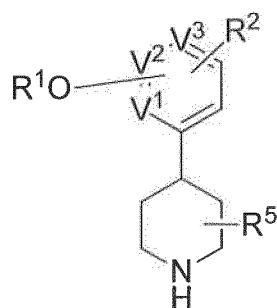
wherein R¹, R², R⁵, V¹, V², V³, W, X, Y, Z and m are as defined in claim 1 or

20 according to formula Ia



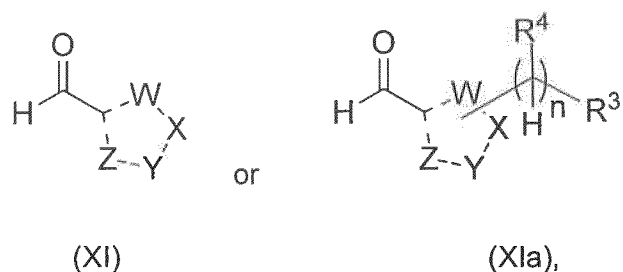
wherein R^1 , R^2 , R^3 , R^4 , R^5 , V^1 , V^2 , V^3 , W , X , Y , Z , n and m are as defined in claim 1

wherein a compound of formula X or its suitable salt like the hydrochloride



(X),

wherein R^1 , R^2 , R^5 , V^1 , V^2 , and V^3 are as defined in claim 1, is reacted with a compound according to formula XI (for a compound according to formula I) or according to formula XIa (for a compound according to formula Ia) under the conditions of Step 1

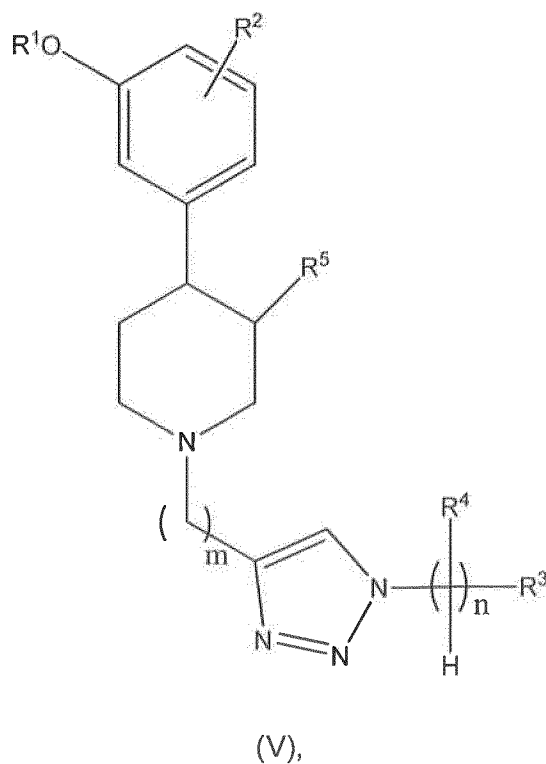


wherein R^3 , R^4 , W, X, Y, Z and n are as defined in claim 1, leading to a compound according to formula (I) or formula (Ia) respectively,

5 wherein the reductive amination reaction of the compounds of formula (X) and (XI or XIa) of Step 1 is carried out with a reductive reagent in an aprotic solvent in the presence of an organic base,

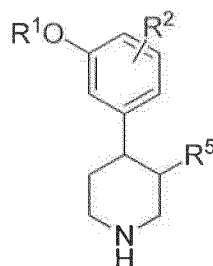
preferably wherein the reductive reagent is sodium triacetoxyborohydride, the aprotic solvent is dichloroethane and/or the organic base is diisopropylethylamine.

13. Process for the production of a compound according to claim 10 according to formula V



wherein R^1 , R^2 , R^3 , R^4 , R^5 , n and m are as defined in claim 10,

wherein a compound of formula VI or its suitable salt like the hydrochloride



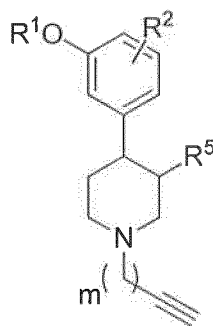
(VI),

5 wherein R^1 , R^2 , and R^5 are as defined in claim 10, is reacted with a compound according to formula VIII under the conditions of Step 2



(VIII),

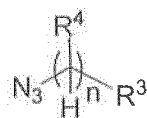
10 wherein m is as defined in claim 10, leading to a compound according to formula VII,



(VII)

wherein R^1 , R^2 , R^5 and m are as defined in claim 10,

15 followed by reacting said compound according to formula VII with a compound according to formula IX under the conditions of Step 3



(IX)

wherein R^3 , R^4 and n are as defined in claim 10, under the conditions of Step 3, leading to a compound according to formula (V),

5 wherein X is a leaving group like a halogen or sulphate like chlorine,

wherein the reaction of Step 2 of said compounds of general formula (VI) with said compounds of formula (VIII) is carried out in the presence of a base in an aprotic solvent, preferably wherein the base is Et_3N , the aprotic solvent is tetrahydrofuran (THF) and/or the reaction is preferably carried out at a
10 temperature range of 25-75 °C;

wherein the reaction of Step 3 of said compounds of general formula (VII) with said compounds of formula (IX) is carried out in the presence of a copper salt and sodium ascorbate in a mixture of protic organic solvent and water, preferably wherein the copper salt is $CuSO_4 \cdot 5H_2O$ and the mixture of protic
15 organic solvent and water is a mixture of $t-BuOH:H_2O$ 1:1 and/or the reaction is preferably carried out at room temperature.

14. A pharmaceutical composition which comprises a compound as defined in any of claims 1 to 11 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant or vehicle.

20 15. A compound as defined in any of claims 1 to 11 for use as a medicament.

16. A compound as defined in any of claims 1 to 11 for use as a medicament for the treatment of pain, especially medium to severe pain, visceral pain, chronic pain, cancer pain, migraine, inflammatory pain, acute pain or neuropathic pain, allodynia or hyperalgesia.

25

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/078811

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D401/06 A61K31/4439 A61P25/04 A61P25/06
ADD.

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

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 practicable, search terms used)

EPO-Internal, WPI 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.
X	EP 1 072 596 A2 (PFIZER [US]; PFIZER LTD [GB]) 31 January 2001 (2001-01-31)	1-16
Y	claim 1 example 44 paragraph [0003]	1-16
Y	----- WO 2011/137331 A2 (KINENTIA BIOSCIENCES LLC [US]; FAIRFAX DAVID J [US]) 3 November 2011 (2011-11-03) claim 1 example 23	1-16
X	----- EP 1 072 592 A2 (PFIZER [US]; PFIZER LTD [GB]) 31 January 2001 (2001-01-31)	1-16
Y	claim 1 ----- -/-	1-16



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

4 February 2015

Date of mailing of the international search report

12/02/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Gutke, Hans-Jürgen

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/078811

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	INEKE VAN WIJNGAARDEN ET AL: "2-Phenylpyrroles as conformationally restricted benzamide analogs. A new class of potential antipsychotics. 2", JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 10, 1 October 1988 (1988-10-01), pages 1934-1940, XP055103009, ISSN: 0022-2623, DOI: 10.1021/jm00118a011 table 1 -----	1,7,8, 10,14
X	GB 2 083 476 A (WYETH JOHN & BROTHER LTD) 24 March 1982 (1982-03-24) claim 1 example 10 -----	1,7,8, 10,14
X	EP 0 241 053 A1 (DUPHAR INT RES [NL]) 14 October 1987 (1987-10-14) claim 1 page 13; compounds 33-37 -----	1,7,8, 10,14
X	EP 0 634 398 A1 (MERCK PATENT GMBH [DE]) 18 January 1995 (1995-01-18) claim 1 page 9, line 13 -----	1,7,8, 10,14
X	DATABASE PUBCHEM [Online] NCBI; 29 March 2011 (2011-03-29), XP002720596, Database accession no. CID50963011 the whole document -----	1,2,8
X	DATABASE PUBCHEM [Online] NCBI; 17 August 2007 (2007-08-17), XP002720597, Database accession no. CID16667981 the whole document -----	1,2,8
X	DATABASE PUBCHEM [Online] NCBI; 29 March 2011 (2011-03-29), XP002720598, Database accession no. CID50984530 the whole document -----	1,2,8
X	DATABASE PUBCHEM [Online] NCBI; 29 March 2011 (2011-03-29), XP002720599, Database accession no. CID50977733 the whole document -----	1,2,8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/078811

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 1072596	A2	31-01-2001	BR	0002505 A		02-01-2001
			CA	2309474 A1		28-11-2000
			EP	1072596 A2		31-01-2001
			JP	3616555 B2		02-02-2005
			JP	2001019673 A		23-01-2001
			US	6479516 B1		12-11-2002

WO 2011137331	A2	03-11-2011	US	2013045165 A1		21-02-2013
			WO	2011137331 A2		03-11-2011

EP 1072592	A2	31-01-2001	BR	0002515 A		02-01-2001
			CA	2309434 A1		28-11-2000
			EP	1072592 A2		31-01-2001
			JP	2000344746 A		12-12-2000
			JP	2004107324 A		08-04-2004
			US	2002099216 A1		25-07-2002
			US	2005085456 A1		21-04-2005

GB 2083476	A	24-03-1982	NONE			

EP 0241053	A1	14-10-1987	AU	585131 B2		08-06-1989
			AU	6924787 A		03-09-1987
			CA	1279645 C		29-01-1991
			DE	3782525 D1		17-12-1992
			DE	3782525 T2		27-05-1993
			DK	93087 A		28-08-1987
			EP	0241053 A1		14-10-1987
			ES	2052545 T3		16-07-1994
			GR	3006689 T3		30-06-1993
			IE	61724 B1		30-11-1994
			IL	81669 A		29-11-1990
			JP	H0798800 B2		25-10-1995
			JP	S62205058 A		09-09-1987
			NZ	219380 A		26-06-1990
			PH	22783 A		12-12-1988
			US	4772604 A		20-09-1988
			US	4874770 A		17-10-1989
			ZA	8701335 A		30-09-1987

EP 0634398	A1	18-01-1995	AU	6487294 A		05-01-1995
			CA	2126719 A1		27-12-1994
			CN	1102649 A		17-05-1995
			CZ	9401559 A3		18-10-1995
			DE	4321366 A1		05-01-1995
			EP	0634398 A1		18-01-1995
			JP	H0725851 A		27-01-1995
			NO	942411 A		27-12-1994
			PL	303978 A1		09-01-1995
			RU	94022271 A		20-04-1996
			SK	77494 A3		11-07-1995
			TW	293818 B		21-12-1996
			US	5495022 A		27-02-1996
			ZA	9404573 A		14-02-1995
