(12) **Oversettelse av europeisk patentskrift**

(11) **NO/EP 2740476 B1**

NORGE

(19) NO

(51) Int Cl.

A61K 31/438 (2006.01)
A61P 25/04 (2006.01)
C07D 471/10 (2006.01)

Patentstyret

(21)	Oversettelse publisert	2019.02.18
(80)	Dato for Den Europeiske Patentmyndighets publisering av det meddelte patentet	2018.12.05
(86)	Europeisk søknadsnr	14000496.1
(86)	Europeisk innleveringsdag	2011.07.27
(87)	Den europeiske søknadens Publiseringsdato	2014.06.11
(30)	Prioritet	2010.07.28, EP, 10007822
(84)	Utpekte stater	AL ; AT ; BE ; BG ; CH ; CY ; CZ ; DE ; DK ; EE ; ES ; FI ; FR ; GB ; GR ; HR ; HU ; IE ; IS ; IT ; LI ; LT ; LU ; LV ; MC ; MK ; MT ; NL ; NO ; PL ; PT ; RO ; RS ; SE ; SI ; SK ; SM ; TR
(62)	Avdelt fra	EP2598503, filing date 2011.07.27
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(54) Benevnelse **Cis-tetrahydro-spiro(cyclohexan-1,1'-pyrido[3,4-b]indol)-4-amine derivatives**

(56) Anførte publikasjoner WO-A1-2007/124903, WO-A1-2006/108565, WO-A1-2009/118173

Vedlagt foreligger en oversettelse av patentkravene til norsk. I hht patentloven § 66i gjelder patentvernet i Norge bare så langt som det er samsvar mellom oversettelsen og teksten på behandlingsspråket. I saker om gyldighet av patentet skal kun teksten på behandlingsspråket legges til grunn for avgjørelsen. Patentdokument utgitt av EPO er tilgjengelig via Espacenet (http://worldwide.espacenet.com), eller via søkemotoren på vår hjemmeside her: https://search.patentstyret.no/

The invention uses compounds which act on the nociceptin/ORL-1 receptor system as well as on the μ-opioid receptor system and which are distinguished in particular by selective efficacy in the treatment of chronic pain (*inter alia* inflammatory pain, visceral pain, tumour pain, preferably neuropathic pain), without at the same time developing pronounced efficacy in the case of acute, nociceptive pain. The compounds used according to the invention are cis-tetrahydro-spiro(cyclohexane-1,1'-pyrido[3,4-b]indole)-4-amine derivates.

Chronic pain can be divided into two major groups. Pathophysiological nociceptor pain is triggered following tissue traumas by the excitation of intact nociceptors. It includes in particular chronic inflammatory pain. On the other hand, pain caused by mechanical, metabolic or inflammatory damage to nerves themselves is referred to as neuropathic pain. The treatment of chronic pain poses a major medical challenge, since although some of the medicaments on the market are highly effective in the case of acute pain, in many cases they do not result in satisfactory treatment for pain in the case of chronic and, in particular, neuropathic pain.

Inflammatory events are among the most important mechanisms of pain formation. Typical inflammatory pain is triggered by the release of bradykinin, histamine and prostaglandins with acidification of the tissue and the pressure of the exsudate on the nociceptors. As a consequence there frequently occur in the central nervous system sensitisation phenomena which manifest themselves in an increase in spontaneous neural activity and in stronger stimulus responses of central neurons (Coderre et al., Pain 1993, 52, 259-285). These changes in the response behaviour of central neurons can contribute to spontaneous pain and hyperalgesia (increased pain sensitivity to a noxious stimulus), which are typical of inflamed tissue (Yaksh et al., PNAS 1999, 96, 7680-7686).

Non-steroidal antiphlogistics (NSAIDs), which also have an anti-inflammatory component in addition to the analgesic action, have proved to be particularly successful in the treatment of inflammatory pain. (Dickensen, A., International Congress and Symposium Series - Royal Society of Medicine (2000), 246, 47-54). Their use in the long term therapy of chronic pain is limited, however, by sometimes considerable undesirable effects, such as gastroenteral ulcers or toxic kidney damage. In the case of severe to very severe inflammatory pain (for example in the context of chronic pancreatitis), NSAIDs possibly reduce the pain only slightly, but lead to high risk due to the increased danger of bleeding. The next step is generally treatment with μ-opioids, with dependency on narcotics being widespread among the persons concerned (Vercauteren et

al., Acta Anaesthesiologica Belgica 1994, 45, 99- 105). There is therefore an urgent need for compounds which are highly effective in the case of inflammatory pain and have a reduced dependency potential.

Neuropathic pain occurs when peripheral nerves are damaged in a mechanical, metabolic or inflammatory manner. The pain profiles occurring here are characterised predominantly by the appearance of spontaneous pain, hyperalgesia and allodynia (pain is already triggered by non-toxic stimuli) (cf. Baron, Clin. J. Pain 2000; 16 (2 Suppl), 12-20). The causes and characteristics, and hence also the treatment needs, of neuropathic pain are many and varied. It occurs as a result of damage to or disease of the brain, spinal cord or peripheral nerves. Causes may be operations (e.g. phantom pain following amputation), spinal cord injuries, stroke, multiple sclerosis, alcohol or medicament abuse or other toxic substances, cancer, and also metabolic diseases such as diabetes, gout, renal insufficiency or cirrhosis of the liver, as well as infectious diseases (*inter alia* Herpes zoster, Pfeiffer's glandular fever, erlichiosis, typhus, diptheria, HIV, lues or borreliosis). The pain experience has very different signs and symptoms (e.g. tingling, burning, shooting electrifying or radiating pain), which can change over time in number and intensity.

The basic pharmacological therapy of neuropathic pain includes tricyclic antidepressants and anticonvulsives, which are used as monotherapy or also in combination with opioids. These medicaments generally bring only a certain degree of pain relief, while freedom from pain is often not achieved. The side effects which frequently occur often prevent dosage increases of the medicaments in order to achieve adequate pain alleviation. In fact the satisfactory treatment of neuropathic pain often requires a higher dosage of a μ-opioid than does the treatment of acute pain, as a result of which the side effects gain even more importance. This means that today neuropathic pain is difficult to treat. It is only partially alleviated even by high doses of stage 3 opioids (Saudi Pharm. J. 2002, 10 (3), 73-85).

Opioids which are used in the treatment of neuropathic pain are usually also effective against acute pain at the same time. So far it has not been possible to separate the treatment of neuropathic pain on the one hand and acute pain on the other. Depending on the dose of the opioids, therefore, any pain sensation of the patient is suppressed, which can be really disadvantageous. Acute pain fulfills a protective function for the body, which is lost if the sensation of acute pain is impaired or suppressed. There is therefore a need to maintain the general sensation of pain while at the same time controlling neuropathic pain.

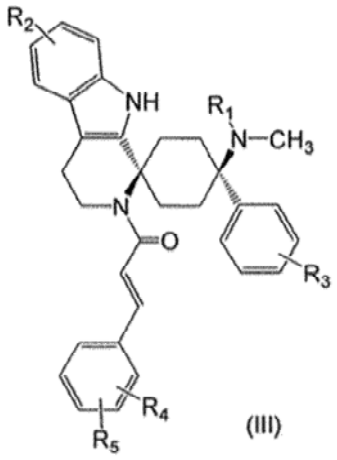
Spirocyclic cyclohexane derivatives which act on the nociceptin/ORL-1 and μ-opioid receptor system are known in prior art. These compounds are distinguished by, among other things, extraordinarily great structural variability and are suitable for, among other things, the treatment of inflammatory and neuropathic pain. In this connection reference may be made, for example, to the whole of WO 2004/043967, WO2005/063769, WO2005/066183 and WO2006/108565.

There is a need for medicaments which are effective in the treatment of chronic, in particular neuropathic pain, and which at the same time affect the perception of acute pain to the least possible extent. Where possible these medicaments should contain such a small dose of active ingredient as to ensure satisfactory pain therapy without intolerable side effects occurring.

The object underlying the invention is to provide novel compounds which are suitable as medicaments and have advantages over the prior art.

This object is achieved by the subject matter of the patent claims.

The invention relates to compounds of the general formula (III)



(III)

in which

R_1 is -H or CH_3;

R_2 is -H or -halogen;

R_3 is -H or -halogen;

R_4 is -H, -halogen or -OC_{1-3}-alkyl; and

R_5 is -H, -halogen or -OC_{1-3}-alkyl;

wherein the compound is present as hydrochloride, citrate or hemi-citrate salt.

It has been found, surprisingly, that the compounds according to the general formula (III) act on the nociceptin/ORL-1 and the μ-opioid receptor system, and are particularly effective in the treatment of chronic pain, especially neuropathic pain, without at the same time suppressing the perception of acute pain. Moreover, surprisingly, these compounds exhibit - if at all - only very slight opioid-typical side effects in the analgesically effective dosage range.

The compounds according to the general formula (III) exhibit a very high analgesic efficacy in the treatment of chronic pain, in particular neuropathic pain, preferably resulting from poly- or mononeuropathic diseases.

It has been found, surprisingly, that the compounds have no effect on normal nociception in healthy animals or in the healthy tissue of mononeuropathic animals at doses which lead to virtually complete elimination of neuropathic pain in mono- or poly-neuropathy models. This means that these compounds eliminate the pathological condition (allodynia or hyperalgesia), but at the same time impair the normal sensation of pain only slightly - if at all. The antinociceptive action of the compounds in acute pain is therefore negligible.

The compounds according to the general formula (III) thus permit selective efficacy against chronic pain, preferably against neuropathic pain, more preferably against mononeuropathic/neuralgic or polyneuropathic pain, even more preferably against pain in the case of postherpetic neuralgia or in the case of diabetic polyneuropathy, preferably with negligible antinociceptive efficacy in the case of acute pain. This unusual property of the compounds according to the invention is of fundamental importance for pain therapy as a whole.

The compounds according to the general formula (III) represent a selection of the compounds disclosed in WO2004/043967, WO2005/066183 and WO2006/108565. It has been found, surprisingly, that the spiroamines according to the invention, which have the cis configuration (cis-tetrahydro-spiro(cyclohexane-1,1'-pyrido[3,4-b]indole)-4-amine derivatives) on the cyclohexane ring in respect of the two nitrogens, have advantages over the other heterocycles.

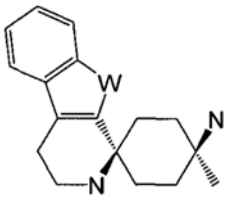
Thus the cis-spiroamides according to the invention, in contrast to the other compounds according to WO2004/ 043967, WO2005/066183 and WO2006/108565, in the animal model exhibit an outstanding action against chronic, preferably neuropathic, pain, more preferably pain in the case of diabetic polyneuropathy, without demonstrating a significant action against acute pain in the therapeutic dose required therefor. Since numerous side effects of conventional

analgesics are associated with the mechanism of action against acute pain, the spirocyclic cis-substituted cyclohexane derivatives according to the invention are distinguished by a particularly advantageous side effect profile, particularly with regard to opioid-typical side effects.

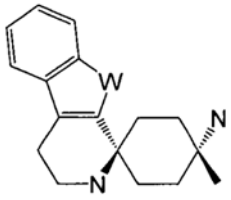
The compounds according to the general formula (III) are preferably achiral; the basic structure of the general formula (III) does not contain a chirality element (centre, axis or plane).

The compounds according to the general formula (III) in relation to the spiro ring system are isomers in which the substitution pattern on the spiro-cyclohexane ring system (not on the indole) can be denoted cis/trans, Z/E or syn/anti. “Cis-trans isomers” are a sub-group of the stereoisomers (configuration isomers).

In the compounds according to the general formula (III) the two nitrogen atoms of the spiroamine are in each case in the syn or cis or Z configuration relative to one another:



cis-spiroamine

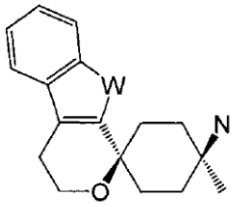


trans-spiroamine

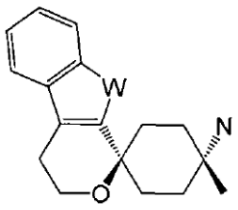
In a preferred embodiment of the invention the excess of the cis-isomer so designated is at least 50%de, more preferably at least 75%de, even more preferably at least 90%de, most preferably at least 95%de and in particular at least 99%de.

Suitable methods for separating the isomers (diastereomers) are known to the person skilled in the art. Column chromatography, preparative HPLC and crystallisation processes may be mentioned as examples. Targeted synthesis processes, in which one isomer is formed in excess, are also know in principle to those skilled in the art.

The advantages of the cis isomer are further particularly surprising in that, in the case of the structurally related spiroethers, it is usually not the cis isomer but the trans isomer which has advantageous properties from the pharmacological point of view (but which are occasionally of a different nature than the advantages of the cis spiroamines according to the invention).



cis-spiroether

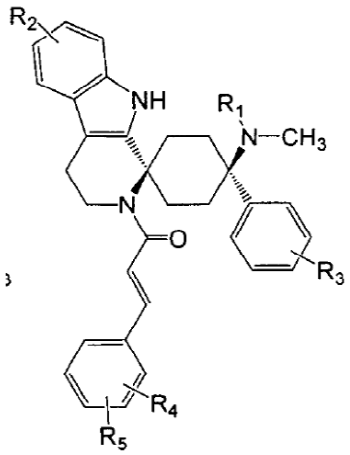


trans-spiroether

For the purposes of the description, “halogen” means preferably -F, -Cl, -Br or -I, more preferably -F or -Cl, in particular -F.

For the purposes of the description “C_{1-3}-alkyl”, in each case independently, is linear or branched, saturated or mono- or polyunsaturated. Thus “C_{1-3}-alkyl” includes acyclic saturated or unsaturated hydrocarbon residues which can be branched or straight-chain, i.e. C_{1-3}-alkanyls, C_{1-3}-alkenyls and C_{1-3}-alkinyls.

Preferred are compounds of the general formula (III):



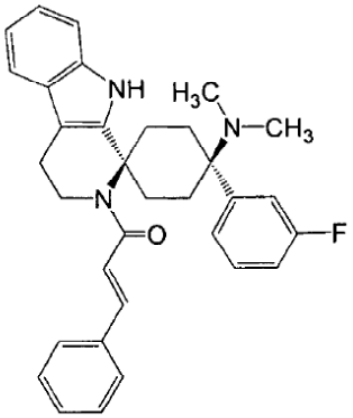
(III)

wherein the compound is present as hydrochloride, citrate or hemi-citrate salt.

R_2 -H and/or R_3 -F is preferred.

R_4 and R_5 are preferred, either both -H or both -OCH_3.

In another particularly preferred embodiment the invention relates to the compound of the general formula (VI)



(VI)

wherein the compound is present as hydrochloride, citrate or hemi-citrate salt.

The free base of the compound of the general formula (VI) can systematically be designated (E)-2',3',4',9'-tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer) or also as (E)-1-((1s,4s)-4-(dimethylamino)-4-(3-fluorophenyl)-3',4'-dihydrospiro[cyclohexane-1,1'-pyrido-[3,4-b]indole]-2'(9'H)-yl)-3-phenylprop-2-en-1-one. This compound is present in the form of hydrochloride, citrate or hemi-citrate.

According to the invention the compounds are selected in particular from the group consisting of

(E)-2',3‘4',9'-tetrahydro-N,N-dimethyl-4-phenyl-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer) or	AMD-1^{cis}

(E)-1-((1s,4s)-4-(dimethylamino)-4-phenyl-3',4'-dihydrospiro[cyclohexane-1,1'-pyrido[3,4-b]indole]-2'(9'H)-yl)-3-phenylprop-2-en-1-one	

(E)-2',3',4',9'-tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(2-phenylvinyl)-carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer) or (E)-1-((1s,4s)-4-(dimethylamino)-4-(3-fluorophenyl)-3',4'-dihydro-spiro[cyclohexane-1,1'-pyrido[3,4-b]indole]-2'(9'H)-yl)-3-phenylprop-2-en-1-one	AMD-5^{cis} AMD-6^{cis}

(E)-2',3',4',9'-tetrahydro-N,N-dimethyl-6'-fluoro-4-(3-fluorophenyl)-2'-(2-phenyl-vinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-dia-	AMD-8^{cis}

stereomer) or (E)-1-((1s,4s)-4-(dimethylamino)-6'-fluoro-4-(3-fluorophenyl)-3',4'-dihydrospiro[cyclohexane-1,1'-pyrido[3,4-b]indole]-2'(9'H)-yl)-3-phenylprop-2-en-1-one	

(E)-2',3'4',9'-tetrahydro-N,N-dimethyl-6'-fluoro-4-phenyl-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer) or (E)-1-((1s,4s)-4-(dimethylamino)-6'-fluoro-4-phenyl-3'4'-dihydrospiro-[cyclohexane-1,1'-pyrido[3,4-b]indole]-2'(9'H)-yl)-3-phenylprop-2-en-1-one	AMD-10^{cis}

(E)-2',3',4',9'-tetrahydro-N,N-dimethyl-4-(4-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer) or (E)-1-((1s,4s)-4-(dimethylamino)-4-(4-fluorophenyl)-3',4'-dihydrospiro-[cyclohexane-1,1'-pyrido[3,4-b]indole]-2'(9'H)-yl)-3-phenylprop-2-en-1-one	AMD-12^{cis}

in each case in the form of hydrochloride, citrate or hemi-citrate salt.

In a preferred embodiment of the invention the compounds according to the general formula (III) are used twice daily, once daily or less frequently, particularly preferably no more than once daily.

In a further embodiment, compounds according to the general formula (III) are used in the treatment of chronic pain. Chronic pain is preferably selected from the group comprising inflammatory pain, visceral pain, tumour pain and neuropathic pain. Neuropathic pain may be of mononeuropathic/neuralgic or polyneuropathic origin.

In a further preferred embodiment the compounds according to the general formula (III) are used in the treatment of pain in the case of diabetic polyneuropathy.

In a further preferred embodiment the compounds according to the general formula (III) are used in the treatment of pain resulting from postherpetic neuralgia.

The compounds according to the general formula (III) are suitable for use in the treatment of neuropathic pain, preferably of mononeuropathic/neuralgic or polyneuropathic pain. The pain is preferably peripheral polyneuropathic pain or central polyneuropathic pain.

The polyneuropathy or polyneuropathic pain is preferably acute (up to four weeks), subacute (four to eight weeks) or chronic (more than eight weeks).

In the polyneuropathy the motor, sensory, autonomic, sensorimotor or central nervous system is preferably affected. The symptoms are preferably distributed symmetrically or asymmetrically. The pain can be mild, moderate, medium-severe, severe or very severe. The neuropathic pain scale (NPS) can be used as a measure (cf. B.S. Galer et al., Neurology 1997, 48, 332-8).

Examples of causes of peripheral neuropathic pain are diabetic polyneuropathy, postherpetic neuralgia, radioculopathy, post-traumatic neuralgia, polyneuropathy induced by chemical substances, e.g. by chemotherapy, phantom pain of the limbs, complex regional syndrome, HIV-induced sensory polyneuropathy and alcoholic polyneuropathy. Examples of causes of central neuropathic pain are compressive myelopathy resulting from narrowed canal stenosis, post-traumatic spinal pain, pain due to stroke, post-ischemic myelopathy, radiation-induced myelopathy, myelopathy induced by multiple sclerosis and HIV-induced myelopathy.

In one preferred embodiment the neuropathy causing the neuropathic pain is associated with a disease selected from the group comprising diabetes mellitus, vasculitis, uraemia, hypothyroidism, alcohol abuse, postherpetic neuralgia, idiopathic neuropathy, chronic inflammatory demylinating neuropathy, multifocal motor neuropathy, hereditary polyneuropathy, Guillain-Barré syndrome, intoxication [e.g. caused by alcohol, heavy metals {in particular Pb, Hg, As}, hydrocarbons, resulting from chemotherapy with cytostatics], porphyria, infectious diseases, cancerous diseases [e.g. myeloma, amyloid, leukaemia, lymphoma], pernicious anaemia, vitamin E deficiency, Refsum's disease, Bassen-Kornzweig syndrome, Fabry's disease, vasculitis and amyloidosis. Diabetic polyneuropathy and postherpetic neuralgia are particularly preferred. If it is an infectious disease, it is preferably selected from the group comprising mononucleosis, ehrlichiosis, typhus, diphtheria, leprosy, HIV, lues and borreliosis.

The polyneuropathic pain is preferably pain caused by a polyneuropathy within the meaning of ICD-10 (International Statistical Classification of Diseases and Related Health Problems, WHO Edition, preferably 2008 issue).

A further subject matter of the invention relates to the compounds according to the invention for use in the treatment of anxiety states, stress and stress-associated syndromes, depression, epilepsy, Alzheimer's disease, senile dementia, general cognitive dysfunctions, learning and

memory disorders (as a nootropic), withdrawal symptoms, alcohol and/or drug and/or medicament abuse and/or dependency, sexual dysfunctions, cardiovascular diseases, hypotension, hypertension, tinnitus, pruritus, migraine, hardness of hearing, insufficient intestinal motility, impaired food intake, anorexia, obesity, locomotor disorders, diarrhoea, cachhexia, urinary incontinence, or as a muscle relaxant, anticonvulsive or anaesthetic or for coadministration in the case of treatment with an opioid analgesic or with an anaesthetic, for diuresis or antinatriuresis, anxiolysis, for the modulation of locomotor activity, for the modulation of neurotransmitter excretion and treatment of neurodegenerative diseases associated therewith, for the treatment of withdrawal symptoms and/or to reduce the addictive potential of opioids.

A further subject matter of the invention relates to the compounds according to the invention for use, in particular in one of the aforementioned indications, in the treatment of a non-human mammal or a human requiring treatment for chronic pain, preferably neuropathic pain, more preferably pain in diabetic polyneuropathy or postherpetic neuralgia, by administering an individually therapeutic necessary daily dose of a compound according to the invention, or of a form of administration according to the invention, with preferably at the same time no significant suppression of the sensation of acute nociceptor pain and/or no significant opioid-typical side affects occurring, in particular substantially no respiratory depression and/or constipation and/or urinary retention and/or nausea and/or vomiting and/or hypotonia and/or bradycardia and/or addiction and/or dependency and/or euphoria and/or depression and/or sedation and/or dizziness.

A further subject matter of the invention relates to the compounds according to the invention for use, in particular in one of the afore-mentioned indications, in the treatment of a non-human mammal or a human requiring treatment for chronic pain, preferably neuropathic pain, more preferably pain in diabetic polyneuropathy or postherpetic neuralgia, by administering a daily dose X of a compound according to the invention, or of a form of administration according to the invention, with preferably no significant simultaneous suppression of the sensation of acute nociceptor pain and/or no significant opioid-typical side affects occurring, in particular substantially no respiratory depression and/or constipation and/or urinary retention and/or nausea and/or vomiting and/or hypotonia and/or bradycardia and/or addiction and/or dependency and/or euphoria and/or depression and/or sedation and/or dizziness; with the daily dose being selected from the group comprising 0.001, 0.002, 0.003, 0.004, 0.005, 0.006, 0.007, 0.008, 0.009, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mg.

A further subject matter of the invention relates to the compounds according to the invention of the general formula (III) having affinity for the μ-opioid receptor and the ORL-1 receptor for use

- in the treatment of neuropathic pain, preferably in the rat, more preferably as mononeuropathic pain in the model according to Chung, which are significantly effective and are characterised by a half-maximum effective dose ED_{50}^{n}, and
- which are substantially not significantly effective in the treatment of acute pain, preferably in the rat, more preferably in the *tail*- flick test, in a dose which is higher than ED_{50}^{n} by a factor of 5.

Thus, the compounds according to the general formula (III) when administered in this half-maximum dose ED_{50}^{n}, which is defined in relation to the efficacy of the compound against neuropathic pain, and even in a dose which is higher than ED_{50}^{n} by a factor of 5, exhibit - if at all - at most a negligible antinociceptive action in the case of acute pain, preferably in the rat, more preferably in the tail-flick test.

In a preferred embodiment the neuropathic pain is mononeuropathic or neuralgic pain, preferably pain resulting from postherpetic neuralgia. In another preferred embodiment the pain is polyneuropathic pain, preferably pain in the case of diabetic polyneuropathy.

Preferably the compounds according to the general formula (III) are used in a dose substantially not significantly effective in the treatment of acute or nociceptive pain which is higher than the half-maximum effective dose ED_{50}^{n} by a factor of 10, 20, 30, 40 or 50, more preferably by a factor of 75, 100, 125, 150 or 175, even more preferably by a factor of 200, 300, 400 or 500, most preferably by a factor of 600, 700, 800 or 900, and in particular by a factor of 1000.

The half-maximum effective dose ED_{50}^{n} is known to the person skilled in the art. It is preferably defined as the dose at which, with regard to the treatment of neuropathic pain, 50% of the maximum therapeutic action is achieved. Accordingly a half-maximum effective dose ED_{50}^{a} can be defined as the dose at which, with regard to the treatment of acute pain, 50% of the maximum therapeutic action is achieved. The compounds according to the invention are, however, defined by ED_{50}^{n}, not by ED_{50}^{a}.

Suitable methods for studying the efficacy of an active ingredient in the treatment of neuropathic pain and for determining the half-maximum effective dose ED_{50}^{n} in the treatment of neuropathic

pain are known to the person skilled in the art. The same applies to studying the efficacy of an active ingredient against acute pain.

For example, the determination can be carried out in an animal model (e.g. mouse or rat), wherein

- mononeuropathic pain can be studied according to Chung (S.H. Kim, J.M. Chung, Pain. 1992, 50(3), 355-63) or Bennett (G.J. Bennett, Y.K. Xie, Pain. 1988, 33 (1), 87-107),
- Pain in the case of diabetic polyneuropathy after streptozotocin (STZ) -induced diabetes (E.K. Joseph, J.D. Levine, Neuroscience. 2003;120(4):907-13) and
- acute pain can be studied in the so-called tail-flick test (D'Amour and Smith, J. Pharm. Exp. Ther. 72, 1941, 74-9).

The determination is preferably carried out in the animal model, with regard to the efficacy against neuropathic pain as efficacy against mononeuropathic pain in the rat in the model according to Chung, and with regard to the efficacy against acute pain in the rat tail-flick *test,* preferably in each case as described in the experimental section.

Thus the compounds according to the invention preferably have an affinity for the μ-opioid receptor and the ORL-1 receptor, which in the rat

- are significantly effective in the treatment of mononeuropathic pain in the model according to Chung and are characterised by a half-maximum effective dose ED_{50}^{n} , and
- which are not significantly effective in the treatment of acute pain in the tail-flick test in a dose which is higher than ED_{50}^{n} by a factor of 5.

The evaluation of the experimental findings in respect of statistically significant differences between the respective dose groups and the vehicle control groups is preferably carried out by means of variance analysis with repeated measures (repeated measures ANOVA) as well as a post hoc analysis according to Bonferroni, preferably as described in the experimental section. Here the significance level is set at $p < 0.05$. The group sizes are usually n=10.

In principle the comparative determination of analgesic efficacy against neuropathic pain and acute, nociceptive pain can also be carried out in humans, but this is less preferred, for ethical considerations among other things. The study of efficacy against neuropathic pain, i.e. in patients suffering from neuropathic pain, can then be carried out according to Hansson P, Backonja M, Bouhassira D. (2007). Usefulness and limitations of quantitative sensory testing: clinical and

research application in neuropathic pain states. Pain. 129(3): 256-9. The study of efficacy against acute pain can then be carried out according to Posner J, Telekes A, Crowley D, Phillipson R, Peck AW. (1985). Effects of an opiate on cold-induced pain and the CNS in healthy volunteers. Pain. 23(1):73-82.

Surprisingly, it was found that the compounds according to the general formula (III) are distinguished by a very advantageous side-effects profile by comparison with conventional stage 3 opioids. Thus, even on administration of therapeutically effective doses as are required in particular for the treatment of neuropathic pain, no or at most only slightly pronounced opioid-typical side effects are observed, such as, for example, respiratory depression, constipation, urinary retention, nausea, vomiting, hypotonia, bradycardia, addiction, dependency, euphoria, depression, sedation and dizziness. Hitherto the greatly reduced occurrence of the opioid-typical side effects respiratory depression, constipation, hypotonia, bradycardia, disturbance of motor coordination capacity (as a measure of central nervous side effects), physical and mental dependency has been shown experimentally in animal models.

In a preferred embodiment of the application according to the invention the compounds according to the general formula (III), when administered in the half-maximum effective dose ED_{50}^{n}, which is defined with regard to the efficacy of the compound against neuropathic pain, and preferably even in a dose which is higher than ED_{50}^{n} by a factor of 5, do not exhibit significant respiratory depression as a side-effect, preferably in the rat, more preferably in the blood gas analysis model. Preferably the compounds according to the general formula (III), even when used in a dose which is higher than the half-maximum effective dose ED_{50}^{n} by a factor of 10, 20, 30, 40 or 50, more preferably by a factor of 75, 100, 125, 150 or 175, even more preferably by a factor of 200, do not exhibit significant respiratory depression as a side effect.

Suitable methods for studying active-ingredient-induced respiratory depression are known to the person skilled in the art. The study is preferably carried out in a blood gas analysis model in the rat as the change in arterial O_2 und CO_2 partial pressures. Evaluation of the experimental findings in respect of statistically significant differences between the respective dose groups and the vehicle control groups is preferably carried out by means of single-factor variance analysis (one-way ANOVA) as well as by post hoc analysis according to Dunnett, preferably as described in the experimental section. Here the significance level is set at $p < 0.05$. The group sizes are usually n=6. For further details of this animal model reference is also made to the experimental section.

In a preferred embodiment of the application according to the invention the compounds according to the general formula (III), when administered in the half-maximum effective dose ED_{50}^{n}, which is defined with regard to the efficacy of the compound against neuropathic pain, and preferably even in a dose which is higher than ED_{50}^{n} by a factor of 5, do not exhibit significant constipation as a side effect, preferably in the mouse, more preferably in the charcoal passage test. Preferably compounds do not exhibit any significant constipation as a side effect, even in a dose which is higher than the half-maximum effective dose ED_{50}^{n} by a factor of 10, 20, 30, 40 or 50, more preferably by a factor of 75, 100, 125, 150 or 175, even more preferably by a factor of 200, 300, 400 or 500, most preferably by a factor of 600.

Suitable methods for studying active-ingredient-induced constipation are known to the person skilled in the art. The study is preferably carried out in a charcoal passage model in the mouse as the change in gastrointestinal transit speed. Evaluation of the experimental findings in respect of statistically significant differences between the respective dose groups and the vehicle control groups is preferably carried out by means of single-factor variance analysis (one-way ANOVA) as well as by post hoc analysis according to Dunnett, preferably as described in the experimental section. Here the significance level is set at $p < 0.05$. The group sizes are usually n=10. For further details of this animal model reference is also made to the experimental section.

In one preferred embodiment of the application according to the invention the compounds according to the general formula (III), when administered in the half-maximum effective dose ED_{50}^{n}, which is defined with regard to the efficacy of the compound against neuropathic pain, and preferably even in a dose which is higher than ED_{50}^{n} by a factor of 5, do not exhibit significant hypotonia as a side effect, preferably in awake rabbits, more preferably in the circulatory model in awake rabbits with telemetry. Preferably the compounds do not exhibit any significant hypotonia as a side effect, even in a dose which is higher than the half-maximum effective dose ED_{50}^{n} by a factor of 10, 20, 30, 40 or 50, more preferably by a factor of 75, 100, 125, 150 or 175, even more preferably by a factor of 200.

Suitable methods for studying active-ingredient-induced hypotonia are known to the person skilled in the art. The study is preferably carried out in a circulatory model in awake rabbits with telemetry as the change in arterial blood pressure (systolic, diastolic and mean value). Evaluation of the experimental findings in respect of statistically significant differences between the respective dose groups and the vehicle control groups is preferably carried out by means of

single-factor variance analysis (one-way ANOVA) as well as by post hoc analysis according to Dunnett, preferably as described in the experimental section. Here the significance level is set at $p < 0.05$. The group sizes are usually n=6. For further details of this animal model reference is also made to the experimental section.

In one preferred embodiment of the application according to the invention the compounds according to the general formula (III), when administered in the half-maximum effective dose ED_{50}^{n}, which is defined with regard to the efficacy of the compound against neuropathic pain, and preferably even in a dose which is higher than ED_{50}^{n} by a factor of 5, do not exhibit significant bradycardia as a side effect, preferably in awake rabbits, more preferably in the circulatory model in awake rabbits with telemetry. Preferably the compounds do not exhibit any significant bradycardia as a side effect, even in a dose which is higher than the half-maximum effective dose ED_{50}^{n} by a factor of 10, 20, 30, 40 or 50, more preferably by a factor of 75, 100, 125, 150 or 175, even more preferably by a factor of 200.

Suitable methods for studying active-ingredient-induced bradycardia are known to the person skilled in the art. The study is preferably carried out in a circulatory model in awake rabbits with telemetry as a change in cardiac frequency. Evaluation of the experimental findings in respect of statistically significant differences between the respective dose groups and the vehicle control groups is preferably carried out by means of single-factor variance analysis (one-way ANOVA) as well as by post hoc analysis according to Dunnett, preferably as described in the experimental section. Here the significance level is set at $p < 0.05$. The group sizes are usually n=6. For further details of this animal model reference is also made to the experimental section.

In one preferred embodiment of the application according to the invention the compounds according to the general formula (III), when administered in the half-maximum effective dose ED_{50}^{n}, which is defined with regard to the efficacy of the compound against neuropathic pain, and preferably even in a dose which is higher than ED_{50}^{n} by a factor of 5, do not exhibit significant disturbance of motor coordination capacity (as a measure of central-nervous side effects) as a side effect, preferably in the mouse, more preferably in the RotaRod test. Preferably the compounds do not exhibit any significant disturbance of motor coordination capacity (as a measure of central-nervous side effects) as a side effect, even in a dose which is higher than the half-maximum effective dose ED_{50}^{n} by a factor of 10, 20, 30, 40 or 50, more preferably by a factor of 75, 100, 125, 150 or 175, even more preferably by a factor of 200, 300, 400 or 500, most preferably by a factor of 600, 700, 800 or 900, and in particular by a factor of 1000.

Suitable methods for studying active-ingredient-induced disturbance of motor coordination capacity are known to the person skilled in the art. The study is preferably carried out in a RotaRod model in the mouse (analogously to Kuribara H., Higuchi Y., Tadokoro S. (1977), Effects of central depressants on Rota-Rod and traction performance in mice. Japan. J. Pharmacol. 27, 117-126.) as the change in the ability to run on a rotating rod. Evaluation of the experimental findings in respect of statistically significant differences between the respective dose groups and the vehicle control groups is preferably carried out by means of single-factor variance analysis (one-way ANOVA) as well as by post hoc analysis according to Dunnett, preferably as described in the experimental section. Here the significance level is set at $p < 0.05$. The group sizes are usually n=10. For further details of this animal model reference is also made to the experimental section.

In one preferred embodiment of the application according to the invention the compounds according to the general formula (III), when administered in the half-maximum effective dose ED_{50}^{n}, which is defined with regard to the efficacy of the compound against neuropathic pain, and preferably even in a dose which is higher than ED_{50}^{n} by a factor of 5, do not exhibit significant physical dependency or withdrawal symptom as a side effect, preferably in the mouse, more preferably in the jumping test.

Preferably the compounds do not exhibit any significant physical dependency or withdrawal symptoms as a side effect, even in a dose which is higher than the half-maximum effective dose ED_{50}^{n} by a factor of 10, 20, 30, 40 or 50, more preferably by a factor of 75, 100, 125, 150 or 175, even more preferably by a factor of 200, 300, 400 or 500, most preferably by a factor of 600, 700, 800 or 900, and in particular by a factor of 1000.

Suitable methods for studying active-ingredient-induced physical dependency are known to the person skilled in the art. The study is preferably carried out in the jumping model in the mouse (analogously to Saelens JK, Arch Int Pharmacodyn 190: 213-218, 1971) as naloxone- induced withdrawal. The evaluation of the experimental findings in respect of statistically significant differences between the respective dose groups and the vehicle control groups is preferably carried out by means of Fisher's exact test for the parameter "number of animals with withdrawal symptoms" as well as by means of the Kruskal-Wallis test for the parameter "jumping frequency", preferably as described in the experimental section. Here the significance level is set at $p < 0.05$ in each case. The group sizes are usually n=12. For further details of this

animal model reference is also made to the experimental section.

In one preferred embodiment of the application according to the invention the compounds according to the general formula (III), when administered in the half-maximum effective dose ED_{50}^{n}, which is defined with regard to the efficacy of the compound against neuropathic pain, and preferably even in a dose which is higher than ED_{50}^{n} by a factor of 5, do not exhibit significant mental dependency or addiction as a side effect, preferably in the rat, more preferably by means of conditioned place preference. Preferably the compounds do not exhibit any significant mental dependency or addiction as a side effect, even in a dose which is higher than the half-maximum effective dose ED_{50}^{n} by a factor of 10, 20, 30, 40 or 50, more preferably by a factor of 75, 100, 125, 150 or 175, even more preferably by a factor of 200, 300, 400 or 500, most preferably by a factor of 600, 700, 800 or 900, and in particular by a factor of 1000.

Suitable methods for studying active-ingredient-induced mental dependency and addiction are known to the person skilled in the art. The study is preferably carried out by means of conditioned place preference in rats, preferably as described in Tzschentke, T.M., Bruckmann, W. and Friderichs, F. (2002) Lack of sensitization during place conditioning in rats is consistent with the low abuse potential of tramadol. Neuroscience Letters 329, 25-28. The evaluation of the experimental findings in respect of statistically significant differences in the animals' preferences for the active ingredient or the vehicle is preferably carried out by means of the paired t-test. The significance level is set at $p < 0.05$. The group sizes are usually n=8. For further details of this animal model reference is made to the description of the method in Tzschentke, T.M., Bruckmann, W. and Friderichs, F. (2002) Neuroscience Letters 329, 25-28.

The compounds according to the general formula (III) are suitable for use in the treatment of chronic pain, preferably neuropathic pain, more preferably against mononeuropathic/neuralgic or polyneuropathic pain, even more preferably against pain in the case of postherpetic neuralgia or in the case of diabetic polyneuropathy.

The definitions of the different forms of chronic pain are known to the person skilled in the art. In this connection reference may be made, for example to Merskey H., Bogduk N. Classification of chronic pain. Seattle: IASP Press 1994, Bennett G.J., Anesth Analg. 2003, 97, 619-20, and Backonja M.M., Anesth Analg. 2003, 97, 785-90.

For the purposes of the description, chronic pain is preferably defined as pain symptoms which

exist over a prolonged period (normally at least 3, 4, 5 or 6 months) and which persist beyond the normal healing time. Neuropathic pain is preferably described as pain or a sensory phenomenon caused by lesion, disease or dysfunction of the central or peripheral nervous system. For the purposes of the description, acute pain is preferably described as an unpleasant sensory and emotional experience accompanying acute or potential tissue damage or described in terms of such damage (cf. definition of the International Association for the Study of Pain® (IASP)).

The compounds used according to the invention in accordance with the general formula (III) have a K_i value on the μ-opioid receptor of preferably not more than 1000 nM, more preferably not more than 500 nM, even more preferably 100 nM, most preferably not more than 50 nM and in particular not more than 25 nM.

Methods of determining the K_i value on the μ-opioid receptor are known to the person skilled in the art. The determination is preferably carried out in a homogeneous batch in microtitre plates. To this end serial dilutions of each of the substances to be tested are preferably incubated for 90 minutes at room temperature with a receptor membrane preparation (15-40 μg protein per 250 μl of incubation batch) of CHO-K1 cells which express the human μ-opiate receptor (RB-HOM receptor membrane preparation from NEN, Zaventem, Belgium) in the presence of 1 nmol/l of the radioactive ligand [^{3}H]-naloxone (NET719, NEN, Zaventem, Belgium) and 1 mg WGA-SPA beads (wheat germ agglutinin SPA Beads from Amersham/Pharmacia, Freiburg, Germany) in a total volume of 250 μl. 50 mmol/l Tris-HCI supplemented by 0.05 wt.% of sodium azide and 0.06 wt.% of bovine serum albumin is preferably used as the incubation buffer. For the determination of non-specific binding, 25 μmol/l of naloxone is preferably added as well. On completion of the ninety-minute incubation time the microtitre plates are preferably centrifuged off for 20 minutes at 1000 g and the radioactivity is measured in a β counter (Microbeta-Trilux, PerkinElmer Wallac, Freiburg, Germany). The percentage displacement of the radioactive ligand from its binding to the human μ-opiate receptor at a concentration of the test substances of preferably 1 μmol/l is determined and indicated as the percentage inhibition (%inhibition) of the specific binding. On the basis of the percentage displacement by different concentrations of the compounds to be tested it is possible to calculate IC_{50} inhibition concentrations which effect a 50 percent displacement of the radioactive ligand. The K_i values for the test substances can be calculated by conversion by means of the Cheng-Prusoff equation.

The compounds used according to the invention in accordance with the general formula (III)

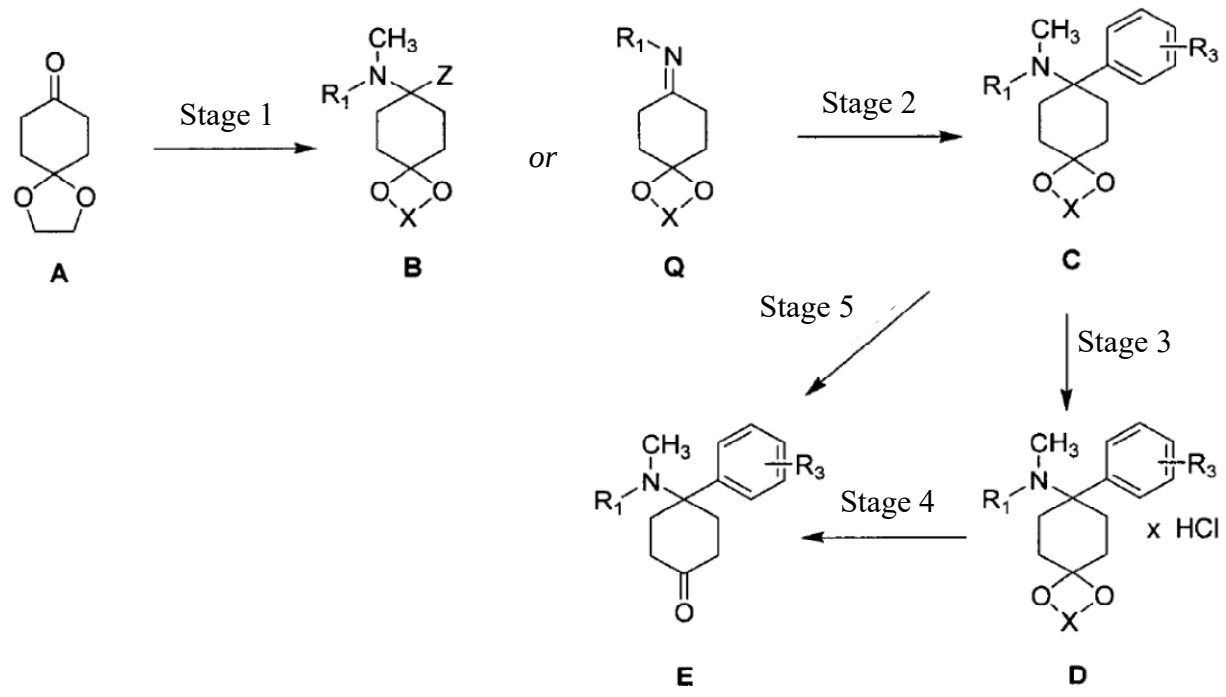
have a K_i value on the ORL1 receptor of preferably not more than 500 nM, more preferably not more than 100 nM, most preferably not more than 50 nM and in particular not more than 10 nM.

Methods of determining the K_i value on the ORL1 receptor are known to the person skilled in the art. The determination is preferably carried out in a receptor binding assay with ^{3}H-nociceptin/orphanin FQ with membranes of recombinant CHO-ORL1 cells. This test system is preferably carried out in accordance with the method put forward by Ardati et al. (Mol. Pharmacol., 51, 1997, pp. 816-824). The concentration of ^{3}H-nociceptin/orphanin FQ in these tests is preferably 0.5 nM. The binding assays are preferably carried out with in each case 20 µg of membrane protein per 200 µl batch in 50 mM Hepes, pH 7.4, 10 mM $MgCl_2$ and 1 mM EDTA. Binding to the ORL1 receptor is preferably determined using in each case 1 mg of WGA-SPA beads (Amersham-Pharmacia, Freiburg), by incubating the batch for one hour at RT and then measuring in a Trilux scintillation counter (Wallac, Finland).

A further subject matter of the invention relates to a process for preparing the compounds according to the invention. Suitable processes for the synthesis of the compounds according to the invention are known in principle to the person skilled in the art.

Preferred synthesis routes are described below:

Synthesis of the ketone structural units E:



Stage 1 *(*Via B*)*

Structures of formula B can be prepared by reaction of ketones A with amines and acidic

reactants Z-H. Suitable reactants Z-H are, for example, hydrogen cyanide, 1,2,3- triazole, benzotriazole or pyrazole. A particularly preferred route to compounds of structure B is the reaction of ketones with metal cyanides and the corresponding amine in the presence of acid, preferably in an alcohol, at temperatures of - 40 to 60 °C, preferably at room temperature with alkali metal cyanides in methanol. Another particularly preferred route to compounds of structure B is the reaction of ketones with 1,2,3-triazole and the corresponding amine in the presence under water-removing conditions, preferably using a water separator at elevated temperature in an inert solvent or using molecular sieve or another drying agent. In an analogous manner, structures analogous to B can be introduced using benzotriazole or pyrazole groups instead of triazole groups.

Stage 1 (Via Q)

The preparation of imines of the general formula Q from ketones A is to be found in the general prior art.

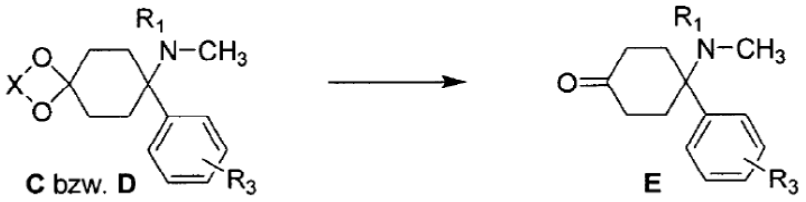
Stage 2 (*via* B*)*

In general, acetals C can be obtained by substitution of suitable leaving groups Z in structures of formula B. Suitable leaving groups are preferably cyano groups; 1,2,3-triazole-1-yl groups. Further suitable leaving groups are 1H- Benzo[d][1,2,3]triazol-1-yl groups and pyrazol-1-yl groups (Katritzky et al., Synthesis 1989, 66-69). A particularly preferred route to compounds of structure C is the reaction of amino nitriles B (Z= CN) with corresponding organometallic compounds, preferably Grignard compounds, preferably in ethers, preferably at RT. The organometallic compounds are either commercially available or can be prepared according to the general prior art. A further particularly preferred route to compounds of structure C is the reaction of aminotriazoles B (Z= triazole) with corresponding organometallic compounds, preferably Grignard compounds, preferably in ethers, preferably at RT. The organometallic compounds are either commercially available or can be prepared according to the general prior art.

Stage 2 (*via* Q*)*

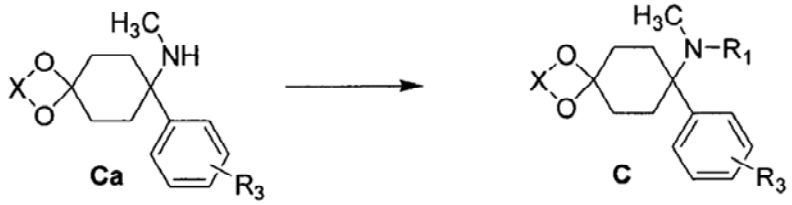
Aminoacetals C with a maximum of one substituent on the nitrogen atom can be obtained according to processes known in principle to the person skilled in the art by the addition of carbon nucleophiles to imines Q, preferably organometallic compounds in inert solvents, particularly preferably with Grignard reagents or organolithium compounds, preferably in ethers, preferably at temperatures from 100 to RT.

Stage 4/5:



Compounds of formula E can be freed from corresponding acetals C or from their salts D according to generally know prior art by deprotection by means of acids. Here X is selected from the group alkyl, alkyl/ alkylidene/ alkylidene substituted by aryl or aklyl (saturated/unsaturated).

Preparation of C ($R_1 \neq$ -H) from Ca (R_1 = -H)



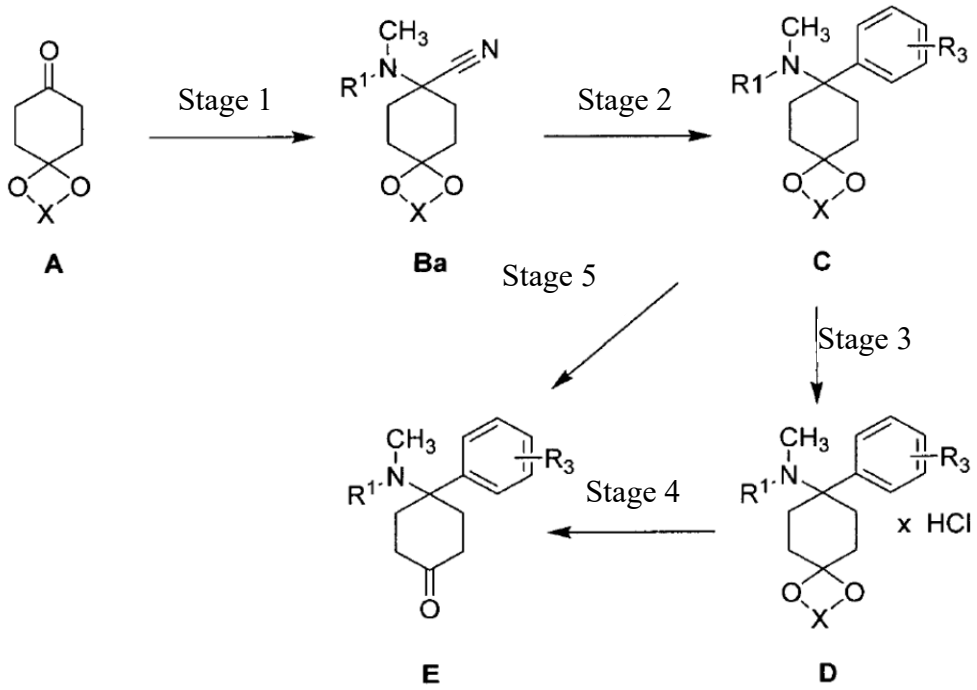
Aminoacetals Ca having a maximum of one substituent on the nitrogen atom can be converted according to processes known in principle to the person skilled in the art, for example by reductive amination, into corresponding aminoacetals C having one or two further substituents on the nitrogen.

Aminonitrile Route, Imine Route and Triazole Route

The requisite ketone intermediate E can be prepared, for example, according to the following three different routes: (1) Aminonitrile Route (2) Imine Route and (3) Triazole Route.

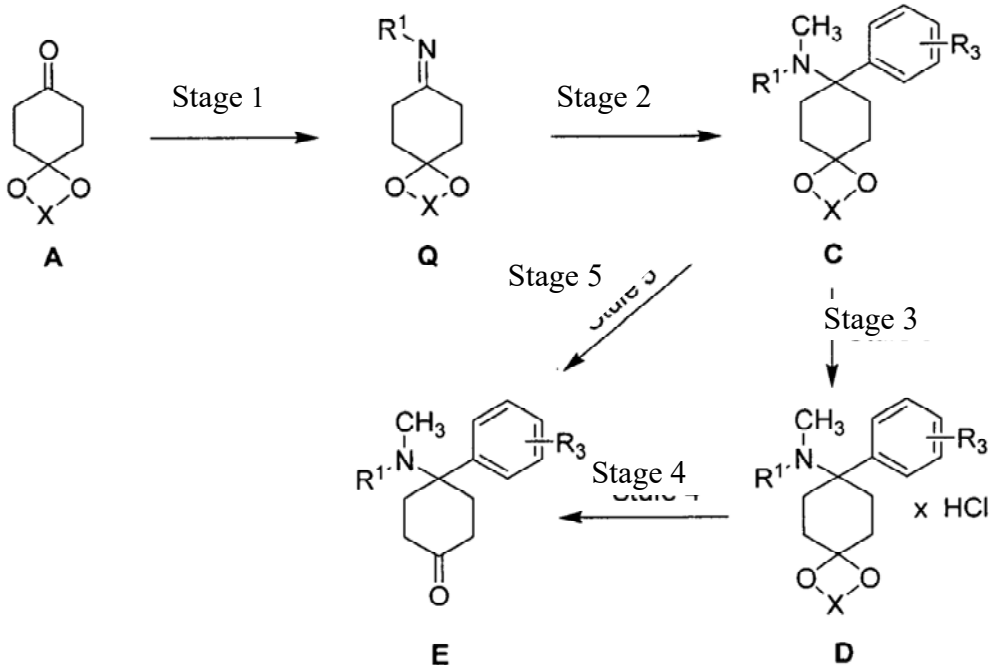
(1) Aminonitrile Route:

In the aminonitrile route there is synthesised, as described in the following synthesis scheme, from a ketone precursor A the aminonitrile Ba, which is converted into the structural units C or D and further into E using a nucleophile MR3. This synthesis route has already been described and used in WO 2004/043967.



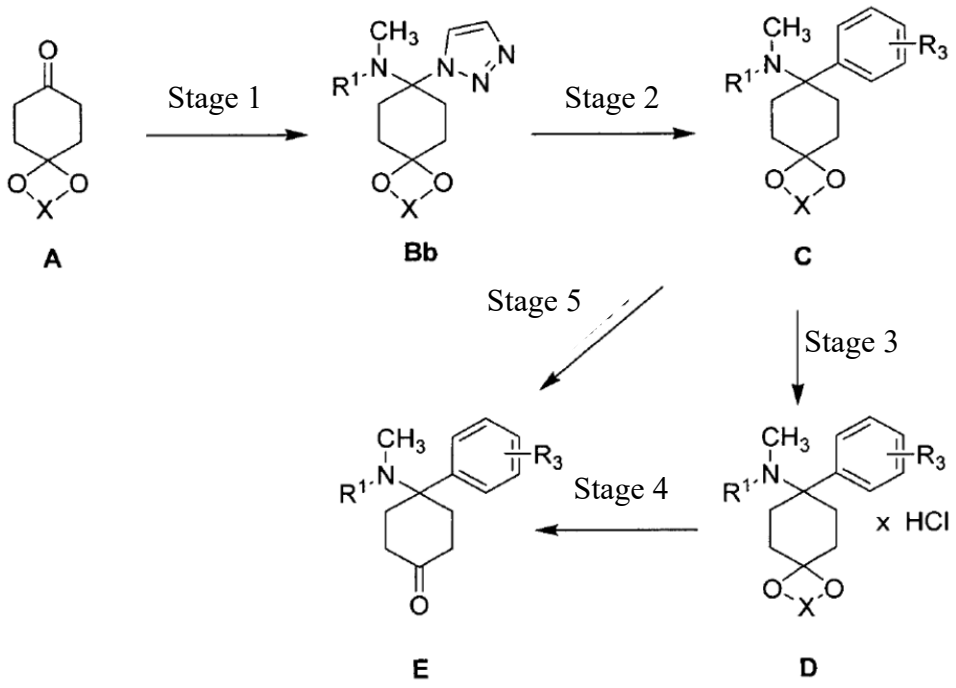
(2) Imine Route:

In the imine route there is synthesised, as described in the following scheme, from a ketone precursor A the imine Q, which is converted into the structural units C or D and further into E using a nucleophile MR3. The requisite structural units Q can be prepared according to a method known to the person skilled in the art (Layer, Chem. Rev., 1963, 8, 489- 510). For addition of the organometallic species MR3 to the imine Q, processes known in the literature (e.g. Maddox et al., J. Med. Chem., 1965, 8, 230-235. Kudzma et al., J. Med. Chem., 1989, 32, 2534-2542.) were used. Stages 3, 4 and 5 are carried out analogously to the aminonitrile route.

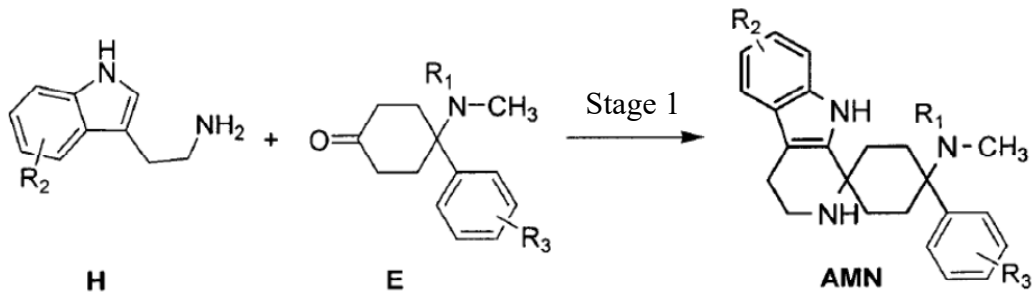


(3) Triazole Route:

In the triazole route there was synthesised, as described in the following scheme, from a ketone precursor A the triazole Bb, which is converted into the structural units C or D and further into E using a nucleophile MR3. The conditions can be found in the literature references indicated: (a) Katritzky et al. Synthesis, 1992, 1295- 1298. (b) Prashad, et al., Tetrahedron Lett. 2005, 46, 5455-5458.



Synthesis of the spiroamines (AMN)



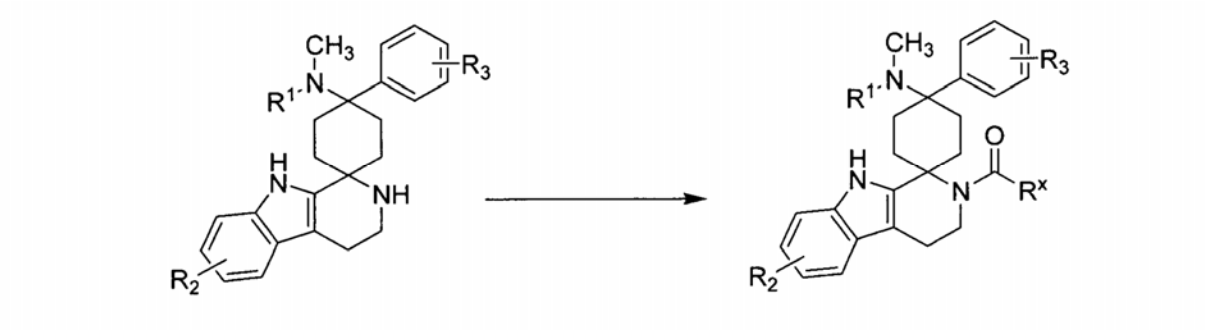
Tryptamines of type H can be reacted in reactions of the Pictet-Spengler type with ketones E, with the addition of at least one reagent from the group of the acids, acid anhydrides, esters, weakly acid-reacting salts or Lewis acids to form products of the formula AMN.

Use is preferably made of at least one reagent from the group carboxylic acids, phosphoric acids or sulphonic acids or their respective anhydrides, carboxylic acid trialkylsilyl esters, acid-reacting salts, mineral acids or Lewis acids selected from the group comprising boron trifluoride, indium(III) chloride, titanium tetrachloride, aluminium(III) chloride, or with the addition of at least one transition metal salt, preferably with the addition of at least one transition metal triflate (transition metal trifluoromethanesufonate), particularly preferably with the addition of at least one transition metal trifluoromethanesulfonate selected from the group comprising scandium(III) trifluoromethanesulfonate, ytterbium(III) trifluoromethane- sulfonate and indium(III) trifluoromethanesulfonate, if appropriate with the addition of celite, with solid-phase-bound reactants or reagents, at elevated or reduced temperature, with or without microwave radiation, if appropriate in an appropriate solvent or solvent mixture such as, for example, chlorinated or unchlorinated, then preferably aromatic, hydrocarbons, acetonitrile; in ethereal solvents, preferably in diethyl ether or THF; or in nitromethane, in appropriate cases also in alcohols or water. Particular preference is given to pyridinium para-toluenesulfonate, phosphorous pentoxide in the presence of celite, boron trifluoride etherate, trifluoroacetic acid, ortho-titanic acid tetraisopropyl ester together with trifluoroacetic acid, trifluoromethanesulphonic acid trimethylsilyl ester, trifluoromethanesulfonic acid, methanesulfonic acid, trifluoroacetic acid, acetic acid, phosphoric acid, polyphosphoric acid, polyphosphate esters, p-toluene-sulfonic acid, hydrochloric acid, HCl gas, sulfuric acid together with acetate buffer, tin tetrachloride.

The conditions indicated in the following examples are again preferably used.

Compounds of the general formulae H and E are either available commercially or their preparation is know from prior art or can be derived from prior art in a manner obvious to the person skilled in the art. The following citations are particularly relevant in this context: Jirkovsky et al., J. Heterocycl. Chem., 12, 1975, 937-940; Beck et al., J. Chem. Soc. Perkin 1, 1992, 813-822; Shinada et al., Tetrahedron Lett., 39, 1996, 7099-7102; Garden et al., Tetrahedron, 58, 2002, 8399-8412; Ledniceret al., J. Med. Chem., 23, 1980, 424-430; Bandini et al. J. Org. Chem. 67, 15; 2002, 5386 - 5389; Davis et al., J.Med.Chem. 35, 1, 1992, 177-184; Yamagishi et al., J.Med.Chem. 35, 11, 1992, 2085-2094; Gleave et al.; Bioorg.Med.Chem.Lett. 8, 10, 1998, 1231-1236; Sandmeyer, Helv.Chim.Acta; 2; 1919; 239; Katz et al.; J. Med. Chem. 31, 6, 1988; 1244-1250; Bac et al. Tetrahedron Lett. 1988, 29, 2819; Ma et al. J. Org. Chem. 2001, 66, 4525; Kato et al. J. Fluorine Chem. 99, 1, 1999, 5 - 8.

Synthesis of the spiroamides (AMD)



AMN **AMD**

Compounds of the general formula AMN can be reacted with carboxylic acids in at least one solvent, preferably selected from the group comprising dichloromethane, acetonitrile, dimethylformamide, diethyl ether, dioxane and tetrahydrofuran, with the addition of at least one coupling agent, preferably selected from the group comprising carbonyldiimidazole (CDI), 2-chloro-1 methylpyridium iodide (Mukaiyama reagent), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDCI), *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU), *N'*,*N'*-dicyclohexylcarbodiimide (DCC) and 1-benzotriazolyloxy-tri-(dimethylamino)-phosphonium hexafluorophosphate (BOP), if appropriate in the presence of at least one inorganic base, preferably selected from the group comprising potassium carbonate and caesium carbonate, or an organic base, preferably selected from the group comprising triethylamine, diisopropylethylamine and pyridine and, if appropriate, with the addition of 4-(dimethylamino)pyridine or 1-hydroxybenzotriazole at temperatures of preferably between 25°C and 150°C, if appropriate with microwave radiation to give compounds of the general formula AMD.

Compounds of the general formula AMN can be reacted with acid anhydrides and carboxylic acid chlorides in at least one solvent, preferably selected from the group comprising dichloromethane, acetonitrile, dimethylformamide, diethyl ether, dioxane and tetrahydrofuran, if appropriate in the presence of at least one inorganic base, preferably selected from the group comprising potassium carbonate and caesium carbonate, or of an organic base preferably selected from the group comprising triethylamine, diisopropylethylamine and pyridine and if appropriate with the addition of 4-(dimethylamino)pyridine or 1-hydroxybenzotriazole, at temperatures of preferably between 25°C and 150°C, if appropriate with microwave radiation to give compounds of the general formula AMD.

For further comprehensive details relating to the synthesis of the compounds used according to the invention, particularly with regard to the synthesis of suitable starting structural units, reference is made to WO2004/043967, WO2005/063769, WO2005/066183, WO2006/018184,

WO2006/108565, WO2007/124903 and WO2008/009416. A person skilled in the art will recognise that suitable starting structural units for the synthesis of the compounds according to the invention can be prepared analogously to the synthesis schemes and exemplary embodiments disclosed in these publications.

The compounds used according to the invention act, for example on the ORL-1 and μ-opioid receptors which are relevant in connection with various diseases, so that they are suitable as an active ingredient (medicament) in a pharmaceutical composition.

A further subject matter of the invention relates to the application of a pharmaceutical composition for use in the treatment of neuropathic and/or chronic pain, with the composition containing a physiologically acceptable carrier and at least one compound according to the general formula (III).

Preferably the composition used is

- solid, liquid or pasty; and/or
- contains the compound according to the invention in an amount of from 0.001 to 99 wt. %, preferably from 1.0 to 70 wt. %, relative to the total weight of the composition.

The pharmaceutical composition used according to the invention may, if appropriate, contain suitable additives and/or auxiliary substances and/or, if appropriate, further active ingredients.

Examples of suitable physiologically acceptable carriers, additives and/or auxiliary substances are fillers, solvents, diluents, colourings and/or binders. These substances are known to the person skilled in the art (cf. H.P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, Editio Cantor Aulendoff).

Preferably the composition used according to the invention contains the compound according to the invention in an amount of preferably from 0.001 to 99 wt. %, more preferably 0.1 to 90 wt. %, even more preferably 0.5 to 80 wt. %, most preferably 1.0 to 70 wt. % and particularly 2.5 to 60 wt. %, relative to the total weight of the composition.

The composition for use according to the invention is produced preferably for systemic, topical or local administration, preferably for oral administration.

A further embodiment of the use according to the invention provides for a pharmaceutical form of administration which contains the pharmaceutical composition according to the invention.

In one preferred embodiment the form of administration used according to the invention is produced for administration twice daily, for administration once daily or for administration less frequently than once daily, preferably for administration not more than once daily.

Administration is preferably systemic, in particular oral.

In one preferred embodiment the form of administration used according to the invention contains the compound according to the general formula (III) in such a small dose that it is not significantly effective in the treatment of acute pain. This dose is preferably within the range of between 1.0 μg and 10 mg, relative to the molecular weight of the free base.

The dose is preferably 0.001 mg±50%, 0.002 mg±50%, 0.003 mg±50%, 0.004 mg±50%, 0.005 mg±50%, 0.006 mg±50%, 0.007 mg±50%, 0.008 mg±50%, 0.009 mg±50%, 0.01 mg±50%, 0.02 mg±50%, 0.03 mg±50%, 0.04 mg±50%, 0.05 mg±50%, 0.06 mg±50%, 0.07 mg±50%, 0.08 mg±50%, 0.09 mg±50%, 0.1 mg±50%, 0.15 mg±50%, 0.2 mg±50%, 0.25 mg±50%, 0.3 mg±50%, 0,35 mg±50%, 0,4 mg±50%, 0.45 mg±50%, 0.5 mg±50%, 0.55 mg±50%, 0.6 mg±50%, 0.65 mg±50%, 0.7 mg±50%, 0.75 mg±50%, 0.8 mg±50%, 0.85 mg±50%, 0.9 mg±50%, 0.95 mg±50%, 1 mg±50%, 1.5 mg±50%, 2 mg±50%, 2.5 mg±50%, 3 mg±50%, 3,5 mg±50%, 4 mg±50%, 4.5 mg±50%, 5 mg±50%, 5.5 mg±50%, 6 mg±50%, 6.5 mg±50%, 7 mg±50%, 7.5 mg±50%, 8 mg±50%, 8.5 mg±50%, 9 mg±50%, 9.5 mg±50% or 10 mg±50%, relative to the molecular weight of the free base.

More preferably the dose is 0.001 mg±25%, 0.002 mg±25%, 0.003 mg±25%, 0.004 mg±25%, 0.005 mg±25%, 0.006 mg±25%, 0.007 mg±25%, 0.008 mg±25%, 0.009 mg±25%, 0.01 mg±25%, 0.02 mg±25%, 0.03 mg±25%, 0.04 mg±25%, 0.05 mg±25%, 0.06 mg±25%, 0.07 mg±25%, 0.08 mg±25%, 0.09 mg±25%, 0.1 mg±25%, 0.15 mg±25%, 0.2 mg±25%, 0.25 mg±25%, 0.3 mg±25%, 0.35 mg±25%, 0.4 mg±25%, 0.45 mg±25%, 0.5 mg±25%, 0.55 mg±25%, 0.6 mg±25%, 0.65 mg±25%, 0.7 mg±25%, 0.75 mg±25%, 0.8 mg±25%, 0.85 mg±25%, 0.9 mg±25%, 0.95 mg±25%, 1 mg±25%, 1.5 mg±25%, 2 mg±25%, 2.5 mg±25%, 3 mg±25%, 3.5 mg±25%, 4 mg±25%, 4.5 mg±25%, 5 mg±25%, 5.5 mg±25%, 6 mg±25%, 6.5 mg±25%, 7 mg±25%, 7.5 mg±25%, 8 mg±25%, 8.5 mg±25%, 9 mg±25%, 9.5 mg±25% or 10 mg±25%, relative to the molecular weight of the free base.

Particularly preferably the dose is 0.001 mg, 0.002 mg, 0.003 mg, 0.004 mg, 0.005 mg, 0.006 mg, 0.007 mg, 0.008 mg, 0.009 mg, 0.01 mg, 0.02 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.06 mg, 0.07 mg, 0.08 mg, 0.09 mg, 0.1 mg, 0.15 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.35 mg, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg or 10 mg, relative to the molecular weight of the free base.

In one preferred embodiment the form of administration used according to the invention contains a compound according to the general formula (III) in the amount of 10 µg±90%, more preferably 10 µg±75%, even more preferably 10 µg±50%, most preferably 10 µg±25%, and in particular 10 µg±10%, relative to the molecular weight of the free base.

In another preferred embodiment the form of administration used according to the invention contains a compound according to the general formula (III) in the amount of 100 µg±90%, more preferably 100 µg±75%, even more preferably 100 µg±50%, most preferably 100 µg±25%, and in particular 100 µg±10%, relative to the molecular weight of the free base.

In a further preferred embodiment the form of administration used according to the invention contains a compound according to the general formula (III) in the amount of 250 µg±90%, more preferably 250 µg±75%, even more preferably 250 µg±50%, most preferably 250 µg±25%, and in particular 250 µg±10%, relative to the molecular weight of the free base.

In a further preferred embodiment the form of administration used according to the invention contains a compound according to the general formula (III) in the amount of 500 µg±90%, more preferably 500 µg±75%, even more preferably 500 µg±50%, most preferably 500 µg±25%, and in particular 500 µg±10%, relative to the molecular weight of the free base.

In another preferred embodiment the form of administration used according to the invention contains a compound in accordance with the general formula (III) in the amount of 750 µg±90%, more preferably 750 µg±75%, even more preferably 750 µg±50%, most preferably 750 µg±25%, and in particular 750 µg±10%, relative to the molecular weight of the free base.

In a further preferred embodiment the form of administration used according to the invention contains a compound according to the general formula (III) in the amount of 1000 µg±90%,

more preferably 1000 µg±75%, even more preferably 1000 µg±50%, most preferably 1000 µg±25%, and in particular 1000 µg±10%, relative to the molecular weight of the free base.

The form of administration used according to the invention may be administered, for example, as a liquid dosage form in the form of injection solutions, drops or juices, or as a semi-solid dosage form in the form of granules, tablets, pellets, patches, capsules, plastsers/spray-on plasters or aerosols. The choice of auxiliary substances etc. as well as the amounts thereof to be used depend on whether the form of administration is to be oral, peroral, parenteral, intravenous, intraperitoneal, intradermal, intramuscular, intranasal, buccal, rectal or local, for example applied to the skin, the mucosa or into the eyes.

Forms of administration in the form of tablets, coated tablets, capsules, granules, drops, juices and syrups are suitable for oral application, and solutions, suspensions, readily reconstitutable dry preparations as well as sprays are suitable for parenteral, topical and inhalatory application. Compounds in a depot, in dissolved form or in a plaster, if applicable with the addition of agents promoting penetration through the skin, are suitable percutaneous administration preparations for the application according to the invention.

Forms of administration which can be applied orally or percutaneously can effect delayed release of the compounds used according to the invention. The compounds used according to the invention can also be administered in parenteral long-term depot forms such as, for example, implants or implanted pumps. Other active ingredients known to the person skilled in the art may, in principle, be added to the forms of administration used according to the invention.

In a preferred embodiment the compounds used according to the invention are released from the form of administration immediately (*immediate release*, IR), i.e. preferably at least 80% of the active ingredient originally included is released under *in vitro* conditions, preferably in accordance with Ph. Eur., after 20 minutes.

Surprisingly, it was found that the compounds used according to the invention in accordance with the general formula (III) are distinguished by an unusually long half-life ($t_{1/2}$) or pharmacodynamic duration of action, so that a comparatively infrequent administration is sufficient to achieve comparatively long-lasting pharmacological efficacy and hence pain relief.

Forms of administration with prolonged release of the compounds used according to the

invention are not absolutely necessary for this, even in the case of immediate release (IR) long-lasting action is achieved due to the long half-life. The additional advantage of the IR property of such forms of administration is that, with long-lasting efficacy, rapid uptake of the active ingredient and thus rapid onset of pharmacological efficacy are nevertheless achieved after the first administration. Properties of IR forms of administration are therefore combined with properties of PR forms of administration (PR, prolonged release).

In a preferred embodiment the form of administration used according to the invention is a form of administration with immediate release (IR) of the active ingredient which contains a compound according to the invention, preferably of the general formula (VI) as the free base or a physiologically acceptable salt, preferably the hydrochloride, citrate or hemi-citrate, and is produced preferably for oral administration not more than once daily, preferably exactly once daily. In this connection "immediate release of the active ingredient" means that under in vitro conditions, preferably according to Ph. Eur., at least 80% of the active ingredient originally included has been released after 20 minutes.

The amount of the compounds used according to the invention to be administered to the patient varies depending on the weight of the patient, the type of administration, the indication and the severity of the disease. Usually, from 0.00005 to 50 mg/kg, preferably 0.001 to 0.5 mg/kg, more preferably 1 to 10 µg/kg of at least one compound according to the general formula (III) is administered.

For all the above embodiments of the forms of administration used according to the invention it is particularly preferred for the form of administration to contain, in addition to at least one compound according to the general formula (III), a further active ingredient.

The ORL1 receptor and the µ-opioid receptor are associated in particular with the occurrence of pain. Accordingly, the compounds used according to the invention can be used for the preparation of a medicament for the treatment of chronic pain, preferably of neuropathic pain, more preferably of mononeuropathic/neuralgic or polyneuropathic pain, even more preferably of pain in the case of post-herpetic neuralgia or in the case of diabetic polyneuropathy.

The following examples serve to explain the invention, but should not be interpreted as being limiting.

In the following nomenclature of the stereochemistry of the example compounds, "(E)" refers to substitution on a double bond, e.g. on a cinnamic acid derivative, and "cis" and "trans" to substitution on the cyclohexyl ring.

Synthesis of the indole Structural Units (H)

Structural unit H-1:

2-(1H-indole-3-yl)ethanamine (H-1)

Available commercially at the time of synthesis from Aldrich.

Structural unit H-2:

2-(5-fluoro-1H-indole-3-yl)ethanamine (H-2)

Available commercially at the time of synthesis from Fluorochem.

Synthesis of the Ketone Structural Units (E)

Structural unit E-1:

Dimethyl-(8-phenyl-1,4-dioxaspiro[4.5]dec-8-yl)amine-hydrochloride (D-1)

The aminonitrile B-1 (21 g, 0.1 mol), dissolved in THF (210 ml), was added in the course of 15 minutes, under argon and while cooling with ice, to a 1.82M phenylmagnesium chloride solution in THF (109 ml, 0.198 mol), and then stirred for 16 h at room temperature. To work up the reaction mixture saturated ammonium chloride solution (150 ml) was added, while cooling with ice, and extracted with diethyl ether (3 x 100 ml). The organic phase was extracted by shaking with water (100 ml) and saturated NaCl solution (100 ml) and concentrated. A yellow oil (25.2 g) remained. The crude product was dissolved in ethyl methyl ketone (280 ml), and $ClSiMe_3$ (18.8 ml, 0.15 mol) was added while cooling with ice. After a reaction time of 6 h the hydrochloride D-1 could be isolated in the form of a white solid in a yield of 35 % (10.5 g).

4-dimethylamino-4-phenylcyclohexanone (E-1)

The hydrochloride D-1 (10.5 g, 35.2 mmol) was dissolved in 7.5N hydrochloric acid (36 ml) and stirred for 96 h at room temperature. Once hydrolysis was complete the reaction mixture was extracted with diethyl ether (2 x 50 ml). While cooling with ice the aqueous phase was rendered alkaline with 5N sodium hydroxide solution, extracted with dichloromethane (3 x 50 ml) and concentrated. The ketone 6 could thus be isolated as a yellow solid with a melting point of 104-108 °C in a yield of 97 % (7.4 g).

Structural unit E-2:

Variant 1:

[8-(3-Fluorophenyl)-1,4-dioxaspiro[4.5]dec-8-yl]dimethylamine-hydrochloride (D-2)

0.5M 3-Fluorophenylmagnesiumbromide solution in THF (3, 750 ml, 375 mmol) was added in the course of 15 minutes, under argon and while cooling with ice, to a solution of the aminonitrile B-1 (19.8 g, 94 mmol) in THF (100 ml) and then stirred for 16 h at room temperature. To work up the reaction mixture saturated ammonium chloride solution (150 ml) and water (60 ml) were added, while cooling with ice, and extracted with diethyl ether (3 x 100 ml). The organic phase was extracted by shaking with water (50 ml) and saturated NaCl solution (50 ml) and concentrated. There remained a brown oil (26.5 g), which in addition to the phenyl compound 4 also contained the ketal 2. The crude product was dissolved in ethyl methyl ketone (156 ml), and $ClSiMe_3$ (17.8 ml, 141 mol) was added while cooling with ice. After a reaction time of 6 h the hydrochloride D-2 could be isolated in the form of a white solid having a melting point of 275-278 °C in a yield of 55 % (16.3 g).

Variant 2:

[8-(3-Fluorophenyl)-1,4-dioxaspiro[4.5]dec-8-yl]dimethyl-amine-hydrochloride (D-2)

A solution of 1-bromo-3-fluorobenzine (5.00 g, 28.6 mmol) in abs. ether (15 mL) was added dropwise to a suspension of magnesium (694 mg, 28.6 mmol) in abs. ether (10 mL) in such a manner that the ether boiled. Once addition was complete stirring was carried out for 10 min at RT, following which the magnesium was completely dissolved. The reaction solution was cooled in an ice bath and the aminonitrile B-1 (3.00 g, 14.3 mmol) in abs. THF (30 mL) was added dropwise at at 10 °C. The batch was stirred overnight at room temperature, the reaction mixture was added to 20 % NH_4Cl solution (20 mL) and water (30 mL) while cooling with ice, and extraction carried out with ether (3 x 50 mL). The org. phase was washed with water (50 mL) and then with saturated NaCl solution (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in ethyl methyl ketone (25 mL), $ClSiMe_3$ (3.2 mL, 25 mmol) was added while cooling with ice, and stirring was carried out for 5 h at room temperature. The resulting precipitate was filtered off and dried in vacuo.

Yield of D-2: 2.8 g (62 %)

^{1}H-NMR (DMSO-d_6): 1.91 (8 H, m); 2.54 (6 H, s); 3.91 (4 H, d); 7.37 (1 H, m); 7.61 (3 H, m).

Variant 1:

4-Dimethylamino-4-(3-fluoro-phenyl)-cyclohexanone (E-2)

The hydrochloride D-2 (7.2 g, 22.75 mmol) was dissolved in water (9.6 ml), concentrated

hydrochloric acid (14 ml, 455 mmol) was added, and stirring was carried out for 4 d at room temperature. Once hydrolysis was complete the reaction mixture was extracted with diethyl ether (2 x 50 ml), the aqueous phase was rendered alkaline with 5N sodium hydroxide solution while cooling with ice, whereupon the product precipitated. The ketone E-2 could be isolated as a yellow solid having a melting point of 83-88 °C and a yield of 50 % (6.05 g).

Variant 2:

4-Dimethylamino-4-(3-fluoro-phenyl)-cyclohexanone (E-2)

The hydrochloride D-2 (2.80 g, 8.86 mmol) was dissolved in water (3.7 mL), concentrated hydrochloric acid (5.5 mL) was added, and stirring was carried out for 4 d at RT. Once hydrolysis was complete the reaction mixture was extracted with ether (2 x 10 mL), the aqueous solution rendered alkaline with 5 N sodium hydroxide solution while cooling with ice, the reaction mixture extracted with dichloromethane (3 x 50 mL), the organic phase dried over sodium sulphate and concentrated in vacuo. The crude product was purified by flash chromatography with $CHCl_3$/MeOH (20:1).

Yield of E-2: 676 mg (32 %), colourless solid

Melting point: 62-67 °C

^{1}H-NMR (DMSO-d_6): 2.02 (6 H, s); 2.12 (5 H, m); 2.45 (3 H, m); 7.24 (3 H, m); 7.43 (1 H, m).

Structural unit E-3:

[8-(4-Fluorophenyl)-1,4-dioxaspiro[4.5]dec-8-yl]dimethylamine-hydrochloride (D-3)

1M 4-fluorophenylmagnesium bromide solution in THF (3, 125 ml, 125 mmol) was added in the course of 15 min to a solution of the aminonitrile B-1 (10.5 g, 50 mmol) in THF (150 ml) under argon and while cooling with ice, and then stirred for 16 h at room temperature. To work up the reaction mixture, saturated ammonium chloride solution (37 ml) and water (50 ml) were added while cooling with ice, and extraction was carried out with diethyl ether (3 x 100 ml). The organic phase was extracted by shaking with water (50 ml) and saturated NaCl solution (50 ml) and concentrated. There remained a brown oil (12.55 g), which contained, in addition to the phenyl compound C-3, also the ketal B-1. The crude product was dissolved in ethyl methyl ketone (75 ml) and $ClSiMe_3$ (9.5 ml, 75 mmol) was added while cooling with ice. After a reaction time of 6 h the hydrochloride D-3 could be isolated as a white solid in a yield of 47 % (7.48 g).

4-Dimethylamino-4-(4-fluorophenyl)cyclohexanone (E-3)

The hydrochloride D-3 (7.2 g, 22.75 mmol) was dissolved in water (9.6 ml), concentrated hydrochloric acid (14 ml, 455 mmol) was added, and stirring was carried out for 4 d at room temperature. Once hydrolysis was complete the reaction mixture was extracted with diethyl ether (2 x 50 ml), the aqueous phase rendered alkaline with 5N sodium hydroxide solution while cooling with ice, extracted with dichloromethane (3 x 50 ml) and concentrated. The ketone E-3 could be isolated as a yellow solid with a melting point of 128-133 °C and a yield of 76 % (4.05 g).

Structural unit E-4:

Dimethyl-(8-thiophen-2-yl-1,4-dioxaspiro[4.5]dec-8-yl)amine hydrochloride (D-4)

2-Iodthiophene (1, 22.9 g, 109 mmol) was dissolved under argon in THF (80 ml) and 2M isopropylmagnesium chloride (2, 35.7 ml, 72 mmol) in THF was added at 0 °C in the course of 30 min. After a reaction time of 1 h at 3-5 °C the aminonitrile B-1 (10 g, 47.6 mmol), dissolved in tetrahydrofuran (20 ml), was added and stirring carried out for 20 h at room temperature. The batch was worked up by addition of saturated NH_4Cl solution (85 ml) and extraction with diethyl ether (3x100 ml). The organic phase was extracted by shaking with water (50 ml) and saturated NaCl solution (50 ml) and concentrated. A dark brown oil (21.3 g) was obtained, which, in addition to the desired ketal, contained the aminonitrile B-1 and 2-Iodthiophene. The crude product was dissolved in ethyl methyl ketone (140 ml), and $ClSiMe_3$ (9.1 ml, 71.4 mmol) was added. After a reaction time of 6 h the hydrochloride D-4 was isolated as a white crystalline compound in a yield of 60 % (8.74 g).

4-Dimethylamino-4-thiophen-2-ylcyclohexanone (E-4)

The hydrochloride D-4 (8.68 g, 28.6 mmol) was dissolved in 7.5N hydrochloric acid (29 ml) and stirred for 48 h at room temperature. Once hydrolysis was complete the reaction mixture was extracted with diethyl ether (2 x 50 ml). While cooling with ice the aqueous phase was rendered alkaline with 5N sodium hydroxide solution, extracted with dichloromethane (3 x 50 ml) and concentrated. The ketone E-4 was thus obtained as a yellow solid with a melting point of 108-110 °C in a yield of 89 % (5.66 g).

Structural unit E-5:

N,N-dimethyl-8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decane-8-amine (D-5)

3-Iodthiophene (1.5 g, 23.8 mmol) was dissolved under argon in THF (18 ml) and 2M isopropylmagnesium chloride (2, 7.8 ml, 15.5 mmol) in THF was added at 0 °C in the course of 8 min. After a reaction time of 1 h at 3-5 °C the aminonitrile B-1 (2.16 g, 10.3 mmol), dissolved

in tetrahydrofuran (20 ml), was added. Stirring was the carried out for 20 h at room temperature. The batch was worked up by addition of saturated NH_4Cl solution (20 ml) and extraction with diethyl ether (3 x 50 ml). The organic phase was extracted by shaking with water (20 ml) and saturated NaCl solution (20 ml) and concentrated. A light-brown oil (3.95 g) was obtained. The crude product was dissolved in ethyl methyl ketone (40 ml), and $ClSiMe_3$ (1.95 ml, 15.5 mmol) was added. After a reaction time of 3 h the desired hydrochloride could be isolated in the form of a white crystalline compound in a yield of 60 % (1.86 g) with a melting point of 250-251 °C.

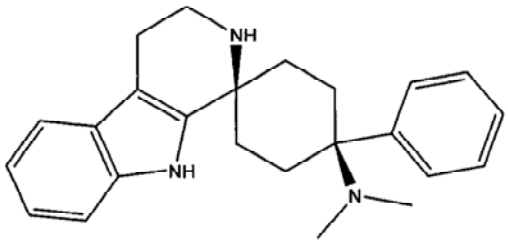
4-(Dimethylamino)-4-(thiophen-3-yl)cyclohexanone (E-5)

The hydrochloride D-5 (1.8 g, 5.9 mmol) was dissolved in 7.5N hydrochloric acid (7 ml) and stirred for 48 h at room temperature. Once hydrolysis was complete the reaction mixture was extracted with diethyl ether (2 x 30 ml), while cooling with ice the aqueous phase was rendered alkaline with 5N sodium hydroxide solution, extracted with dichloromethane (3 x 30 ml) and concentrated. The ketone E-5 could be isolated as a yellow solid with a melting point of 147-150 °C and a yield of 98 % (1.27 g).

Synthesis of the Spiroamine Structural Units (AMN^{cis} / AMN^{trans})

Comparison example AMN-1^{cis}

2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(phenyl)-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)



Note: According to this prescription predominantly the cis product AMN-1^{cis} is obtained. The trans product AMN-1^{trans} is obtained only as a secondary product or in impure form.

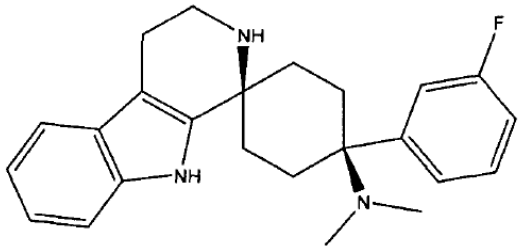
The ketone E-1 (3.26 g, 15 mmol) and tryptamine H-1 (2.4 g, 15 mmol) were dissolved in dry MeOH (100 ml) with the exclusion of oxygen. Sodium sulfate (3 g) was added to this mixture. After a reaction time of 17 h the solvent was distilled off in a rotary separator and the residue was taken up in 1,2-dichloroethane (100 ml). Trifluoroacetic acid (15 ml) was added to the reaction mixture and stirring was carried out for 1 h at room temperature. The progress of the reaction was monitored by TLC. For working up, H_2O (40 ml) was added to the batch and the pH was adjusted to 11 with NaOH (5 mol/l). A white solid precipitated and was filtered off with

suction over a frit. The solid was washed with H_2O (3 x 5 ml) and dried. It was the cis product AMN-1^{cis} which was obtained as a white solid with a melting point of 214- 218 °C in a yield of 4 g (74 %). The mother liquor (aqueous phase) was extracted with 1,2-dichloroethane (3 x 25 ml). The organic phase was dried with Na_2SO_4 and concentrated. The solid brown residue was recrystallised from MeOH (10 ml) and yielded a mixture of cis-AMN-1^{cis} and trans- AMN-1^{trans} spiroamine (1 : 1). The mixture was obtained as a white solid in a yield of 940 mg (17 %).

^{1}H NMR (600 MHz, DMSO-d_6): 1.61 (m, 2 H) 1.63 (m, 2 H) 1.92 (s, 6 H) 2.12 (m, 2 H) 2.39 (m, 2 H) 2.53 (t, J = 5.36 Hz, 2 H) 2.99 (t, J = 5.35 Hz, 2 H) 6.86 (m, 1 H) 6.91 (m, 1 H) 7.16 (d, J= 7.52 Hz, 1 H) 7.28 (d, J = 7.52 Hz, 1 H) 7.31 (m, 1 H) 7.43 (m, 4 H) 10.21 (s, 1 H)

Comparison example AMN-2^{cis}

2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)

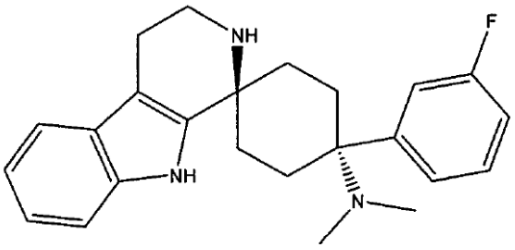


The ketone E-2 (4.71 g, 20 mmol) and tryptamine H-1 (3.2 g, 20 mmol) were dissolved in dry MeOH (200 ml) under argon. After a reaction time of 24 h MeOH was distilled off and the yellow oily residue was suspended in 1,2-dichloroethane (200 ml). Trifluoroacetic acid (20 ml) was added to the residue mixture and stirring was carried out for 2 h at room temperature. The progress of the reaction was monitored by TLC. For working up, the batch was diluted with H_2O (100 ml) adjusted to pH 11 with NaOH (5 mol/l). After addition of ethyl acetate (50 ml), a white solid precipitated upon stirring and was filtered off with suction over a frit. The solid was washed with H_2O (3 x 25 ml) and then dried. It was the cis-diastereomer AMN-2^{cis}, which was obtained as a white solid with a melting point of 220-225 °C in a yield of 5.5 g (73 %).

^{1}H NMR (600 MHz, DMSO-d_6): 1.61 (m, 2 H) 1.62 (m, 2 H) 1.93 (s, 6 H) 2.11 (m, 2 H) 2.38 (m, 2 H) 2.53 (t, J = 5.56 Hz, 2 H) 2.99 (t, J = 5.56 Hz, 2 H) 6.87 (m, 1 H) 6.92 (m, 1 H) 7.14 (m, 1 H) 7.17 (d, J= 8.34 Hz, 1 H) 7.20 (m, 1 H) 7.25 (d, J= 7.82 Hz, 1 H) 7.28 (d, J= 7.47 Hz, 1 H) 7.47 (m, 1 H) 10.26 (s, 1 H)

Comparison example AMN-2^{trans}

2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (trans-diastereomer)

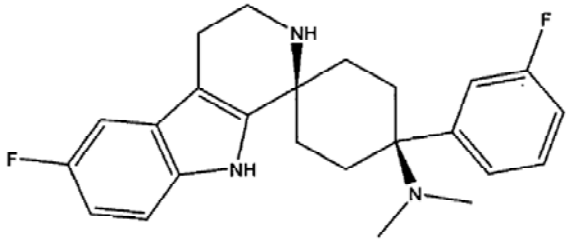


Tryptamine H-1 (2.03 g, 12.7 mmol) and the ketone (E-2, 3.0 g, 12.7 mmol) were dissolved in abs. methanol (130 ml) and stirred for 16 h at room temperature under argon. The reaction mixture was then concentrated. The residue was dissolved in abs. 1,2- dichloroethane (130 ml), trifluoroacetic acid (12.7 ml) was quickly added and stirring was carried out for 2 h at room temperature. While cooling with ice, water (120 ml) and 5N sodium hydroxide solution (40 ml) were added and stirring was carried out for 1 h. The resultant colourless solid was separated off by filtration and washed with 1,2-dichloroethane (30 ml) and water (4 x 25 ml). The cis-spiroamine AMN-2^{cis} was obtained in a yield of 77 % (3.7 g) with traces of the trans-spiroamine AMN-2^{trans}. The phases of the filtrate were separated. The organic phase was dried with sodium sulphate and concentrated, methanol (3 ml) was added, and stirring was carried out for 1 h at room temperature. A white solid precipitate was separated off by filtration and washed with methanol (4x3 ml). The trans-spiroamine AMN-2^{trans} was obtained in a yield of 5 % (250 mg) with traces of the cis-spiroamine AMN-2^{cis}. After purification by chromatography [silica gel 60 (20 g); methanol (200 ml)] the trans-spiroamine AMN-2^{trans} (170 mg) with a melting point of 296-299 °C was obtained.

^{1}H NMR (600 MHz, DMSO-d_6): 1.55 (m, 2 H) 1.62 (m, 2 H) 1.88 (s, 6 H) 2.26 (m, 2 H) 2.43 (m, 2 H) 2.55 (t, **J** = 5.49 Hz, 2 H) 2.96 (t, **J** = 5.25 Hz, 2 H) 6.91 (m, 1 H) 6.99 (m, 1 H) 7.08 (m, 1 H) 7.14 (m, 1 H) 7.20 (d, **J**= 7.64 Hz, 1 H) 7.32 (m, 2 H) 7.40 (m, 1 H) 10.63 (s, 1 H)

Comparison example AMN-3^{cis}

6'-Fluoro-2',3',4',9'-tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)

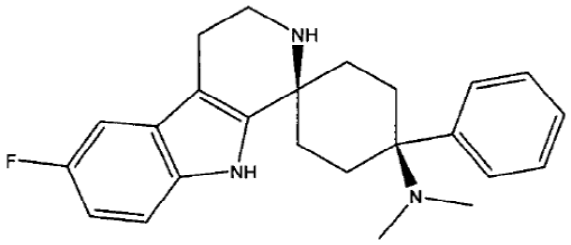


The ketone E-2 (9.6 g, 41.2 mmol) and fluorotryptamine H-2 (7.3 g, 41.2 mmol) were dissolved in ethanol (200 ml) and heated for 12 hours at reflux. The ethanol was then distilled off and the crude product was suspended in 1,2-dichloroethane (100 ml). Trifluoroacetic acid (90 ml) was added to the reaction mixture and stirring was carried out for 12 h at room temperature. The progress of the reaction was monitored by TLC. For working up, the batch was rendered basic with 500 ml of 1N NaOH solution at 0°C and then extracted 3x with 500 ml of ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure. After addition of methanol (100 ml), a white solid precipitated upon stirring and was filtered off with suction over a frit. The solid was washed with methanol (2 **x** 25 ml) and then dried. It was the cis-diastereomer AMN-3^{cis} which was obtained as a white solid in a yield of 3.6 g (22 %).

^{1}H NMR (DMSO-d6, 400 MHz): δ 10.39(s, 1H), 7.44-7.49 (m, 1H), 7.11-7.24 (m, 4H), 7.00-7.04 (m, 1H), 6.72-6.78 (m, 1H), 2.95-2.98 (t, 2H), 2.48-2.50 (m, 1H), 2.36-2.39 (d, 2H), 1.98-2.11 (m, 2H), 1.91 (s, 6H), 1.51-1.67 (m, 5H)
MS m/z (M+1): 396.4; Purity (HPLC): 95.03%

Comparison example AMN-4^{cis}

6'-Fluoro-2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(phenyl)-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)

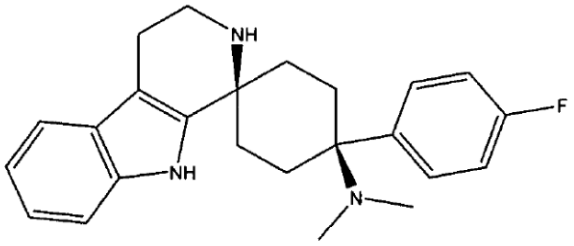


The ketone E-1 (8.4 g, 47 mmol) and fluorotryptamine H-2 (10.2g, 47 mmol) were dissolved in ethanol (200 ml) and heated for 12 hours at reflux. The ethanol was then distilled off and the crude product was suspended in 1,2-dichloroethane (120 ml). Trifluoroacetic acid (100 ml) was added to the reaction mixture and stirring was carried out for 12 h at room temperature. The progress of the reaction was monitored by TLC. For working up, the batch was rendered basic with 1N NaOH solution at 0°C and then extracted 3x with 500 ml of ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure. After addition of methanol (100 ml), a white solid precipitated upon stirring and was filtered off with suction over a frit. The solid was washed with methanol (2 **x** 25 ml) and then dried. It was the cis-diastereomer AMN-4^{cis}, which was obtained as a white solid in a yield of 4 g (28 %).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.36(s, 1H), 7.45-7.42 (t, 4H), 7.32-7.29 (m, 1H), 7.14- 7.10 (m, 1H), 7.03-7.00 (m, 1H), 6.76-6.71 (m, 1H), 2.99-2.96 (t, 2H), 2.40-2.37 (d, 2H), 2.13- (m, 2H), 1.91 (s, 6H), 1.88 (s, 1H), 1.65-1.54 (m, 4H), 1.23 (s, 1H).

Comparison example AMN-5^{cis}

2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(4-fluorophenyl)-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)



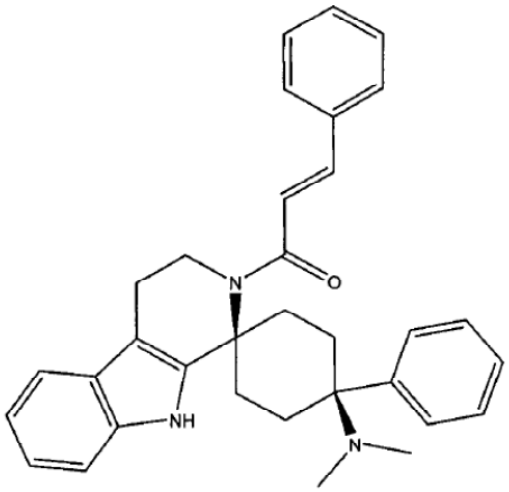
The ketone E-3 (2800 mg, 11.90 mmol) and tryptamine (H-1, 1910 mg, 11.90 mmol) were dissolved under argon in dry methanol (119 ml) and stirred for 18 h. The methanol was distilled off in vacuo and the residue suspended in 1,2-dichloroethane (119 ml). Trifluoroacetic acid (11.9 ml) was added to the reaction mixture and stirring was carried out for 2 h at room temperature. The reaction mixture was then diluted with 1,2-dichloroethane (119 ml) and adjusted to pH 11 with 1N sodium hydroxide solution while cooling with ice. A pale precipitate formed. The mixture was stirred overnight at room temperature. The precipitate was filtered off with suction, washed with water and dried in vacuo. The cis-diastereomer AMN-5^{cis} (m.p. 249-250 °C, in some cases 225-230 °C) could be isolated in a yield of 80 % (3610 mg, 9.56 mmol). The phases were separated. The organic phase was dried with sodium sulphate, filtered, and freed of volatile constituents in vacuo. The pale residue (trans-diastereoisomer AMN-5^{trans}) was taken up in methanol (5 ml) and stirred for 48 h. The precipitate was filtered off and dried in vacuo. The trans-diastereoisomer AMN-5^{trans} (268-271 °C) could be isolated in a yield of 6 % (279 mg, 0.74 mmol).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-D_6) δ ppm: 22.8 (1 C), 27.3 (2 C), 32.6 (2 C), 37.8 (2 C), 38.6 (1 C), 51.2 (1 C), 60.5 (1 C), 106.7 (1 C), 110.8 (1 C), 114.2 (2 C, d, J = 21 Hz), 117.2 (1 C), 117.9 (1 C), 120.0 (1 C), 126.9 (1 C), 129.7 (2 C, d, J = 8 Hz), 132.8 (1 C, d, J = 3 Hz), 135.4 (1 C), 141.4 (1 C), 160.7 (1 C, d, J = 242 Hz)

Synthesis of the cis-spiroamide examples (AMD^{cis})

Example AMD-1^{cis}:

(E)-2',3',4',9'-tetrahydro-N,N-dimethyl-4-phenyl-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine methane sulfonate (1:1) (cis-diastereomer)

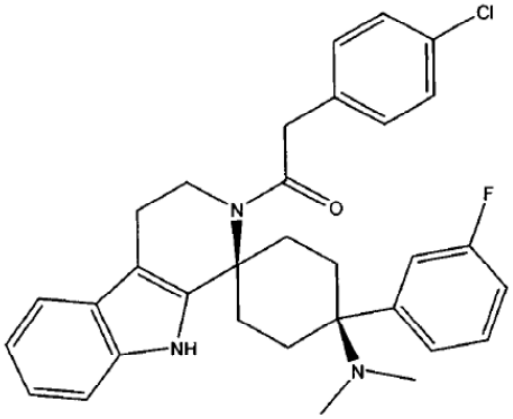


AMN-1^{cis} was dissolved in THF (8 ml). Cinnamic acid chloride (254 mg, 1.53 mmol) and diisopropylethylamine (216 mg, 1.67 mmol) were then added and stirring was carried out for 2 d at RT. Once the reaction was complete the solid was filtered off and saturated Na_2CO_3 solution added to the filtrate. The aqueous phase was extracted three times, each time with 10 ml of ethyl acetate. The organic phase was then dried over $MgSO_4$ and concentrated in a rotary evaporator. The crude product was purified by column chromatography [silica gel 60; DCM/methanol (19 : 1, 570 ml)]. The product was obtained in a yield of 174 mg (26 %). In order to prepare the methanesulfonate, the spiroamide just obtained (174 mg, 0.355 mmol) was suspended in DCM (6 ml) and methanesulfonic acid (23.7 µl, 0.355 mmol) was added at RT. Acetone (0.8 ml) was then added and sufficient diethyl ether was added to disperse the cloudiness that occurred by shaking. Shaking was carried out for a further 30 min. and the resulting solid was then filtered off with suction, washed with diethyl ether, and dried for 3h at 50°C under an oil pump vacuum. The product AMD-1^{cis} was obtained in a yield of 159 mg (76 %).

^{1}H NMR (600 MHz, DMSO-d_6) 1.65 (t, **J** =13.22 Hz, 2 H) 2.20 (t, **J** = 12.84 Hz, 2 H) 2.51 (d, **J** = 4.53 Hz, 9 H) 2.87 - 3.16 (m, 4 H) 4.13 (br. s., 2 H) 6.92 (t, **J** = 7.55 Hz, 1 H) 6.99 (t, **J** = 7.55 Hz, 1 H) 7.20 (d, **J** = 8.31 Hz, 1 H) 7.31 (d, **J**= 7.55 Hz, 1 H) 7.36 - 7.51 (m, 5 H) 7.56 - 7.69 (m, 3 H) 7.74 (d, **J** = 7.55 Hz, 2 H) 7.82 (d, **J** = 7.55 Hz, 2 H) 9.62 (br, s, 1 H)

Comparison example AMD-2^{cis}

2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluoro-phenyl)-2'-(4-chlorobenzyl)-carbonyl-spiro-[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)

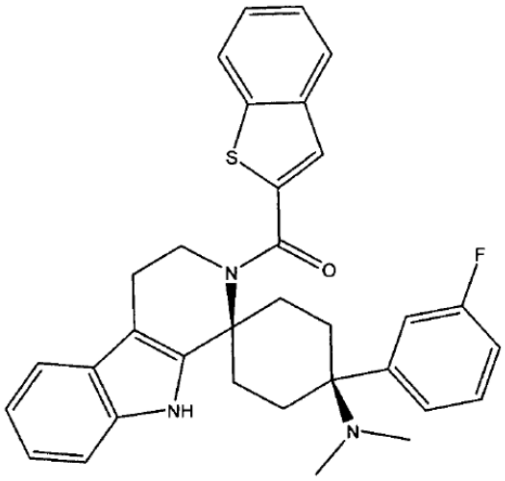


The spiroamine (AMN-2^{cis}; 396 mg, 1.05 mmol) was suspended in DCM (15 ml) in a microwave-compatible vessel and 2-(4-chlorophenyl)acetyl chloride (397 mg, 2.1 mmol) und diisopropylethylamine (269 mg, 2.1 mmol) were added. The reaction mixture was irradiated for 10 min. at 120°C in the microwave (Initiator Eight, Firma Biotage). Once the reaction was complete (TLC monitoring) the reaction mixture was first filtered, diethyl ether (15 ml) was added, and filtering was carried out again. Saturated Na_2CO_3 solution (8ml) was added. Following separation of the phases the aqueous phase was again washed with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated in a rotary evaporator. The crude product was purified by column chromatography [silica gel 60; DCM/methanol (19 : 1)]. The product AMD-2^{cis} was obtained in a yield of 91 mg (16 %).

^{1}H NMR (600 MHz, DMSO-d_6) d ppm 1.55 (t, **J** = 13.60 Hz, 2 H) 1.79 (t, **J** = 12.84 Hz, 2 H) 1.92 (br. s., 6 H) 2.60 - 2.70 (m, 2 H) 2.73 - 2.87 (m, 2 H) 3.17 (d, **J** = 5.29 Hz, 2 H) 3.89 – 4.01 (m, 4 H) 6.90 (t, **J** = 7.55 Hz, 1 H) 6.97 (t, **J** = 7.55 Hz, 1 H) 7.08 - 7,16 (m, 1 H) 7.18 (d, **J** = 8.31 Hz, 1 H) 7.21 - 7.30 (m, 3 H) 7.34 (q, **J** = 8.31 Hz, 4 H) 7.46 (q, **J** = 7.30 Hz, 1 H) 10.53 (s, 1 H)

Comparison example AMD-3^{cis}

2',3',4',9'-tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(benzothiophen-2-yl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)

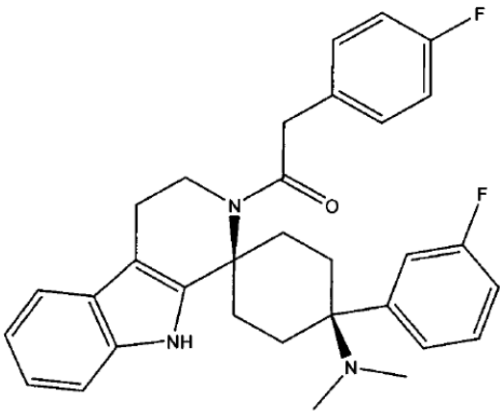


The spiroamine (AMN-2^{cis} 264 mg, 0.7 mmol) was suspended in DCM (7 ml) in a microwave-compatible vessel and benzo[b]thiophen-2-carbonylchloride (239 mg, 1.21 mmol) and diisopropylethylamine (180 mg, 1.4 mmol) were added. The reaction mixture was irradiated for 10 min. at 100°C in the microwave (Initiator Eight, Firma Biotage). Once the reaction was complete (TLC monitoring) the reaction mixture was diluted with DCM (15 ml) and filtered. Saturated Na_2CO_3 solution (8 ml) was added to the mother liquor. Following separation of the phases the aqueous phase was washed twice more with DCM. The combined organic phases were dried over $MgSO_4$ and concentrated in a rotary evaporator. The crude product was purified by column chromatography [silica gel 60; DCM/methanol (19 : 1)]. The product AMD-3^{cis} was obtained in a yield of 125 mg (33 %).

^{1}H NMR (600 MHz, DMSO-d_6) d ppm 1.63 - 1.79 (m, 2 H) 1.83 - 1.93 (m, 2 H) 1.95 (s, 6 H) 2.60 (d, J = 13.60 Hz, 2 H) 2.65 (t, J = 5.67 Hz, 2 H) 2.78 - 2.94 (m, 2 H) 4.08 - 4.22 (m, 2 H) (t, J = 7.55 Hz, 1 H) 6.99 (t, J = 7.55 Hz, 1 H) 7.16 (t, J = 8.31 Hz, 1 H) 7.23 (d, J = 8.31 Hz, 1 H) 7.26 - 7.36 (m, 3 H) 7.44 - 7.54 (m, 3 H) 7.95 (s, 1 H) 8.03 (d, J = 7.55 Hz, 1 H) 8.07 (d, J = 8.31 Hz, 1 H) 10.66 (s, 1 H)

Comparison example AMD-4^{cis}

2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluoro-phenyl)-2'-(4-fluorobenzyl)-carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine methane-sulfonate (cis-diastereomer)

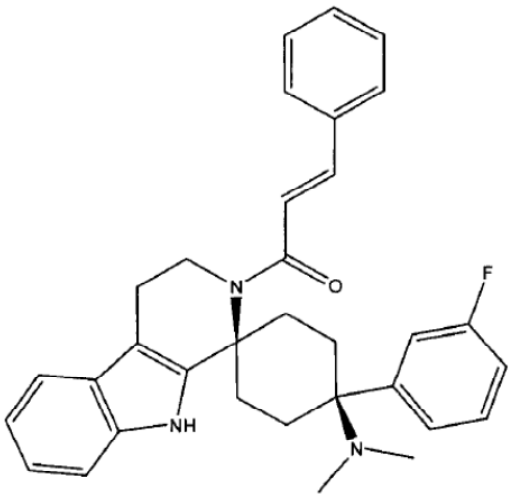


The spiroamine (AMN-2^{cis};600 mg, 1.59 mmol) was suspended in DCM (15 ml) in a microwave-compatible vessel and 2-(4-fluorophenyl)acetyl chloride (548 mg, 3.18 mmol) and diisopropylethylamine (408 mg, 3.18 mmol) were added. The reaction mixture was irradiated for 10 min. at 130°C in the microwave (Initiator Eight, Firma Biotage). Once the reaction was complete (TLC monitoring) the reaction mixture was first filtered, the mother liquor was diluted with DCM (45 ml), and saturated Na_2CO_3- solution (25 ml) was added. After separation of the phases the organic phase was again washed with saturated Na_2CO_3 solution. The organic phase was dried over $MgSO_4$ and concentrated in a rotary evaporator. The crude product was purified by column chromatography [silica gel 60; DCM/methanol (4 : 1)]. The product was obtained in a yield of 150 mg (18 %). In order to prepare the methanesulfonate, the spiroamide (150 mg, 0.29 mmol) was dissolved in DCM (1 ml) and methanesulfonic acid (18.9 µl, 0.29 mmol) was added at RT. It was diluted with diethyl ether so that a stirrable mixture formed. The solid was filtered off with suction, with the exclusion of air, washed with diethyl ether, and dried at 50°C under oil pump vacuum. The product AMD-4^{cis} was obtained in a yield of 148 mg (83 %).

^{1}H NMR (600 MHz, DMSO-d_6) d ppm 1.58 (t, J = 12.84 Hz, 2 H) 2.16 (t, J = 12.09 Hz, 2 H) 2.31 (s, 3 H) 2.53 - 2.58 (m, 6 H) 2.58 - 2.68 (m, 2 H) 2.83 - 3.03 (m, 4 H) 3.98 (s, 2 H) 3.99 - 4.06 (m, 2 H) 6.92 (t, J = 7.18 Hz, 1 H) 6.99 (t, J = 7.18 Hz, 1 H) 7.14 (t, J = 8.31 Hz, 2 H) 7.18 (d, J = 8.31 Hz, 1 H) 7.29 (d, J = 7.55 Hz, 1 H) 7.36 (t, J = 6.42 Hz, 2 H) 7.45 (t, J = 7.93 Hz, 1 H) 7.58 - 7.75 (m, 3 H) 9.65 (br. s., 1 H)

Example AMD-5^{cis}

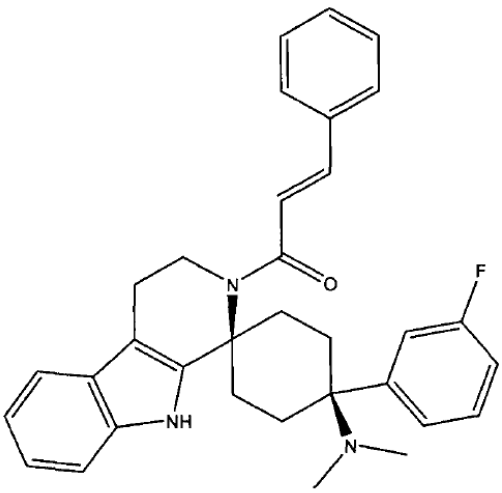
(E)-2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)



The spiroamine (AMN-2^{cis}; 378 mg, 1.0 mmol) was dissolved in dry aprotic solvent (6 ml), cinnamoyl chloride (183 mg, 1.1 mmol) and diisopropylethylamine (155 mg, 1.2 mmol) were added and stirring was carried out overnight at RT. Once the reaction was complete (TLC monitoring) the solvent was removed, the residue subject to aqueous working up, and extraction carried out with halogenated solvent. The combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography. During the concentration a solid precipitated, was filtered off and then dried. The product was obtained in a yield of 220 mg (43 %).

^{1}H NMR (600 MHz, DMSO-d_6) d ppm 1.63 (t, J = 13.60 Hz, 2 H) 1.84 (t, J = 13.22 Hz, 2 H) 1.91 (s, 6 H) 2.54 - 2.63 (m, 2 H) 2.65 (t, J = 5.67 Hz, 2 H) 2.82 - 3.02 (m, 2 H) 3.17 (d, J = Hz, 2 H) 4.00 - 4.22 (m, 2 H) 6.90 (t, J = 7.18 Hz, 1 H) 6.97 (t, J = 7.55 Hz, 1 H) 7.11 – 7.18 (m, 1 H) 7.20 (d, J = 8.31 Hz, 1 H) 7.23 - 7.33 (m, 3 H) 7.35 - 7.54 (m, 5 H) 7.72 (d, J = 6.80 Hz, 2 H) 10.59 (s, 1 H)

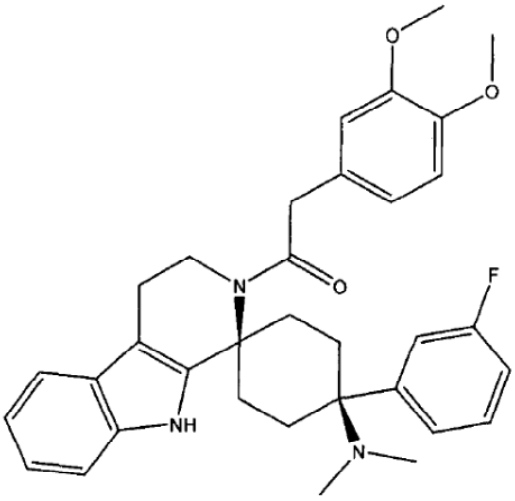
Example AMD-6^{cis}*:*
(E)-2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine citrate (cis-diastereomer)



In order to prepare the salt, the amide AMD-5^{cis} (220 mg, 0.43 mmol) was dissolved in dry aprotic solvent (1.5 ml) and citric acid (83 mg, 0.43 mmol), dissolved in as little protic solvent as possible, was added. In order to precipitate the product, non-polar solvent was added dropwise. The solid was then filtered off with suction, with the exclusion of air, and dried at 50°C under oil pump vacuum. The product AMD-6^{cis} was obtained in a yield of 100 mg (33 %).

Comparison example AMD-7^{cis}

2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(3,4-dimethoxybenzyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)



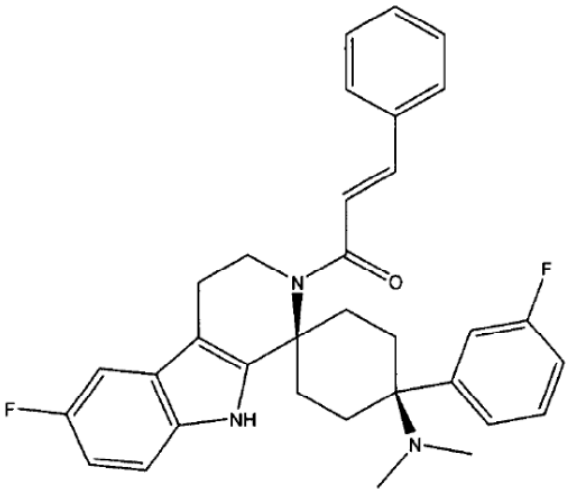
The spiroamine (AMN-2^{cis}; 200 mg, 0.54 mmol) was suspended in halogenated solvent (5 ml) in a microwave-compatible vessel and 2-(3,4-chlorophenyl)acetyl chloride (230 mg, 1.1 mmol) and diisopropylethylamine (138 mg, 1.1 mmol) were added. The reaction mixture was irradiated for 10 min. at 120°C in the microwave (Initiator Eight, Firma Biotage). Once the reaction was complete (TLC monitoring), filtering was first carried out and NaOH solution was then added (5 N, 10 ml) to the mother liquor. Following separation of the phases, the aqueous phase was extracted three times with a polar, aprotic solvent (5 ml in each case). The combined organic

phases were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography. The product AMD-7^{cis} was obtained in a yield of 140 mg (47 %).

^{1}H NMR (600 MHz, DMSO-d_6) d ppm 1.54 (t, J = 12.46 Hz, 2 H) 1.79 (t, J = 13.22 Hz, 2 H) 1.85 - 1.96 (m, 6 H) 2.52 - 2.60 (m, 2 H) 2.62 - 2.72 (m, 2 H) 2.73 - 2.89 (m, 2 H) 3.74 (s, 3 H) 3.77 (s, 3 H) 3.82 (br. s., 2 H) 3.90 (br. s., 2 H) 6.83 - 6.93 (m, 4 H) 6.97 (t, J = 7.55 Hz, 1 H) 7.13 (t, J = 7.18 Hz, 1 H) 7.19 (d, J = 8.31 Hz, 1 H) 7.20 - 7.32 (m, 3 H) 7.41 - 7.54 (m, 1 H) 10.53 (s, 1 H)

Example AMD-8^{cis}

(E)-2',3',4',9'-Tetrahydro-N,N-dimethyl-6'-fluoro-4-(3-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)

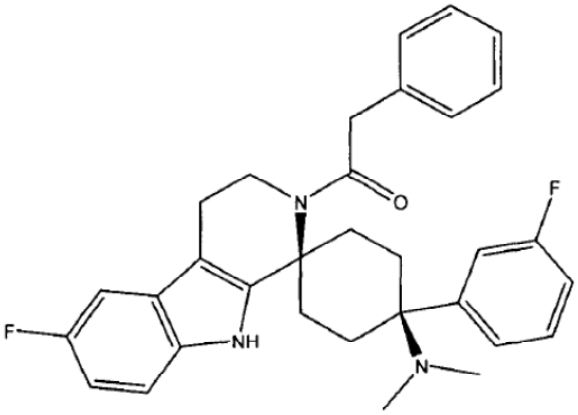


A suspension of the spiroamine AMN-3^{cis} (0.197 g; 0.5 mmol; 1 eq.) in 15 ml of abs DCM was placed in a microwave vessel. Ethyl-diisopropylamine (0.129 g; 1 mmol; 2 eq.) and cinnamic acid chloride (0.166 g; 1 mmol; 2 eq.) were added in succession to this suspension. The microwave vessel was closed and heated in the microwave (Initiator Eight, Firma Biotage) for 10 min at 120°C. For working up, 4 ml of water and 4 ml of 1N sodium hydroxide solution were added to the reaction mixture. The mixture was stirred for 2h at RT. The phases were then separated and the aqueous phase was extracted 3x with DCM. The combined organic phases were washed with water and dried over sodium sulfate. After the solvent was removed at reduced pressure, the residue was purified by column chromatography (silica gel; ethyl acetate/cyclohexane 1:2 → 1:0). 0.087 g of product AMD-8^{cis} (33 %) was obtained.

HPLC/MS analysis: R_t = 4.2 min; Purity (UV 200-400 nm) 97%; m/z = 526.1

Comparison example AMD-9^{cis}

2',3',4',9'-Tetrahydro-N,N-dimethyl-6'-fluoro-4-(3-fluorophenyl)-2'-(benzyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)

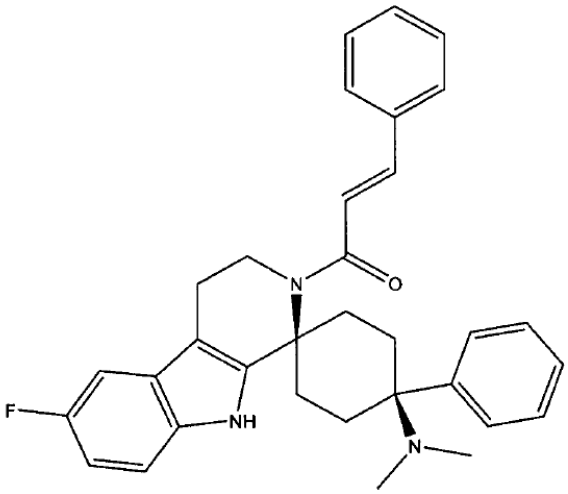


A suspension of the spiroamine AMN-3^{cis} (0.25 g; 0.63 mmol; 1 eq.) in 19 ml of abs DCM was placed in a microwave vessel. Ethyl- diisopropylamine (0.163 g; 1.26 mmol; 2 eq.) and 2-phenylacetyl chloride (0.195 g; 1.26 mmol; 2 eq.) were added in succession to this suspension. The microwave vessel was closed and heated for 10 min at 120°C in the microwave (Initiator Eight, Firma Biotage). For working up, 5 ml of water and 5 ml of 1N sodium hydroxide solution were added to the reaction mixture. The mixture was stirred for 2h at RT. The phases were then separated and the aqueous phase was extracted 3x with DCM. The combined organic phases were washed with water and dried over sodium sulfate. After the solvent was removed at reduced pressure, the residue was purified by column chromatography (silica gel ; ethyl acetate→ ethyl acetate/methanol 9:1). 0.145 g of product AMD-9^{cis} (45 %) was obtained.

HPLC/MS analysis: R_t = 3.9 min; Purity (UV 200-400 nm) 98%; m/z = 514.1

Example AMD-10^{cis}

(E)-2',3',4',9'-Tetrahydro-N,N-dimethyl-6'-fluoro-4-phenyl-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)

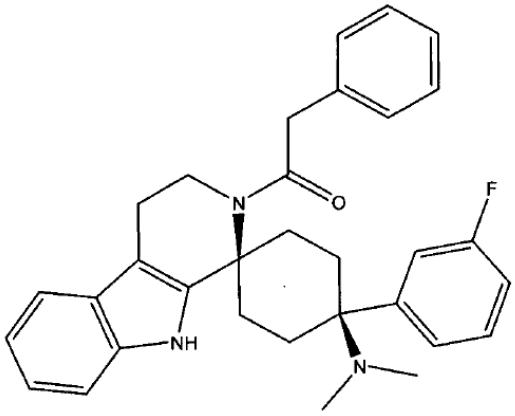


A solution of the spiroamine AMN-4^{cis} (0.15 g; 0.397 mmol; 1 eq.) in 9 ml of abs THF was added under nitrogen at RT to a solution of cinnamic acid chloride (0.198 g; 1.192 mmol; 3 eq.) in 4.5 ml of abs THF. After stirring for 1h at RT, first 3 ml of water and, while cooling with ice, 3 ml of 1N sodium hydroxide solution were added to the cloudy reaction solution. Stirring was carried out for 1.5h. After the solvent had been removed at reduced pressure the resulting solid was filtered off and washed with water. The crude product was purified by column chromatography [silica gel; ethyl acetate). 0.043g of product AMD-10^{cis} (21%) was obtained.

HPLC/MS analysis: R_t = 4.2 min; Purity (UV 200-400 nm) 98%; m/z = 508.2

Comparison example AMD-11^{cis}

2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-benzylcarbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer))



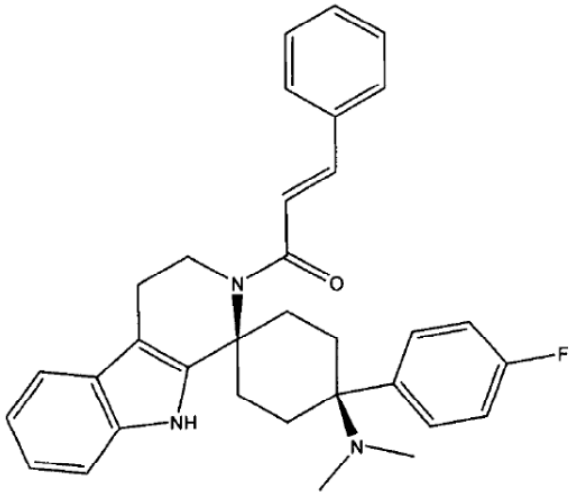
The cis-spiroamine AMN-2^{cis} (1.29 g, 3.4 mmol) was dissolved, with the exclusion of oxygen, in absolute tetrahydrofuran (20 ml) and absolute dichloromethane (120 ml), Hünig base (1.167 ml, 6.8 mmol) was added and 2-phenylacetyl chloride (900 µl, 6.8 mmol) was added at room temperature. After a reaction time of 30 min 5N sodium hydroxide solution (100 ml) was added to the mixture and stirring was carried out for 2 h. The aqueous phase was separated off and

extracted with dichloromethane (3 **x** 10 ml). The combined organic phases were dried over Na_2SO_4 and then concentrated. A crude product was isolated and was separated by chromatography [silica gel 60 (100 g); EtOAc (1000 ml)]. The cis-amide AMD-11^{cis} was obtained as a colourless solid in a yield of 820 mg (49 %) with a melting point of 95-100 °C.

^{13}C-NMR (101 MHz, DMSO-D_6) δ ppm: 22.1, 29.1, 33.0, 38.0, 40.8, 43.1, 60.0, 60.3, 105.5, 111.1, 113.7, 113.2, 114.5, 114.7, 117.3, 118.4, 120.5, 123.8, 126.2, 126.5, 128.2,129.0, 129.3, 135.3, 136.5, 139.5, 140.6, 161.1, 163.5, 173.4

Example AMD-12^{cis}

(E)-2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(4-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (cis-diastereomer)



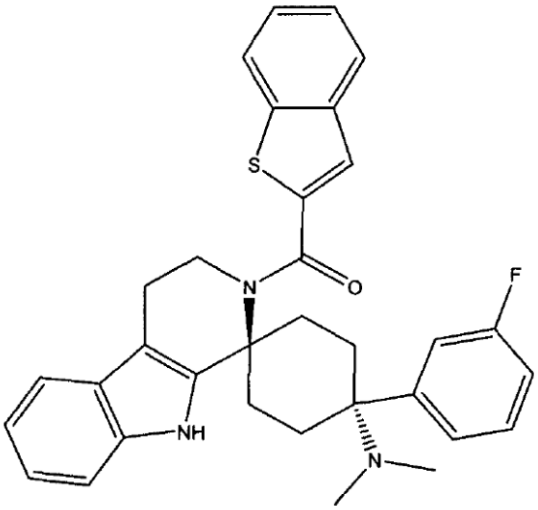
Hünig base (0.45 ml, 342 mg, 2.64 mmol) and cinnamic acid chloride (440 mg, 2.64 mmol), dissolved in absolute dichloromethane (12 ml) were added dropwise in succession in the course of 10 min, under argon, to a suspension of the cis-spiroamine AMN-5^{cis} (500 mg, 1.32 mmol) in absolute dichloromethane (40 ml). The reaction mixture was stirred for 1 h at room temperature, water (30 ml) and 1N sodium hydroxide solution (5 ml) were then added and stirring was carried out for 1.5 h. The dichloromethane was then removed in vacuo. A pale solid precipitate was separated off by filtration and then washed with water (3 x 30 ml). The crude product thus obtained was purified by chromatography [silica gel 60 (70 g), ethyl acetate/cyclohexane 1 : 1 (500 ml), ethyl acetate (1000 ml), ethyl acetate/methanol 10:1 (330 ml), ethyl acetate/methanol 4 : 1 (800 ml), methanol (300 ml)]. For application of the crude product to the column, this had to be dissolved in ethyl acetate/cyclohexane 1 : 1 with a small amount of tetrahydrofuran. The cis-amide AMD-12^{cis} (m.p. 145-155 °C) was obtained as a colourless solid in a yield of 31 % (204 mg, 0.40 mmol).

$^{13}C\{^{1}H\}$-NMR (101 MHz, DMSO-D_6) δ ppm: 22.5 (1 C), 29.3 (2 C), 32.6 (2 C), 37.8 (2 C), 41.3 (1 C), 59.5 (1 C), 60.3 (1 C, br), 105.4 (1 C), 111.1 (1 C), 114.3 (2 C, d, J = 20 Hz), 117.3 (1 C), 118.4 (1 C), 120.5 (1 C), 123.1 (1 C), 126.6 (1 C), 127.9 (2 C), 128.7 (2 C), 129.3 (2 C), 129.8 (2 C, d, J = 8 Hz), 132.4 (1 C, br), 135.1 (1 C), 135.4 (1 C), 139.4 (1 C), 140.4 (1 C), 160.9 (1 C, d, J = 243 Hz), 170.3 (1 C)

Synthesis of the trans-spiroamide comparison examples (AMD^{trans})

Comparison example AMD-3^{trans}

2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(benzothiophen-2-yl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine citrate (1:1) (trans-diastereomer)



2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(benzothiophen-2-yl)carbonyl-spiro[cyclohexane-1,1'(1 'H)-pyrido[3,4-b]indole]-4-amine (trans-diastereoisomer)

Benzo[b]thiophen-2-carboxylic acid chloride (728 mg, 3.96 mmol) was dissolved, under argon, in abs. tetrahydrofuran (30 ml) and the trans-spiroamine AMN-2^{trans} (500 mg, 1.32 mmol), dissolved in abs. tetrahydrofuran (60 ml), was added in the course of 75 min at room temperature. A slight precipitate formed. After a reaction time of 2 h the reaction mixture was diluted with water (15 ml), 1N sodium hydroxide solution (15 ml) was added while cooling with ice, and stirring carried out for 2.5 h. Tetrahydrofuran was removed in vacuo. A solid formed, and was separated by filtration and washed with water (3 **x** 20 ml). The crude product (587 mg) was separated by chromatography [silica gel 60 (80 g); ethyl acetate/cyclohexane 1 : 1 (1 l), ethyl acetate/methanol 4 : 1 (500 ml)]. The trans-amide was thus obtained as a colourless solid in a yield of 12 % (82 mg) with a melting point of 219-221 °C.

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 22.4, 30.0, 30.9, 38.2, 46.4, 58.3, 59.5, 106.2, 111.0, 113.5,

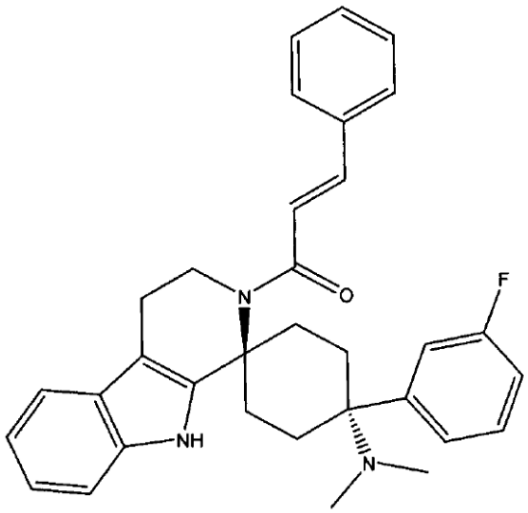
113.7, 114.4, 114.7, 118.0, 119.1, 121.4, 122.5, 123.1, 124.7, 125.5, 125.8, 126.4, 128.7, 136.0, 138.7, 140.1, 140.4, 141.1, 142.1, 161.2, 163.7, 167.1

2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(benzothiophen-2-yl)carbonyl-spiro-[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine citrate (1:1) (trans-diastereomer; AMD-3^{trans})

The trans-amide just prepared (82 mg, 0.152 mmol) was suspended at 80 °C in ethanol (8 ml) and an ethanolic solution (3 ml) of citric acid (32 mg, 0.167 mmol) was added. On cooling to room temperature a solid precipitated from the clear solution. After 1.5 h the mixture was concentrated to 2 ml, diethyl ether (20 ml) was added and stirring was carried out for 20 min. A colourless solid was separated off by filtration and washed with diethyl ether(2x3 ml) (64 mg). After 3 days further solid had precipitated from the filtrate at room temperature and was filtered off with suction and washed with diethyl ether (2x2 ml) (35 mg). The two fractions were combined. The trans-citrate AMD- 3^{trans} was thus obtained in a yield of 81 % (89 mg) with a melting point of 175-185 °C.

Comparison example AMD-6^{trans}

(E)-2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro-[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine citrate (1:1) (trans-diastereomer)



2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (trans-diastereomer)

Cinnamic acid chloride (1.32 g, 7.92 mmol) was dissolved under argon in abs. tetrahydrofuran (30 ml) and impure spiroamine AMN-2^{cis} (1.0 g, 2.64 mmol, contained almost 10% trans-diastereoisomer AMN-2^{trans}), dissolved in abs. tetrahydrofuran (60 ml) was added in the course

of 40 min at room temperature. After a reaction time of 1 h water (20 ml) and, while cooling with ice, 1N sodium hydroxide solution (20 ml) were added to the cloudy reaction solution and stirring was carried out for 1.5 h. Tetrahydrofuran was removed in vacuo. A solid precipitated and was separated off by filtration and washed with water (3 **x** 25 ml). The crude product (1.16 mg) was separated by chromatography [silica gel 60 (200 g); ethyl acetate/cyclohexane 1 : 1 (1.3 l), ethyl acetate (1.6 l)]. The cis-amide was obtained as a colourless solid in a yield of 40 % (540 mg) with a melting point of 155-158 °C. The trans-amide was isolated in a yield of 7 % (93 mg) with a melting point of 151-155 °C.

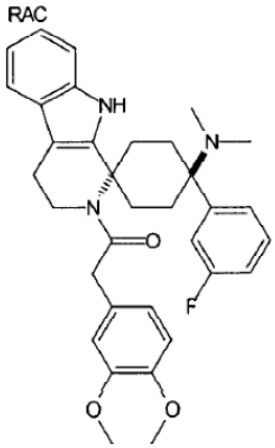
2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(2-phenylvinyl)carbonyl-spiro[cyclo-hexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine citrate (1:1) (trans-diastereomer; AMD-6^{trans})

The trans-amide just obtained (188 mg, 0.37 mmol) was dissolved at 80 °C in ethanol (35 ml) and an ethanolic solution (2 ml) of citric acid (77 mg, 0.4 mmol) was added. Stirring was carried out for 2 h at room temperature, with crystallisation occurring gradually. The mixture was stored for 1.5 h at 5 °C, the colourless solid was separated off by filtration and washed with diethyl ether (3x3 ml) (146 mg). The filtrate was concentrated, taken up in ethanol (1 ml) and diethyl ether (20 ml) was added. After 16 h further colourless salt was separated off and washed with diethyl ether (2x2 ml) (36 mg). The two fractions were combined and the trans-citrate AMD-6^{trans} was obtained in a yield of 71 % (182 mg) with a melting point of 161-164 °C.

^{13}C-NMR (101 MHz, DMSO-D_6) δ ppm: (trans-diastereoisomer) 22.4, 29.2, 30.7, 37.9, 41.5, 58.5, 59.6, 72.0, 105.5, 111.3, 113.2, 113.4, 113.5, 113.8, 117.3, 118.4, 120.5, 122.8, 123.1, 126.5, 127.7, 128.6, 129.1, 129.2, 135.0, 135.6, 139.8, 140.1, 160.7, 163.1, 169.9, 171.2, 175.2

Comparison example AMD-7^{trans}

2',3',4',9'-Tetrahydro-N,N-dimethyl-4-(3-fluorophenyl)-2'-(3,4-dimethoxybenzyl)carbonyl-spiro[cyclohexane-1,1'(1'H)-pyrido[3,4-b]indole]-4-amine (trans-diastereomer)



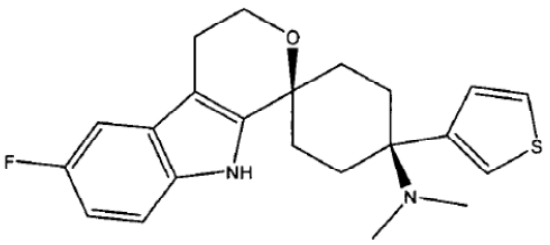
3,4-Dimethoxyphenylacetic acid (1 g, 5.1 mmol, 2.2 eq.) is suspended in 25 ml of abs. toluene and thionyl chloride (0.84 ml, 11.6 mmol, 5.0 eq.) is added. Heating is carried out for 2 h under reflux and the solvent then removed. The residue was codistilled with abs. toluene (3 x 50 ml) and the crude product was dissolved in dichloromethane (37 ml) and transferred to a microwave vessel. Spiroamine AMN-2^{trans} (0.875 mg, 2.32 mmol) and Hünig base (0.78 ml, 580 mmol, 250 eq.) were added, the microwave vessel was closed and heated for 20 min at 120°C in the microwave (Initiator Eight, Firma Biotage). For working up, 17 ml of water and 17 ml of 1N sodium hydroxide solution were added to the reaction mixture. This mixture was stirred for 2h at RT. The phases were then separated and the aqueous phase was extracted 3x with dichloromethane. The combined organic phases were washed with water and dried over sodium sulfate. After the solvent was removed at reduced pressure, the residue was purified by column chromatography (silica gel; ethyl acetate/n-hexane 2:1). 0.236 g of product AMD-7^{trans} (18 %) was obtained.

HPLC/MS analysis: R_t = 5.45 min; Purity (UV 200-400 nm) 99%; m/z = 555.8

Synthesis of the cis spiroether comparison examples (ETHER^{cis})

Comparison example ETHER-1^{cis}

6'-Fluoro-4',9'-dihydro-N,N-dimethyl-4-(3-thienyl)-spiro[cyclohexane 1,1'(3'H)-pyrano[3,4-b]indole]-4-amine, methane sulfonate (2:5) (cis-diastereomer)

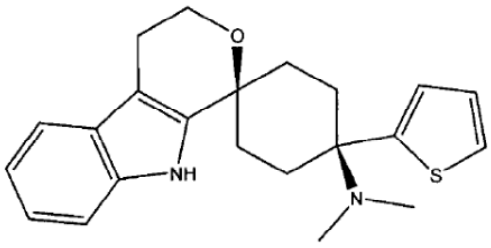


The ketone E-5 (446.6 mg, 2 mmol) was dissolved together with 5-fluorotryptophol (2, 394.4 mg, 2 mmol) in absolute 1,2-dichloroethane (30 ml). Methanesulfonic acid (0.13 ml, 2 mmol) was then added to the mixture, whereupon the colour of the reaction solution changed from reddish brown to dark grey. After 5 min a pale grey solid began to precipitate. The batch was stirred for 20 h at RT. The methanesulfonate of the cis-spiroether was then filtered off with suction and washed with 1,2-dichloroethane (2 x 10 ml). The pale grey solid was obtained in a yield of 76 % (733 mg) and with a melting point of 143-145 °C (ETHER-1^{cis}). 1N NaOH (30 ml) was then added to the filtrate and stirring was carried out for 2 h at RT. The trans-spiroether thereby precipitated as a colourless solid and was obtained after filtration in a yield of 8 % (58.5 mg).

^{1}H NMR (600 MHz, DMSO-d_6): 1.67 (m, 2 H) 1.94 (m, 2 H) 2.24 (m, 2 H) 2.44 (s, 8 H) 2.53 (s, 3 H) 2.54 (s, 3 H) 2.66 (t, J = 5.27 Hz, 2 H) 2.72 (m, 2 H) 3.95 (t, J = 5.28 Hz, 2 H) 6.84 (m, 1 H) 7.14 (m, 1 H) 7.19 (dd, J = 4.50 / 8.70 Hz, 1 H) 7.47 (d, J = 5.10 Hz, 1 H) 7.83 (m, 1 H) 8.07 (m, 1 H) 9.67 (m, 1 H) 10.80 (s, 1 H)

Comparison example ETHER-2^{cis}

4',9'-Dihydro-N,N-dimethyl-4-(2-thienyl)-spiro[cyclohexane 1,1'(3'H)-pyrano[3,4-b]indole]-4-amine, methanesulfonate (1:2) (cis-diastereomer)



The ketone E-4 (223 mg, 1 mmol) was placed together with tryptophol (2, 161 mg, 1 mmol) in absolute dichloromethane (40 ml). Methanesulfonic acid (0.071 ml, 1.1 mmol) was then added. The mixture was stirred for 16 h at RT, whereupon the methanesulfonate of the spiroether precipitated. The pale grey solid (ETHER-2^{cis}) was filtered off with suction, washed with dichloromethane (2 x 10 ml) and obtained in a yield of 25 % (117 mg) with a melting point of 132 °C. 1N NaOH (20 ml) was added to the filtrate and stirring was carried out for 16 h at RT. The organic phase was separated off and the aqueous phase extracted with dichloromethane (2 x 20 ml). The organic phases were combined, dried and concentrated. A substance mixture (274 mg) was thereby obtained and separated by chromatography [silica gel G (20 g); ethyl acetate/methanol 8:1]. The trans-spiroether was obtained in a yield of 54 % ((196 mg, f.p. 235-238 °C), the cis- spiroether in a yield of 10 % (38 mg).

^{1}H NMR (600 MHz, DMSO-d_6)

1.82 (m, 2 H) 1.98 (m, 2 H) 2.33 (m, 2 H) 2.36 (s, 6 H) 2.60 (s, 3 H) 2.61 (s, 3 H) 2.53 (m, 2 H) 2.70 (t, J = 5.23 Hz, 2 H) 3.96 (t, J = 5.23 Hz, 2 H) 6.94 (m, 1 H) 7.00 (m, 1 H) 7.21 (d, J = 8.29 Hz, 1 H) 7.34 (dd, J = 3.74 / 5.28 Hz, 1 H) 7.37 (d, J = 7.37 Hz, 1 H) 7.59 (d, J = 2.76 Hz, 1 H) 7.95 (d, J = 5.32 Hz, 1 H) 9.78 (m, 1 H) 10.74 (s, 1 H)

Equipment and methods for HPLC-MS analysis: HPLC: Waters Alliance 2795 with PDA Waters 996; MS: ZQ 2000 MassLynx Single Quadrupol MS Detector; Column: Waters Atlantis™ dC18, 3 µm, 2.1 x 30 mm; Column temperature: 40°C, Eluent A: purified water + 0.1% formic acid; Eluent B: acetonitrile (gradient grade) + 0.1% formic acid; Gradient: 0% B to 100% B in 8.8 min, 100% B for 0.4 min, 100% B to 0% B in 0.01 min, 0% B for 0.8 min; Flow: 1.0 mL/min; Ionisation: ES+, 25 V; Make up: 100 µL/min 70% methanol + 0.2% formic acid; UV: 200 - 400 nm.

Study of the Pharmacological Properties of the Example Compounds

A) Comparison of the analgesic efficacy (as ED_{50}, or %MPE at a specific test dose) in the acute pain model (tail-flick, rat/mouse) and in mononeuropathy pain models (Chung, Rat; Bennett, Rat) or polyneuropathy pain model (STZ-polyneuropathy, rat).

The surprising pharmacological properties of the compounds according to the invention are described primarily by comparing with one another the results from the mononeuropathy pain model according to Chung in the rate and the tail-flick acute pain model in the rat. This makes it possible to show that the compounds according to the invention do not exhibit a significant anti-nociceptive action in the tail-flick model in the rat at a multiple of a dose which has significant analgesic efficacy in the Chung model (for example ED_{50}^{n}). The findings from further models of neuropathic pain, such as the Bennett model in the rat or STZ polyneuropathy in the rat, underline the generally very good efficacy of the compounds in different forms of neuropathic pain.

Analgesia test in the tail-flick test in the rat

Test animals: female Sprague Dawley rats (crl: CD (SD) outbred; breeder: Charles River, Sulzfeld, Germany); body weight: 130 - 190 g; the animals are kept in standard cages (type IV Makrolon cages, Ebeco, Castrop-Rauxel, Germany) each occupied by a maximum of 8 animals

with a 12:12h light/dark rhythm with feed and tap water ad libitum.

Description of the method: The analgesic efficacy of the test compounds was studied in the burning ray (tail-flick) test in the rat according to the method of D'Amour and Smith (J. Pharm. Exp. Ther. 72, 74 79 (1941)). The animals were placed singly into special test cages and the base of the tail was exposed to a focussed heat ray of a lamp (tail-flick type 50/08/1.bc, Labtec, Dr. Hess). The lamp intensity was so adjusted that the time between the switching on of the lamp and the sudden pulling away of the tail (withdrawal latency) in untreated animals was 2.5-5 seconds. Before administration of a test compound the animals were pre-tested twice within 30 minutes and the mean value of these measurements was calculated as the pre-test mean value. Pain measurement was generally carried out 5, 20, 40, 60, 90, 120, 180 and 240 min following intravenous administration of test compound or its vehicle. The antinociceptive efficacy was determined as the increase in the withdrawal latency according to the following formula: (% MPE) = $[(T_1 - T_0)/(T_2 - T_0)] \times 100$, where T_0 is the control latency period before administration of substance, T_1 the latency period following administration of substance, T_2 the maximum exposure time to the burning ray (12 seconds), MPE: maximum possible effect.

In test compounds having antinociceptive action, the dose dependency was determined by administering 3-5 logarithmically increasing doses, each of which included the threshold dose and the maximum effect dose. The half-maximum effective dose (ED_{50}) with corresponding 95% confidence intervals was determined by semi-logarithmic regression analysis at the time of maximum action.

Statistical evaluation: The group sizes were usually n=10. Variance analysis with repeated measures (repeated measures ANOVA) as well as a post hoc analysis according to Bonferroni were used to test for statistically significant differences in the %MPE data between the respective dose groups and the vehicle control groups. The significance level was set at $p < 0.05$.

Tail-flick with reduced burning ray intensity in the rat

Test animals: male Sprague-Dawley rats (breeder: Janvier, Le Genest St. Isle, France); body weight: 200 - 250 g; the animals are kept in standard cages (type IV Makrolon cages, Ebeco, Castrop-Rauxel, Germany) occupied in each case by a maximum of 5 animals, with a 12:12h light/dark rhythm and with feed and tap water ad libitum.

Description of the method: The modulatory efficacy of the test substances on acute, noxious

thermal stimuli was studied in the burning ray (tail-flick) test in the rat according to the method of D'Amour and Smith (J. Pharm. Exp. Ther. 72, 74 79 (1941)). For this purpose were used. The animals were accommodated singly in special test compartments and the base of the tail was exposed to a focussed burning ray of an analgesia meter (Model 2011, Rhema Labortechnik, Hofheim, Germany). The intensity of the burning ray was so adjusted that the time between the switching on of the burning ray and the sudden pulling away of the tail (withdrawal latency) in untreated animals was approx. 12-13 seconds. Before administration of a substance according to the invention the withdrawal latency was determined twice at an interval of five minutes and the mean value was defined as the control latency period. Measurement of the withdrawal latency of the tail was carried out for the first time 10 minutes after intravenous administration of test compound or its vehicle. Once the antinociceptive effect had subsided (after 2-4 hours) measurements were taken at intervals of 30 minutes up to a maximum of 6.5 hours following substance administration. The anti- or pro-nociceptive action was determined as the increase or reduction in the withdrawal latency period according to the following formula: (% MPE) = [T_1 – $\mathbf{T_0}$)/($\mathbf{T_2}$ - T_0)] x 100. where $\mathbf{T_0}$ is the control latency period before administration of substance, $\mathbf{T_1}$ is the latency period after administration of substance, T_2 is the maximum exposure time to the burning ray (30 seconds), MPE: maximum possible effect. In test compounds having antinociceptive action, the dose dependency was determined by administering 3-5 logarithmically increasing doses, which in each case included the threshold dose and the maximum effective dose. The half-maximum effective dose (ED_{50}) with corresponding 95% confidence intervals was determined by semi-logarithmic regression analysis at the time of maximum action.

Statistical evaluation: The group sizes were usually n=10. Variance analysis with repeated measures (repeated measures ANOVA) as well as a post hoc analysis according to Bonferroni were used to test for statistically significant differences in the %MPE data between the respective dose groups and the vehicle control groups. The significance level was set at $p < 0.05$.

Analgesia test in the tail-flick test in the mouse

Test animals: male NMRI mice (breeder: Charles River, Sulzfeld, Germany); body weight: 20 - 25 g; the animals are kept in standard cages (type III Makrolon cages, Ebeco, Castrop-Rauxel, Germany) each occupied by a maximum of 6 animals, with a 12:12h light/dark rhythm and with feed and tap water ad libitum.

Description of the method: The analgesic efficacy of the test compound was studied in the

burning ray (tail-flick) test in the mouse according to the method of D'Amour and Smith (J. Pharm. Exp. Ther. 72, 74 79 (1941). The animals were placed singly in special test cages and the base of the tail was exposed to a focussed heat ray of an electric lamp (tail-flick type 55/12/10.fl, Labtec, Dr. Hess). The lamp intensity was so adjusted that the time between the switching on of the lamp and the sudden pulling away of the tail (withdrawal latency) in untreated animals was 2.5-5 seconds. Before administration of a test compound the animals were pre-tested twice within 30 minutes and the mean value of these measurements was calculated as the pre-test mean value. Pain measurement was generally carried out 20, 40 and 60 min following intravenous administration of test compound or its vehicle. The antinociceptive action was determined as the increase in the withdrawal latency period according to the following formula: (% MPE) = [(T_1 - T_0)/(T_2 - T_0)] x 100. Where T_0: is the control latency period before administration of substance, T_1: the latency period after substance administration, T_2: the maximum exposure time to the burning ray (12 seconds), MPE: maximum possible effect. In test compounds having antinociceptive action, the dose dependency was determined by administering 3-5 logarithmically increasing doses, each of which included the threshold dose and the maximum effect dose. The half-maximum effective dose (ED_{50}) with corresponding 95% confidence intervals was determined by semi-logarithmic regression analysis at the time of maximum action.

Statistical evaluation: The group sizes were usually n=10. Variance analysis with repeated measures (repeated measures ANOVA) as well as a post hoc analysis according to Bonferroni were used to test for statistically significant differences in the %MPE data between the respective dose groups and the vehicle control groups. The significance level was set at $p < 0.05$.

Chung model: Mononeuropathic pain following spinal nerve ligation

Test animals: Male Sprague Dawley rats (RjHahn:SD outbred; breeder: Janvier, Genest St. Isle, France) with a body weight of 140-160g were kept in standard cages (type IV Makrolon cages, Ebeco, Castrop-Rauxel, Germany) each occupied by a maximum of 8 animals, with a 12:12h light/dark rhythm and with feed and tap water ad libitum. An interval of one week was observed between delivery of the animals and the operation. After the operation the animals were tested several times over a period of 4-5 weeks, with a washout period of at least one week being observed.

Description of the model: Under pentobarbital anaesthesia (Narcoren ®, 60 mg/kg i.p., Merial GmbH, Hallbergmoos, Germany), the left L5, L6 spinal nerves were exposed by removing a piece of the paravertebral muscle and part of the left spinous process of the L5 lumbar vertebra.

The spinal nerves L5 and L6 were carefully isolated and bound with a tight ligature (NC-silk black, USP 5/0, metric 1, Braun Melsungen AG, Melsungen, Germany) (Kim and Chung 1992). After ligation, muscle and adjacent tissue were sutured and the wound closed by means of metal staples. Following a recovery period of one week the animals were placed in cages with a wire floor for measurement of the mechanical allodynia. The withdrawal threshold was determined on ipsi- and/or contralateral rear paws by means of an electronic von Frey filament (Somedic AB, Malmö, Sweden). The median of five stimulations gave a data point. The animals were tested 30 minutes before and at various times after administration of test substance or vehicle solution. The data were determined as % maximum possible effects (%MPE) from the pretests of the individual animals (=0%MPE) and the test values of an independent sham control group (=100%MPE). Alternatively, the withdrawal thresholds were indicated in grams. In test compounds having analgesic action the dose dependency was determined by administering 3-5 logarithmically increasing doses, each of which included the threshold dose and the maximum effective dose. The half-maximum effective dose (ED_{50}) with corresponding 95% confidence intervals was determined by semi-logarithmic regression analysis at the time of maximum action.

Statistical evaluation: The group sizes were usually n=10. Variance analysis with repeated measures (repeated measures ANOVA) as well as a post hoc analysis according to Bonferroni were used to test for statistically significant differences in the %MPE data between the respective dose groups and the vehicle control groups. The significance level was set at $p < 0.05$.

Reference: Kim, S.H. and Chung, J.M., An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat, Pain, 50 (1992) 355-363.

Bennett Model: Mononeuropathic pain in the rat

Test animals: Male Sprague Dawley rats RjHahn:SD outbred; (breeder: Janvier, Genest St. Isle, France) with a body weight of 140-160g were kept in standard cages (type IV Makrolon cages, Ebeco, Castrop-Rauxel, Germany) each occupied by a maximum of 8 animals, with a 12:12h light/dark rhythm and with feed and tap water ad libitum. An interval of one week was observed between delivery of the animals and the operation. After the operation the animals were tested several times over a period of 4 weeks, with a washout period of at least one week being observed.

Description of the method: The study of efficacy in neuropathic pain was carried out in the Bennett model (chronic constriction injury; Bennett and Xie, 1988, Pain 33: 87- 107). Under

narcorene narcosis the rats were provided with four loose ligatures of the right ischiatic nerve. The animals develop oversensitivity of the paw innervated by the damaged nerve, which is quantified, after a recovery phase of one week, for about four weeks by means a 4°C cold metal plate (cold allodynia). The animals are observed on this plate for a period of 2 min. and the number of withdrawal reactions of the damaged paw is measured.

Evaluation and statistics: Based on the preliminary value before substance administration, the action of the substance is determined over a period of one hour at four points in time (e.g. 15, 30, 45, 60 min. following administration), and the resulting area under the curve (AUC) as well as the inhibition of cold allodynia at the individual measuring points are expressed as percentage action relative to the vehicle control (AUC) or the starting value (individual measuring points). The group size is n=10, the significance of an anti-allodynic action ($p<0.05$) is determined by means of a variance analysis with repeated measures and a post hoc analysis according to Bonferroni.

STZ Model: Polyneuropathic pain in the rat

Test animals: Male Sprague-Dawley rats (breeder: Janvier, Le Genest St. Isle, France); body weight: 140 - 160 g; the animals are kept in standard cages (type IV Makrolon cages, Ebeco, Castrop-Rauxel, Germany) each occupied by a maximum of 8 animals, with a 12:12h light/dark rhythm and with feed and tap water ad libitum.

Description of the method: In order to induce diabetes, male Sprague Dawley rats were injected intraperitoneally with streptozotocin (STZ, 75 mg/kg). Diabetic rats had a blood glucose level of at least 17 mM one week after STZ injection. Control animals were injected with a vehicle solution. Determination of the mechanical nociceptive stimulus threshold (in grams) was carried out with an algesiometer in the paw pressure test according to Randall & Selitto (1957). Here an increasing pressure stimulus was exerted on the dorsal surface of the rear paw and the pressure which ultimately led to the reflex withdrawal of the paw or to vocalisation was recorded. The tests took place three weeks after induction of diabetes. The mechanical nociceptive stimulus threshold was measured before and 15, 30, 45 and 60 minutes after administration of substance to diabetic animals and to control animals.

References: Randall LO, Selitto JJ. A method for measurement of analgesic activity on inflamed tissue. Arch. Int. Pharamcodyn. 1957; 111: 409-19

B) Comparison of the analgesically effective dose range in the mononeuropathic pain model (Chung, rat) with the dose range in which opioid-typical side effects are observed.

The surprising pharmacological properties of the compounds according to the invention are described primarily by comparing with one another the results from the Chung model in the rat (as an example of analgesic effectiveness against neuropathic pain) and the blood gas analysis model in the rat (as an example of respiratory depression as a very serious yet readily quantifiable opioid-typical side effect). This makes it possible to show that the compounds according to the invention do not trigger significant respiratory depression in the rat at a multiple of a dose which has significant analgesic efficacy in the Chung model (for example ED_{50}^{n}). The findings from further models of opioid-typical side effects, such as circulatory parameters in the rabbit, gastrointestinal charcoal passage in the mouse, RotaRod test in the mouse, jumping test in the mouse, as well as conditioned place preference in the rat, underline the generally lacking or very slight opioid-typical side effects of the compounds according to the invention.

Blood gas analysis: Method for arterial pCO_2- and pO_2- measurement in the rat

The respiratory depression action of test substances is studied following i.v. administration to awake instrumented rats. The test parameter is the change in the carbon dioxide partial pressure (pCO_2) and oxygen partial pressure (pO_2) in the arterial blood after administration of substance.

Test animals: male Sprague-Dawley rats (crl: CD (SD) outbred; breeder: Charles River, Sulzfeld, Germany); weight: 250 - 275g; the animals are kept singly in standard cages (type II Makrolon cages, Ebeco, Castrop-Rauxel, Germany) with a 12:12h light/dark rhythm and with feed and tap water ad libitum.

Description of the method: At least 6 days before administration of the test substance, a PP catheter is implanted into the femoral artery and the jugular vein of the rats under pentobarbital anaesthesia. The catheters are filled with heparin solution (4000 I.E.) and closed with a wire pin. Administration of the test substance or vehicle is carried out via the venous catheter. Prior to administration of the substance or vehicle and at defined points in time after administration of the substance or vehicle, each arterial catheter is opened and flushed with approx. 500 µl of heparin solution. Approx. 100 µl of blood are then removed from the catheter and taken up by means of a heparinised glass capillary. The catheter is again flushed with heparin solution and reclosed. The arterial blood is immediately analysed using a blood gas analysis device (ABL 5,

Radiometer GmbH. Willich, Germany). After a minimum washout period of one week the animals can again be included in the test.

Test evaluation and statistics: The blood gas analysis device automatically supplies the values for pCO_2 and pO_2 of the blood in mmHg. Effects of the substance on the partial pressure are calculated as percentage changes relative to the preliminary values without substance or vehicle. For statistical evaluation the measured values following administration of the substance and the simultaneous measured values following application of vehicle are compared by means of single-factor variance analysis (one-way ANOVA) as well as a post hoc analysis according to Dunnett. The significance level was set at $p < 0.05$. The group sizes are usually n=6.

Cardiovascular Parameters: Method for measuring blood pressure and cardiac frequency in the awake rabbit.

The action of test substances on the cardiovascular system is studied after i.v. administration to awake rabbits with telemetry. Test parameters are the change in cardiac frequency and arterial blood pressure following administration of substance.

Test animals: female rabbits (New Zealand Whites; breeder: Charles River, Kisslegg, Germany); body weight: approx. 3-5.5 kg; the animals are kept singly in special rabbit cages (W x D x H = 885 x 775 x 600 mm; Ebeco, Castrop-Rauxel, Germany) with a 12:12h light-dark rhythm with feed and tap water ad libitum.

Test preparation: At least 21 days before the start of the experiments a telemetry unit (TL11M2-D70-PCT from DSI, St. Paul, Minnesota, USA) for measuring blood pressure and electrocardiogram (ECG) is implanted into the animals under complete anaesthesia (Isoflurane 2-3%). The pressure catheter of the telemetry unit is thereby introduced into the A. femoralis and the two bipotential electrodes are fixed subcutaneously in the sternum region or in the region of the upper left thorax wall. The transmitter unit is sewn into a skin pocket in the left flank region of the animals. The telemetry signals are recorded by receivers of type RMC-1 (DSI). The Po-Ne-Mah software package (DSI) is used for data recording, data storage and data processing.

Test procedure: Administration of the substance or vehicle is carried out via a venous catheter (V. auricularis). Before administration of the substance or vehicle and at defined points in time after administration of the substance or vehicle, cardiac frequency and arterial blood pressure (systolic, diastolic and mean value) are determined directly by means of the calibrated telemetry

system and stored electronically. After a minimum washout period of one week the animals can again be included in the test.

Test evaluation and statistics: From the measured values for blood pressure (in mmHg) and cardiac frequency (in beats per min) at the defined points in time, the mean values of each of 10 successive heart beats are determined. Effects of the substance on the test parameters are calculated as percentage changes relative to the preliminary values without substance or vehicle. For statistical evaluation, the measured values following administration of substance and the simultaneous measured values following application of vehicle are compared by means of single-factor variance analysis (one-way ANOVA) as well as a post hoc analysis according to Dunnett. The significance level was set at $p < 0.05$. The group sizes are usually n=6.

Charcoal passage test: Method for measuring the gastrointestinal transit speed in the mouse

Test animals: male NMRI mice (breeder: Charles River, Sulzfeld, Germany); body weight: 30 - 35 g; the animals are kept in standard cages (type IV Makrolon cages, Ebeco, Castrop-Rauxel, Germany), each occupied by a maximum of 18 animals, with 12:12h light/dark rhythm and with feed and tap water at libitum.

Description of the test: Before the test the animals are fasted for 20 -24 h on wire-grid cage inserts. An active charcoal suspension (10% active charcoal in 0.5% CMC Lösung; administered volume: 0.1 ml/10g body weight is administered orally to the animals as a marker substance for intestinal passage. The test substance or a vehicle solution is then administered intravenously. Two hours after administration of the active carbon suspension the animals are sacrificed by gassing with CO_2. The intestinal tract is then removed from the stomach up to and including the caecum, and stretched out on a glass plate wetted with 0.9 % NaCl solution. The pylorus - caecum distance and the distance travelled by the charcoal suspension (furthest point) are then immediately measured.

Test evaluation: To determine the relative inhibition of gastrointestinal transit, the quotient distance travelled by the charcoal suspension (in cm) is formed, and indicated in % inhibition. For statistical evaluation the measured values following administration of the substance and the simultaneous measured values following application of vehicle are compared by means of single-factor variance analysis (one-way ANOVA) as well as a post hoc analysis according to Dunnett. The significance level was set at $p < 0.05$. The group sizes are usually n=10.

Rota-Rod Test: Method for studying motor coordination in the mouse

Test animals: male CD-1 mice (breeder: Charles River, Sulzfeld, Germany); body weight: 18 - 25 g; the animals are kept in standard cages (type IV Makrolon cages, Ebeco, Castrop-Rauxel, Germany), each occupied by a maximum of 18 animals, with a 12:12h light/dark rhythm and with feed and tap water ad libitum.

Description of the method: For the description of the method see: Kuribara H., Higuchi Y., Tadokoro S. (1977), Effects of central depressants on Rota-Rod and traction performance in mice. Japan. J. Pharmacol. 27, 117-126.

Statistical evaluation: For statistical evaluation the measured values following administration of the substance and the simultaneous measured values following application of vehicle are compared by means of single-factor variance analysis (one-way ANOVA) as well as a post hoc analysis according to Dunnett. The significance level was set at $p < 0.05$. The group sizes are usually n=10.

Jumping test: Method for studying the physical dependency potential in the mouse

Test animals: male NMRI mice (breeder: Charles River, Sulzfeld, Germany); body weight: 20 - 24 g; the animals are kept in standard cages (type III Makrolon cages, Ebeco, Castrop-Rauxel, Germany) each occupied by a maximum of 6 animals, with a 12:12h light/dark rhythm and with feed and tap water ad libitum.

Description of the method: The test substances are administered intraperitoneally a total of 7x over two days. 5 administrations are carried out on the first day at 9:00, 10:00, 11:00, 13:00 and 15:00 hours and on the second day at 9:00 and 11:00 hours. The first 3 administrations are given in increasing doses (dosage scheme) and further at the dose of the third. Withdrawal is precipitated with naloxone 30 mg/kg (i.p.) 2 hours after the last administration of substance. Immediately afterwards the animals are placed singly in transparent observation boxes (height 40 cm, diameter 15 cm) and the jumping reactions are counted over a period of 15 minutes at 5-minute intervals. Morphine is administered concomitantly in a dose as comparison/standard. Quantification of withdrawal is made by way of the number of jumps 0 to 10 min. following naloxone administration. The number of animals per group with more than 10 jumps / 10 min is determined and documented as “% positive animals”. The average jumping frequency in the

group is also calculated.

Statistical evaluation: The evaluation of the experimental findings in respect of statistically significant differences between the respective dose groups and the vehicle control groups is preferably carried out by means of Fisher's exact test for the parameter "% positive animals" as well as by means of the Kruskal-Wallis test for the parameter "jumping frequency", preferably as described in the experimental section. Here the significance level is set at $p < 0.05$ in each case. The group sizes are usually n=12.

Reference: Saelens JK, Arch Int Pharmacodyn 190: 213-218, 1971

Conditioned place preference: Method of studying the possible induction of mental dependency/addiction in the rat

Description of the method: For the study of place preference see: Tzschentke, T.M., Bruckmann, W. and Friderichs, F. (2002) Lack of sensitization during place conditioning in rats is consistent with the low abuse potential of tramadol. Neuroscience Letters 329, 25-28.

Statistical evaluation: The evaluation of the experimental findings in respect of statistically significant differences in the animals' preference for the active ingredient or the vehicle is preferably carried out by means of the paired t-test. The significance level is set at $p < 0.05$. The group sizes are usually n=8.

Table 1a: Summary of the pharmacological data for example **AMD-6** *cis*

Test system	**Measured parameter**	**Findings** [1]	**Difference factor** [2]
ORL1 receptor binding	Binding affinity	Ki = 0.030 µM	---
µ- opioid receptor binding	Binding affinity	Ki = 0.138 µM	---
Chung, rat	Inhibition of neuropathic pain in mononeuropathy (separation of anti-allodynic and antinociceptive action)	ED_{50} = 9 µg/kg i.V.; up to the highest test dose (21.5 µg/kg i.V.): No antinociceptive action in healthy tissue.	---
Bennett, rat	Inhibition of neuropathic pain in mononeuropathy	ED_{50} = 7 µg/kg i.v.	---
STZ, rat	Inhibition of neuropathic pain in diabetic polyneuropathy	ED_{50} approx. 1 µg/kg i.v.; up to the highest test dose (10 µg/kg i.v.): No antinociceptive action in non-neuropathic control animals.	---
Tail-flick, rat	Inhibition of acute pain (nociceptive pain)	NOEL: 1 mg/kg i.v. or 4.64 mg/kg i.v. at reduced burning ray intensity	220 - 1000x
Blood gas analysis, rat	Respiratory depression measured as increase in arterial pCO_2 and fall in arterial pO_2	NOEL: 1 mg/kg i.v.	220x
Cardiovascular system, rabbit	Arterial blood pressure and cardiac frequency	NOEL: 1 mg/kg i.v.	220x
Charcoal passage,	Gastrointestinal transit	NOEL: 3 mg/kg i.v.	660x

mouse			
RotaRod test, mouse	Motor coordination	NOEL: ≥10 mg/kg i.v.	>2200x
Jumping test, mouse	Physical dependency / withdrawal symptoms	NOEL: 10 mg/kg i.p.	2200x
Place preference, rat	Mental dependency	NOEL: ≥13.8 mg/kg i.p.	>3000x

[1]) NOEL (= No Observed Effect Level) denotes the upper dose without findings (i.e. dose without significant effect)

[2]) The difference factors were calculated as the quotient of NOEL and a mean ED_{50}^{n} from the neuropathy models (here: 4.5 µg/kg)

Table 1b: Summary of the pharmacological data for example **AMD-7** ***cis***

Test system	**Measured parameter**	**Findings** [1]	**Difference factor** [2]
ORL1 receptor binding	Binding affinity	Ki = 0.070 µM	---
µ- opioid receptor binding	Binding affinity	Ki = 0.450 µM	---
Chung, rat	Inhibition of neuropathic pain in mononeuropathy (separation of anti-allodynic and antinociceptive action)	ED_{50} = 88 µg/kg i.v.; no antinociceptive action in healthy tissue. (Test dose: 100 µg/kg i.v.)	---
STZ, mouse	Inhibition of neuropathic pain in diabetic polyneuropathy	68% MPE at 100 µg/kg i.p.; no antinociceptive action in non-neuropathic control animals.	---
Tail-flick, rat	Inhibition of acute pain (nociceptive pain)	NOEL: ≥10 mg/kg i.v.	>110x

Blood gas analysis, rat	Respiratory depression measured as increase in arterial pCO_2 and fall in arterial pO_2	NOEL: 1 mg/kg i.v.	11 x
Cardiovascular system, rabbit	Arterial blood pressure and cardiac frequency	NOEL: ≥3 mg/kg i.v.	>34x
Charcoal passage, mouse	Gastrointestinal transit	NOEL: 1 mg/kg i.v.	11x
RotaRod test, mouse	Motor coordination	NOEL: 10 mg/kg i.v.	110x
Jumping test, mouse	Physical dependency / withdrawal symptoms	NOEL: ≥10 mg/kg i.p.	>110x
Place preference, rat	Mental dependency	NOEL: ≥20 mg/kg i.p.	>220x

[1]) MPE (= Maximum Possible Effect) denotes the size of the maximum possible effect; NOEL (= No Observed Effect Level) denotes the upper dose without findings (i.e.dose without significant effect)

[2]) The difference factors were calculated as the quotient of NOEL and a mean ED_{50}^{n} from the neuropathy models (here: 88 µg/kg)

Conclusion: The example **AMD-6*cis*** was selected to illustrate the surprising pharmacological properties of the compounds used according to the invention.

These are high-affinity ORL1 receptor and μ-opioid receptor ligands having a ratio of ORL1 receptor affinity to μ-opioid receptor affinity of approx. 5 or approx.

6. Example **AMD-6*cis*** proves **that the compounds used according to the invention** have a very high efficacy against neuropathic pain (here: ED_{50}^{n} between 1 and 10 μg/kg i.v. or 88 μg/kg i.V.). In the acute pain model, on the other hand, even at doses which were between 100 and 1000 times higher than the effective doses in the neuropathy model, no significant antinociceptive action was observed. Likewise, in animals for studying side effects, no significant opioid side effects (such as respiratory depression, reduction of blood pressure and cardiac frequency, constipation, central nervous effects, physical dependency, mental dependency/addiction) were observed at doses which were from 11 to more than 3000 times higher.

Table 2: Overview of selected pharmacological or pharmacokinetic characteristics of further examples

Compound	**Ki (ORL_1) [µM]**	**Ki (µ) [µM]**	**Chung, rat**	**Tail-flick, rat**	**Blood gas analysis, rat**	**Charcoal passage, mouse**	**RotaRod, mouse**	**$t_{1/2}$, rat, 100 µg/kg, i.v. *II* pharmacodynamic duration of action (dose)**
AMD-6*cis*	0.030	0.138	ED_{50} = 9 µg/kg i.v.	NOEL[2] = 1000 µg/kg	NOEL = 1000 µg/kg i.v.	NOEL = 3000 µg/kg i.v.	NOEL: ≥10000 µg/kg i.v.	8 h // >> 5 h (10 µg/kg i.v.)
AMD-1*cis*	0.018	0.032	18%MPE at 100 µg/kg	NOEL >100 µg/kg i.v.	NOEL = 1000 µg/kg i.V.	*Not carried out*	*Not carried out*	*not determined II not determined*
AMD-2*cis*	0.017	0.05	35%MPE at 100 µg/kg	NOEL > 1000 µg/kg	*Not carried out*	NOEL = 4600 µg/kg i.v.	*Not carried out*	*not determined II approx.* 3 h (100 µg/kg i.v.)
AMD-3*cis*	0.016	0.059	42%MPE at 100 µg/kg	NOEL > 1000 µg/kg	*Not carried out*	NOEL = 3000 µg/kg i.v.	NOEL: ≥10000 µg/kg i.v.	*not determined II approx.* 3 h (100 µg/kg i.v.)
AMD-4*cis*	0.003	0.009	20%MPE at 100 µg/kg	NOEL >100 µg/kg i.v.	NOEL = 300 µg/kg i.v.	*Not carried out*	*Not carried out*	*not determined II* 1 - 3 h (100 µg/kg i.v.)
AMD-7*cis*	0.070	0.450	ED_{50} = 88 µg/kg i.v.	NOEL ≥ 10000 µg/kg	NOEL = 1000 µg/kg i.v.	NOEL = 1000 µg/kg i.v.	NOEL = 10000 µg/kg i.v.	3 h // approx. 3 h (100 µg/kg i.v.)

[1]) ORL1/µ affinity ratio defined as $1/[K_{i(ORL1)}/K_{i(\mu)}]$

[2]) NOEL (= No Observed Effect Level) denotes the upper dose without findings (i.e. dose without significant effect)

Conclusion: The compounds used according to the invention exhibit very good efficacy against neuropathic pain. Surprisingly, on the other hand, in the acute pain model, even at doses which were between 10 to 100 times higher than the effective doses in the neuropathy model, no significant antinociceptive action was observed. Likewise, surprisingly, no significant opioid-typical side effects were observed in side-effect animal models (e.g. blood gas analysis, gastrointestinal charcoal passage and RotaRod test) at 10 times to more than 300 times higher doses.

Table 3: Comparison of cis- and trans-spiroamine

Compound	**Ki (ORL_1) [µM]**	**Ki (µ) [µM]**	**Chung, rat**	**Tail-flick, rat**	**Blood gas analysis, rat**
AMD-6^{cis}	0.030	0.138	ED_{50} = 9 µg/kg i.v.	NOEL[2] = 1000 µg/kg i.v.	NOEL = 1000 µg/kg i.v.
AMD-6^{trans}	0.002	0.008	NOEL ≥ 100 µg/kg i.v	ED_{50} = 640 µg/kg i.v.	NOEL = 300 µg/kg i.v.
AMD-7^{cis}	0.070	0.450	ED_{50} = 88 µg/kg i.v.	NOEL[2] ≥ 10000 µg/kg i.v.	NOEL = 1000 µg/kg i.v.
AMD-7^{trans}	0.001	0.001	Not carried out	54%MPE at 31.6 µg/kg i.v.	Not carried out
AMN-2^{cis}	0.012	0.031	ED_{50} = 895 µg/kg i.v.	NOEL = 1000 µg/kg i.v.	Not carried out
AMN-2^{trans}	0.0004	0.0005	27%MPE at 30 µg/kg i.v.	60%MPE at 100 µg/kg i.v.	Not carried out

[1]) ORL1/µ affinity ratio defined as $1/[K_{i(ORL1)}/K_{i(\mu)}]$

[2]) NOEL (= No Observed Effect Level) denotes the upper dose without findings (i.e. dose without significant effect)

Conclusion: Surprisingly, only the cis-spiroamines according to the general formula (I) (here example AMD-6^{cis} and comparison example AMN-2$^{\mathbf{cis}}$) exhibit good efficacy against neuropathic pain while at the same time having no antinociceptive action in acute pain. Likewise, no significant opioid-typical side effects are observed in the side-effect animal models (blood gas analysis as an

example here) at doses that are higher by a multiple. The respective trans-spiroamines (here comparison example AMD-6^{trans} and comparison example AMN-2^{trans}), on the other hand, show no difference between doses that are effective against neuropathic pain or against acute pain. Likewise, no difference is observed between doses at which opioid-typical side effects (blood gas analysis as an example here) occur. In the overall comparison AMD-5^{cis} and AMD-6^{cis} show the greatest differences with the highest possible analgesic action.

Table 4: Comparison of cis-spiroamines and cis-spiroethers

Compound	**Ki (ORL_1) [µM]**	**Ki (µ) [µM]**	**Chung, rat**	**Tail-flick, rat or mouse***
AMN-2^{cis}	0.012	0.031	ED_{50} = 895 µg/kg i.v.	$NOEL^2$ = 1000 µg/kg i.v.
Ether-2^{cis}	0.031	0.092	17%MPE at 100 µg/kg i.v	78%MPE at 1000 µg/kg i.v.*
Ether-1^{cis}	0.06	0.12	28%MPE at 100 µg/kg i.v	33%MPE at 1000 µg/kg i.v.

[1]) ORL1/µ affinity ratio defined as $1/[K_{i(ORL1)}/K_{i(\mu)}]$

[2]) NOEL (= No Observed Effect Level) denotes the upper dose without findings (i.e. dose without significant effect)

Conclusion: Surprisingly, when used according to the invention only the cis-spiroamines (here example **AMN-2^{cis}**) exhibit good efficacy against neuropathic pain while at the same time having no antinociceptive action in acute pain. Likewise, no opioid-typical side effects are observed in the side-effect animal models (blood gas analysis as an example here) at doses that are higher by a multiple. Cis-Spiroether (here comparison example **Ether-2^{cis}** and comparison example **Ether-1^{cis}**), on the other hand, show no marked differences between doses which are effective against neuropathic pain or against acute pain.

Table 5: Comparison of AMD-5^{cis} (free base) and AMD-6^{cis} (citrate salt)

Compound	**Ki (ORL_1) [µM]**	**Ki (µ) [µM]**	**Chung, rat**	**Tail-flick, rat**
AMD-5^{cis}	0.030	0.138	ED_{50} = 17 µg/kg i.v.	$NOEL^2$ = 30000 µg/kg i.p.

AMD-6^{cis}	0.020	0.117	ED_{50} = 9 µg/kg i.v.	NOEL > 10000 µg/kg i.v.

[1]) ORL1/µ affinity ratio defined as $1/[K_{i(ORL1)}/K_{i(\mu)}]$

[2]) NOEL (= No Observed Effect Level) denotes the upper dose without findings (i.e. dose without significant effect)

Conclusion: A comparison of **AMD-5^{cis}** (free base) and **AMD-6^{cis}** (citrate salt) revealed no relevant differences in pharmacological properties of base and salt.

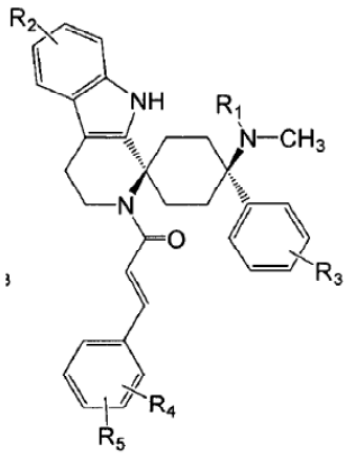
Table 6: Comparison of the affinities towards individual receptors

	ORL1		µ-opioid		k-opioid		d-opioid		pain, rat	
									Acute (tail flick)	neuropathic (SNL [Chung])
	Ki *	**EC_{50}** **	Ki	**EC_{50}**	Ki	**EC_{50}**	Ki	**EC_{50}**	**$ED_{50\ rat}$** [µg/kg] **%mpe** (@µg/kg)	
AMD-3^{cis}	16	102 / 92%	59	1112 / 82%	160	874 / 42%	6.7	41 / 92%	0% (1000) 73% (10000)	106
AMD-**3^{trans}**	14	16 / 81%	12	13 / 66%	49	- / 55%	8	- / 87%	0% (1000)	20% (100)
AMD-5^{cis}	30	76 / 106%	138	300 / 63%	768	1035 / 30%	38	463 / 78%	0% (1000) 58% (10000)	9.2
AMD-6^{trans}	3	47 / 104%	8	79 / 97%	19	59 / 88%	6	19 / 126%	640	400
AMD-**7^{cis}**	70	50 / 90%	450	49 / 94%	542	1170 / 85 %	791	2684 / 106%	0% (10000)	88
AMD-**7^{trans}**	1	16 / 90%	1	3 / 88%	4	29 / 64 %	1	5 / 82 **%**	54 % (31.6)	not carried out
	* Radio-binding assay - Ki in nM									
	** GTPgammaS assay - EC50 in nM and relative efficacy in %									

Ki [nM]

EC_{50} [eff. %]

In a further aspect the invention relates to a compound of the general formula (III)



(III)

wherein the compound is present as hydrochloride, citrate or hemi-citrate salt.

In a further preferred embodiment of the compounds according to the invention, R_2 is -H and/or R_3 is -F.

In a further preferred embodiment of the compounds according to the invention R_4 and R_5 are either both -H or both $-OCH_3$.

In a further preferred embodiment of the compounds according to the invention these are selected from the group consisting of

- (E)-1-((1s,4s)-4-(dimethylamino)-4-phenyl-3',4'-dihydrospiro[cyclohexane-1,1'-pyrido[3,4-b]indole]-2'(9'H)-yl)-3-phenylprop-2-en-1-one;
- (E)-1-((1s,4s)-4-(dimethylamino)-4-(3-fluorophenyl)-3',4'-dihydrospiro[cyclohexane-1,1'-pyrido[3,4-b]indole]-2'(9'H)-yl)-3-phenylprop-2-en-1-one;
- (E)-1-((1s,4s)-4-(dimethylamino)-6'-fluoro-4-(3-fluorophenyl)-3',4'-dihydrospiro-[cyclohexane-1,1'-pyrido[3,4-b]indole]-2'(9'H)-yl)-3-phenylprop-2-en-1-one;

- (E)-1-((1s,4s)-4-(dimethylamino)-6'-fluoro-4-phenyl-3',4'-dihydrospiro[cyclohexane-1,1'-pyrido[3,4-b]indole]-2'(9'H)-yl)-3-phenylprop-2-en-1-one;
- (E)-1-((1s,4s)-4-(dimethylamino)-4-(4-fluorophenyl)-3',4'-dihydrospiro[cyclohexane-1,1'-pyrido[3,4-b]indole]-2'(9'H)-yl)-3-phenylprop-2-en-1-one;

in each case in the form of hydrochloride, citrate or hemi-citrate salt.

In a further preferred embodiment of the invention the compounds according to the invention are medicaments.

A further preferred embodiment of the invention relates to a pharmaceutical composition which contains a physiologically acceptable carrier and one of the compounds according to the invention.

In one preferred embodiment of the pharmaceutical composition according to the invention this is:

- solid, liquid or pasty; and/or
- contains the compound according to the invention in an amount of from 0.001 to 99 wt. % relative to the total weight of the composition.

A further preferred embodiment of the invention relates to a pharmaceutical dosage form containing one of the pharmaceutical compositions described above.

In a further embodiment of the invention the aforementioned dosage form is prepared for administration no more than once daily.

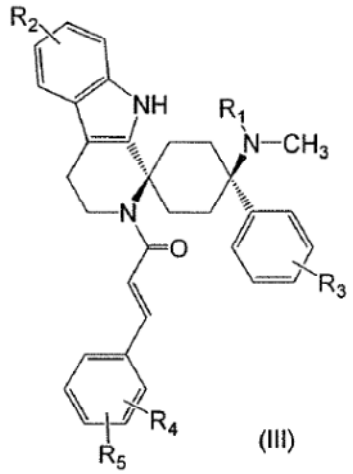
In a further preferred embodiment of the invention the dosage form according to the invention is prepared for systemic administration.

In a further preferred embodiment of the invention the dosage form according to the invention is prepared for oral administration.

In a further preferred embodiment of the invention the dosage form according to the invention contains one of the compounds according to the invention in a dose within the range 1.0 µg to 10 mg, based on the molecular weight of the free base

Endrede patentkrav:

1. Forbindelse av den generelle formelen (III),



(III)

hvor

R_1 er -H eller CH_3;

R_2 er -H eller -halogen;

R_3 er -H eller -halogen;

R_4 er -H, -halogen eller -OC_{1-3}-alkyl; og

R_5 er -H, -halogen eller-OC_{1-3}-alkyl;

hvori forbindelsen er tilstede som hydroklorid, citrat- eller hemi-citratsalt.

2. Forbindelse ifølge krav 1, hvori R_2 er -H og/eller R_3 er -F.

3. Forbindelse ifølge krav 1 eller 2, hvori R_4 og R_5 er enten begge -H eller begge- **OCH_3**.

4. Forbindelse ifølge ett av kravene ovenfor, valgt fra gruppen som består av

- (E)-1-((1s,4s)-4-(dimetylamino)-4-fenyl-3',4'-dihydrospiro[cykloheksan-1,1'-pyrido[3,4-b]indol]-2'(9'H)-yl)-3-fenylenylprop-2-en-1-one;
- (E)-1-((1s,4s)-4-(dimehylamino)-4-(3-fluorofenyl)-3',4'-dihydrospiro[cykloheksan-1,1'-

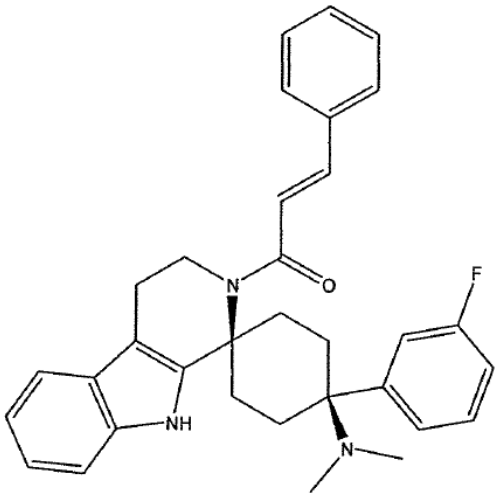
pyrido[3,4-b]indol]-2'(9'H)-yl)-3-fenylprop-2-en-1-one;

- (E)-1-((1s,4s)-4-(dimetylamino)-6'-fluoro-4-(3-fluorofenyl)-3',4'-dihydrospiro-[cykloheksan-1,1'-pyrido[3,4-b]indole]-2'(9'H)-yl)-3-fenylprop-2-en-1-one;

- (E)-1-((1s,4s)-4-(dimetylamino)-6'-fluoro-4-fenyl-3',4'-dihydrospiro[cykloheksan-1,1'-pyrido[3,4-b]indol]-2'(9'H)-yl)-3-fenylprop-2-en-1-one;
- (E)-1-((1s,4s)-4-(dimetylamino)-4-(4-fluorofenyl)-3',4'-dihydrospiro[cykloheksan-1,1'-pyrido[3,4-b]indol]-2'(9'H)-yl)-3-fenylprop-2-en-1-one,

i hvert tilfelle i formen av hydroklorid, citrat- eller hemi-citratsalt.

5. Forbindelser ifølge et hvilket som helst av krav 1 til 4, med strukturen



i formen av hydroklorid, citrat- eller hemi-citratsalt.

6. Forbindelse ifølge ett av krav 1 til 4 for bruk som et legemiddel.

7. Farmasøytisk sammensetning som inneholder en fysiologisk akseptabel bæresubstans og en forbindelse ifølge ett av krav 1 til 5.

8. Sammensetning ifølge krav 7 som

- er fast, flytende eller deigaktig; og/eller

- inneholder forbindelsen ifølge ett av krav 1 til 5 i en mengde fra 0,001 til 90 vekt% relativ til den samlede vekten til sammensetningen.

9. Farmasøytisk doseringsform som inneholder den farmasøytiske sammensetningen ifølge krav 7 eller8.

10 Doseringsform ifølge krav 9, som forberedes for administrasjon ikke mer enn én gang daglig.

11. Doseringsform ifølge krav 9 eller 10 som forberedes for systemisk administrasjon.

12. Doseringsform ifølge krav 11 som forberedes for oral administrasjon.

13. Doseringsform ifølge krav 12, som inneholder forbindelsen ifølge ett av krav 1 til 5 i en dose innenfor området 1,0 µg til 10 mg relative til molekylvekten til den frie basen.

14. Forbindelse ifølge ett av krav 1 til 5 for bruk i behandlingen av nevropatisk og/eller kronisk smerte.

15. Forbindelse for bruk ifølge krav 14, med bruk foretatt ikke mer enn én gang daglig.