Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3139357 A1 2020/11/12

(21) 3 139 357

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2020/05/04
(87) Date publication PCT/PCT Publication Date: 2020/11/12
(85) Entrée phase nationale/National Entry: 2021/11/05
(86) N° demande PCT/PCT Application No.: EP 2020/062268
(87) N° publication PCT/PCT Publication No.: 2020/225189
(30) Priorité/Priority: 2019/05/09 (EP19173586.9)

(51) Cl.Int./Int.Cl. *A61K 31/4375* (2006.01), *A61K 45/06* (2006.01), *A61P 43/00* (2006.01)

(71) Demandeur/Applicant:
BAYER AKTIENGESELLSCHAFT, DE

(72) Inventeurs/Inventors:
DELBECK, MARTINA, DE;
HAHN, MICHAEL, DE

(74) Agent: SMART & BIGGAR IP AGENCY CO.

(54) Titre : DERIVES D'ARYLQUINOZILINE UTILISES COMME ANTAGONISTES DU SOUS-TYPE C DE L'ADRENOCEPTEUR ALPHA2 (ALPHA-2C) POUR LE TRAITEMENT DE L'APNEE DU SOMMEIL

(54) Title: ARYLQUINOZILINE DERIVATIVES AS ALPHA2-ADRENOCEPTOR SUBTYPE C (ALPHA-2C) ANTAGONISTS FOR THE TREATMENT OF SLEEP APNEA

(57) Abrégé/Abstract:
The present invention relates to α2 -Adrenoceptor subtype C (alpha-2C) antagonists, in particular arylquinolizine derivatives of formula (I) for the use in a method for the treatment and/or prophylaxis of sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 November 2020 (12.11.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/225189 A1

(51) International Patent Classification:
A61K 31/4375 (2006.01) *A61P 43/00* (2006.01)
A61K 45/06 (2006.01)

(21) International Application Number:
PCT/EP2020/062268

(22) International Filing Date:
04 May 2020 (04.05.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
19173586.9 09 May 2019 (09.05.2019) EP

(71) Applicant: **BAYER AKTIENGESELLSCHAFT** [DE/DE]; Kaiser-Wilhelm-Allee 1, 51373 Leverkusen (DE).

(72) Inventors: **DELBECK, Martina**; Müllerweg 10, 42579 Heiligenhaus (DE). **HAHN, Michael**; Rietherbach 42D, 40764 Langenfeld (DE).

(74) Agent: **BIP PATENTS**; Alfred-Nobel-Str. 10, 40789 Monheim am Rhein NRW (DE).

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

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

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*

(54) **Title:** ARYLQUINOZILINE DERIVATIVES AS ALPHA2-ADRENOCEPTOR SUBTYPE C (ALPHA-2C) ANTAGONISTS FOR THE TREATMENT OF SLEEP APNEA

(57) **Abstract:** The present invention relates to α2 -Adrenoceptor subtype C (alpha-2C) antagonists, in particular arylquinolizine derivatives of formula (I) for the use in a method for the treatment and/or prophylaxis of sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

WO 2020/225189 A1

ARYLQUINOLINE DERIVATIVES AS ALPHA2-ADRENOCEPTOR SUBTYPE C (ALPHA-2C) ANTAGONISTS FOR THE TREATMENT OF SLEEP APNEA

The present invention relates to α2-Adrenoceptor subtype C (alpha-2C) antagonists, in particular arylquinolizine derivatives of formula (I) for the use in a method for the treatment and/or prophylaxis of sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

Background of the invention

Obstructive sleep apnoea (OSA) is a sleep-related respiratory disorder which is characterized by repeat episodes of obstruction of the upper airways. When breathing in, the patency of the upper airways is ensured by the interaction of two opposite forces. The dilative effects of the musculature of the upper airways counteract the negative intraluminal pressure, which constricts the lumen. The active contraction of the diaphragm and the other auxiliary respiratory muscles generates a negative pressure in the airways, thus constituting the driving force for breathing. The stability of the upper respiratory tract is substantially determined by the coordination and contraction property of the dilating muscles of the upper airways.

Upper airway collapse in OSA is thought to occur at sleep onset because of the reduction of activity of several upper airway dilator muscles, which as a consequence are unable to maintain the anatomically vulnerable airway open. However, some upper airway dilator muscles, including the genioglossus muscle, which is the most important of the dilating muscles of the upper respiratory airway and which is innervated by the hypoglossal nerve, can increase activity during sleep in response to respiratory stimuli, potentially counteracting some of these changes at sleep onset. It was observed that OSA patients have apnea free intervals in which the genioglossus muscle activity is only 25-40% higher compared with sleep phases with frequent obstructive apneas (*Jordan AS, White DP, Lo YL et al., Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea. Sleep 2009, 32(3): 361-8*). Noradrenaline is one of the most potent neuromodulators of hypoglossal motoneuron activity (*Horner R.L. Neuromodulation of hypoglossal motoneurons during sleep. Respir Physiol Neurobiol 2008, 164 (1-2): 179-196*). It is thought, that decreased noradrenergic drive leads to sleep-dependent decline of hypoglossal motoneuron excitability resulting in reduced upper airway dilator muscle activity, especially reduced genioglossus muscle activity.

Alpha2C adrenoceptors regulate the release of noradrenaline from central noradrenergic neurons, they are autoreceptors involved in presynaptic feedback inhibition of noradrenaline (*Hein L. et al, Two functionally distinct alpha2-adrenergic receptors regulate sympathetic neurotransmission Nature 1999, 402(6758): 181-184*). An increase in the activity of the motoneurons of the hypoglossal nerve through Alpha2c adrenoceptor antagonism can stabilize the upper airways and protect them from collapse and occlusion. Moreover, also snoring can be inhibited through the mechanism of stabilization of the upper respiratory airways.

For simple snoring, there is no obstruction of the upper airways. By the narrowing of the upper airways, the flow velocity of the inhaled and exhaled air increases. This together with the relaxed muscles causes fluttering of the soft tissues of the mouth and throat in the airflow. This slight vibration generated the typical snoring sounds.

Obstructive snoring (upper airway resistance syndrome, heavy snoring, hypopnea syndrome) is caused by a recurrent partial obstruction of the upper airway during sleep. This results in an increase in airway resistance and thus to an increase in work of breathing with significant intrathoracic pressure fluctuations. The negative intrathoracic pressure development during inspiration can thereby reach values as they occur as a result of a complete airway obstruction in OSA. The pathophysiological effects on the heart, circulation and sleep quality are the same as in obstructive sleep apnea. The pathogenesis is likely the same as in OSA. Obstructive snoring often provides the precursor for OSA (*Hollandt J.H. et al., Upper airway resistance syndrome (UARS)-obstructive snoring. HNO 2000, 48(8): 628-634*).

Central sleep apnea (CSA) occurs as a result of disturbed brain function or impaired respiratory regulation. CSA is characterized by a lack of drive to breathe during sleep, resulting in repetitive periods of insufficient or absent ventilation and compromised gas exchange. There are several manifestations of CSA. These include high altitude-induced periodic breathing, idiopathic CSA (ICSA), narcotic-induced central apnea, obesity hypoventilation syndrome (OHS), and Cheyne-Stokes breathing (CSB). While the precise precipitating mechanisms involved in the various types of CSA may vary considerably, unstable ventilatory drive during sleep is a principal underlying feature (*Eckert D.J. et al., Central sleep apnea: Pathophysiology and treatment. Chest 2007, 131(2): 595-607*).

US 2018/0235934 A1 describes methods for treating disorders such as obstructive sleep apnea using agents for promoting hypoglossal motoneuron excitability. As agents for promoting hypoglossal motoneuron excitability a disinhibtor and/or stimulant of central noradrenic neurons is described. In some embodiments the disinhibitor of central noradrenergic neurons is an alpha2-adrenoceptor antagonist such as yohimbine or an alpha2-adrenoceptor subtype A (alpha-2A) antagonists or alpha2-adrenoceptor subtype C (alpha-2C) antagonist.The alpha2-adrenoceptor antagonist are selected from the group consisting of Atipamezole, MK-912, RS-79948, RX 821002, [3H]2-methoxy-idazoxan and JP-1302.

Alpha2C adrenoceptors belong to the family of G-protein coupled receptors. Beside the different Alpha1-adrenoceptors three different Alpha2-adrenoceptor subtypes exist (Alpha2A, Alpha2B and Alpha2C). They are involved in the mediation of several diverse physiologic effects in different tissues upon stimulation by endogeneous catecholamines (epinephrine, norepinephrine), either derived from

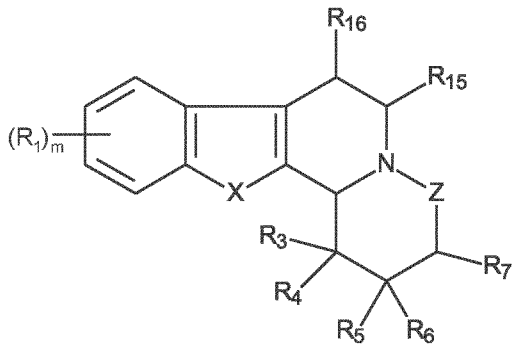
synapses or via the blood. Alpha2 adrenoceptors plays an important physiological role, mainly in the cardiovascular system and in the central nervous system. Alpha2A- and Alpha2C-adrenoceptors are the main autoreceptors involved in presynaptic feedback inhibition of noradrenaline in the central nervous system. The potency and affinity of noradrenaline at the Alpha2C-adrenoceptor is higher than that for the Alpha2A-adrenoceptor. The Alpha2C-adrenoceptor inhibits noradrenaline release at low endogenous concentrations of noradrenaline, while Alpha2A -adrenoceptors inhibit noradrenaline release at high endogenous noradrenaline concentrations (*Uys M.M. et al. Therapeutic Potential of Selectively Targeting the α2C-Adrenoceptor in Cognition, Depression, and Schizophrenia - New Developments and Future Perspective. Frontiers in Psychiatry 2017, Aug 14;8:144. doi: 10.3389/fpsyt.2017.00144. eCollection 2017*).

Aryl piperazines as α2-Adrenoceptor subtype C (alpha-2C) antagonists as well as their preparation and the use thereof as a medicament are known from *WO 03/082866 A1* where the compounds are disclosed as useful for the treatment for disorders such as disorder propagated by stress, Parkinson's disease, depression, schizophrenia, attention deficit hyperactivity disorder, post-traumatic stress disorder, obsessive compulsive disorder, Tourette's syndrome, blepharospasm or other focal dystonias, temporal lobe epilepsy with psychosis, a drug-induced psychosis, Huntington's disease, a disorder caused by fluctuation ofthe levels of sex hormones, panic disorder, Alzheimer's disease or mild cognitive impairment. There is nothing disclosed about the use of these compounds in the treatment of sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

The current gold standard treatment for patients with OSA is continuous positive airway pressure (CPAP). The positive airflow pressure that is generated by an airflow turbine pump splints open the upper airway, reversing all potential causes of pharyngeal collapse, thereby preventing hypopneas, apneas and sleep fragmentation. Unfortunately, up to 50% of all patients with OSA do not tolerate CPAP in the long-term *(M. Kohler, D. Smith, V. Tippett et al., Thorax 2010 65(9):829-32: Predictors of long-term compliance with continuous positive airway pressure).* Therefore, there is still the need to find effective therapeutic agents for the treatment and/or prophalxis of sleep-related breathing disorders such as obstructive sleep apnea. Therefore the object of the present invention is to provide an effective therapeutic agent for the treatment and/or prophalxis of sleep-related breathing disorders, for example of obstructive sleep apnea, central sleep apnea and snoring.

Surprisingly, it has now been found that aryl piperazines of formula (I) of the present invention inhibit upper airway collapsibility and are thus suitable for the production of medicaments for the use in the treatment and/or prophylaxis of sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

The present invention relates to compounds of formula (I)



(I)

wherein

X is CR_2R_2', O, S or NR_2;

Z is $-CHR_8-(CH_2)n-$ or a single bond;

R_1 is is hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C=O)-, CO-, CN, NO_2, NH_2, mono- or di(C_1-C_6)alkylamino or carboxyl;

R_2 and R_2' are independently H, hydroxy or (C_1-C_6)alkyl or R_2 and R_2' form, together with the carbon ring atoms to which they are attached, a carbonyl group;

R_3 is H, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, aryloxy, aryl(C_1-C_6)alkoxy, aryloxy(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, NH_2, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl, carboxyl or (C_1-C_6)alkyl-S-(C_1-C_6)alkyl, wherein the said (C_3-C_7)cycloalkyl or aryl is unsubstituted or substituted with 1or 2 substituents each independently being hydroxy, (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, NH_2, CN or NO_2, or one of R_3 or R_4 and R_6 together form a bond between the ring atoms to which they are attached;

R_4 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl;

R_5 is H, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, aryloxy, aryl(C_1-C_6)alkoxy, aryloxy(C_1-

C_6)alkyl, aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C1-C6)alkyl-CO-O-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl, carboxyl or (C_1-C_6)alkyl-S-(C_1-C_6)alkyl, wherein the said (C_3-C_7)cycloalkyl or aryl is unsubstituted or substituted with 1 or 2 substituents each independently being hydroxy, (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, NH_2, CN or NO_2, or R_4 and R_5 form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring unsubstituted or substituted with 1 to 3 substituent(s) R_9 each independently being hydroxy, (C_1-C_6)alkyl, halogen, NH_2, NO_2, (C_3-C_7)cycloalkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino, mono- or di(C_1-C_6)alkylamino (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, carboxyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, carbamoyl mono- or di(C_1-C_6)alkylcarbamoyl or oxo;

R_6 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl or R_6 forms a bond between the ring atom to which it is attached and the ring atom to which R_7 is attached;

R_7 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl;

R_8 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl or, only when n is 0, R_7 and R_8 form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring unsubstituted or substituted with 1 to 3 substituent(s) R_{10} each independently being hydroxy, (C_1-C_6)alkyl, halogen, NH_2, NO_2, (C_3-C_7)cycloalkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, carboxyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl or oxo;

R_{15} is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl or carboxyl;

R_{16} is H or (C_1-C_6)alkyl;

R_7 and R_8 are attached to the carbon ring atoms, which are adjacent;

m is 0 to 2; and

n is 0 or 1,

or a pharmaceutically acceptable salt or ester thereof, for the use in a method for the treatment and/or prophylaxis of sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

In a possible subgroup of the compounds of formula I X is NR_2.

In another possible subgroup of the compounds of formula I

m is 0; n is 0;

R_2 is H;

R_3 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-COO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO- or (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl;

R_4 is H, hydroxy, (C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl;

R_5 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkyl-CO-;

R_6 is H or (C_1-C_6)alkyl and

R_7 is H, (C_1-C_6)alkyl or hydroxy(C_1-C_6)alkyl.

In another possible subgroup of the compounds of formula I

R_3 is H or (C_1-C_6)alkyl and

R_4 is hydroxy or hydroxy(C_1-C_6)alkyl.

In another possible subgroup of the compounds of formula I R_4 and R_5 form, together with the carbon ring atoms to which they are attached, a condensed six membered saturated carbocyclic ring.

In another possible subgroup of the compounds of formula I R_4 and R_6 together form a bond between the ring atoms to which they are attached or R_6 forms a bond between the ring atom to which it is attached and the ring atom to which R_7 is attached.

In a further possible subgroup of the compounds of formula I the compound is 1α-ethyl-1 ,2,3,4,6,7,12, 12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (1β-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-1-y1)-methanol, 1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, (1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-y1)-methanol, 1,2,3,4,4aβ,5,6,7,8, 13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno-[1,2-*c*]phenanthrene, 1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cβ-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene or 3,4,4aβ,5,6,7,8,13,13bβ,13cα-decahydro-2H-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-one.

In another possible subgroup of the compounds of formula I X is CR_2R_2'.

In a further possible subgroup of the compounds of formula I X is S.

In yet another possible subgroup of the compounds of formula I X is O.

When X is O, one possible subgroup of the compounds of formula I includes R_5 and R_6 as defined in the description of the use of the compounds of formula I above.

Another possible subgroup of the compounds of formula I when X is O is where R_5 is H, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, aryloxy, aryl(C_1-C_6)alkoxy, aryloxy(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl, carboxyl or (C_1-C_6)alkyl-S-(C_1-C_6)alkyl and R_6 is H, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)a1koxy(C_1-C_6)alkyl.

In a further possible subgroup of the compounds of formula I the compound is 1α-Methyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ol, (1α-Methyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (-)-(1α-Methyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (+)-(lα-Methyl-1,3,4,5,6,11-bßhexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, lα-Isopropyl-1,3,4,5,6,11b-Hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ol, 1α-Ethyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ol, (lα-Ethyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, 5,6,7,7aß,8,9,10,11,11aß,11bα-Decahydro-12-oxa-6a-aza-indeno[l,2-*a*]fluorene, 1-Methyl-lα,3,4,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (1-Hydroxymethyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl]-methanol, 1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (-)-1-Methoxymethyl-la-methyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (+)-1-Methoxymethyl-lα-methyl-

1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, 2,3,4,4aß,5,6,7,8,13bß,13cß-Decahydro-1H-13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene, 2,3,4,4aß,5,6,7,8,13bα,13cß-Decahydro-1H-13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene, 1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-carboxylic acid ethyl ester, 1-Ethoxymethyl-lα-methyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (-)-(1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-l-yl)-methanol, (+)-(1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, 1α-Ethyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-carboxylic methyl ester, 1-Methoxymethyl-lα-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (-)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (+)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H11-oxa-4a-aza-benzo[*a*]fluorene, (1α-Ethyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-yl)-methanol, acetic acid 1α-Methyl-1,3,4,5,6,11bßhexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ylmethyl ester, (1α-Methyl-1,2,3,4,6,7,12,12bα-octahydroindeno[2,1-*a*]quinolizin-1-yl)-methanol or (-)-(1S,12bS)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-[1]benzofuro[2,3-a]quinolizine.

In a further possible subgroup of the compounds of formula I the compound is 1α-Ethyl-12-methyl-1,2,3,4,6,7,12bß-octahydroindolo[2,3-*a*]quinolizin-1-ol or 1α-Ethyl-12-ethyl-1,2,3,4,6,7,12bß-octahydroindolo[2,3-*a*]quinolizin-1-ol.

In a further possible subgroup of the compounds of formula I the compound is 2,3,4,4aß,5,6,7,8,13,13bß-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cß-ol, (-)-2,3,4,4aß,5,6,7,8,13,13bß-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cß-ol, (+)-2,3,4,4aß,5,6,7,8,13,13bßdecahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cß-ol, (2,3,4,4aß,5,6,7,8,13,l3bß-Decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthrenyl)-13cß-methanol, 5,6,7,7a,11,11b,12-Decahydro-6a,12-diaza-indeno[1,2-*a*]fluoren11a-ol, 3,4,4aß,5,6,7,8,13,13bß,13cα-decahydro-2H-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-one, 1,2,3,4,5,6,7,8,13,13b-decahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene, acetic acid 1α,2,3,4,4aß,5,6,7,8,13,13bß,13cα-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-yl ester or acetic acid 1ß,2,3,4,4aß,5,6,7,8,13,13bß,13c*α*-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-yl ester.

Another embodiment of the invention provides new compounds which are 2,3,4,5,7,8,13,13b-Octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole, 2ß-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine, 2α-methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine, 1*a*-Ethyl-2α-methyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-1-ol, 1α-Isopropyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-l-ol, (-)-1α-isopropyl-1,2,3,4,6,7,12,12bß-

octahydroindolo[2,3-*a*]quinolizin-1-ol, (+)-1α-isopropyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-l-ol, 1ß-Isopropyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizine, (1α-Isopropyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α-n-Propyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 2-(1α,2,3,4,6,7,12,12bß-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-butan-2-ol, 1-(1,2α,3,4,6,7,12,12bα-Octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-1-ol, 2-(1α,2,3,4,6,7,12,12bß-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-propan-2-ol, 1-*s*-Butyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-l-ol, 1-Cyclohexyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-1-ol, 9-Fluoro-la-isopropyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-l-ol, (1α-Methyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (-)-(1α-Methyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-a]quinolizin-1-yl)-methanol, (+)-(1α-Methyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α-Ethyl-1,4,6,7,12,12bß-hexahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, 3ß,4α-Dimethyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizine, (1,2α,3,4,6,7,12,12bα-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (1,2α,3,4,6,7,12,12bß-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol, (2α-Ethyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol, (1-αEthyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-1-ylmethoxy)-acetic acid ethyl ester, 1-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-ethanone, 1-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-ethanol, 2-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, 2-(3-ethyl-1,2α,3α,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (3-ethyl-2-methyl-1α,2ß,3ß,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-l-yl)-methanol, 3-ethyl-1,2-dimethyl-1α,2ß,3ß,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizine, 1,2-dimethyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-1ß-ol, (1-ethyl-2-methyl-1ß,2ß,3ß,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-3-yl)-methanol or 1-ß-Hydroxymethyl-1-methyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizine-6ß-carboxylic acid methyl ester.

A preferred compound of formula (I) is (-)-(1S,12bS)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-[1]benzofuro[2,3-a]quinolizine.

The terms employed herein have the following meanings:

The term "halo" or "halogen", as employed herein as such or as part of another group, refers to chlorine, bromine, fluorine or iodine.

The term "carboxyl", as employed herein, refers to a -COOH group.

The term "oxo", as employed herein, refers to an = O group.

The term "(C_1-C_6)alkyl", as employed herein as such or as part of another group, refers to a straight or branched carbon chain having 1 to 6 carbon atoms. Representative examples of (C_1-C_6)alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, and the like.

The term "(C_2-C_6)alkenyl", as employed herein as such or as part of another group, refers to a straight or branched chain radical having 2 to 6 carbon atoms, and containing (a) double bond(s).

The term "(C_3-C_7)cycloalkyl", as employed herein as such or as part of another group, refers to a saturated cyclic hydrocarbon group containing 3 to 7 carbons. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

The term "(C_3-C_7)cycloalkyl(C_1-C_6)alkyl", as employed herein refers to a (C_3-C_7)cycloalkyl group, as defined herein, appended to the parent molecular moiety through a (C_1-C_6)alkyl group, as defined herein.

The term "aryl", as employed herein as such or as part of another group, refers to a monocyclic or bicyclic aromatic group containing 6 to 12 carbon atoms. Representative examples of aryl include, but are not limited to, phenyl, naphthyl, and the like.

The term "aryl(C_1-C_6)alkyl", as employed herein as such or as part of another group, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein.

The term "aryloxy", as employed herein as such or as part of another group, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an -O- group.

The term "aryl(C_1-C_6)alkoxy", as employed herein as such or as part of another group, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkoxy group, as defined herein.

The term "aryloxy(C_1-C_6)alkyl", as employed herein, refers to an aryloxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein.

The term "aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl", as employed herein, refers to an aryl(C_1-C_6)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein.

The term "hydroxy", as employed herein as such or as part of another group, refers to an -OH group.

The term "hydroxy(C_1-C_6)alkyl", as employed herein as such or as part of another group, refers to at least one hydroxy group, as defined herein, appended to the parent molecular moiety through a (C_1-C_6)alkyl group, as defined herein. Representative examples of hydroxy(C_1-C_6)alkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 1-hydroxypropyl, 1-methyl-1-hydroxyethyl, 1-methyl-1-hydroxypropyl, and the like.

The term "halo(C_1-C_6)alkyl", as employed herein, refers to one or more halogen, as defined herein, appended to the parent molecular moiety through a (C_1-C_6)alkyl group, as defined herein. Representative examples of halo(C_1-C_6)alkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl, 3-bromopropyl, and the like.

The term "amino", as employed herein as such or as part of another group, refers to a -NH2 group.

The term "amino(C_1-C_6)alkyl", as employed herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through a (C_1-C_6)alkyl group, as defined herein. Representative examples of amino(C_1-C_6)alkyl include, but are not limited to, aminomethyl, 2-aminoethyl, 1-aminoethyl, 3-aminopropyl, 2-aminopropyl, 4-aminobutyl, 1-methyl-1-aminoethyl, and the like.

The term "mono- or di(C_1-C_6)alkylamino", as employed herein as such or as part of another group, refers to one or two (C_1-C_6)alkyl group(s), as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of mono- or di(C_1-C_6)alkylamino include, but are not limited to methylarnino, ethylamino, propylamino, butylarnino, dimethylamino, diethylamino, N-ethyl-N-methylamino, and the like.

The term "mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl", as employed herein, refers to a mono- or di(C_1-C_6)alkylamino group, as defined herein, appended to the parent molecular moiety through a (C_1-C_6)alkyl group, as defined herein. Representative examples of mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl include, but are not limited to, N,N-dimethylaminomethyl, N,N-diethylaminomethyl, Nmethylaminoethyl, N-methylaminopropyl, N-ethyl-N-methylaminomethyl, and the like.

The term "(C_1-C_6)alkoxy", as employed herein as such or as part of another group, refers to a (C_1-C_6)alkyl, as defined herein, appended to the parent molecular moiety through an -O- group. Representative examples of (C_1-C_6)alkoxy include, but are not limited to methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec-butoxy, tertbutoxy, and the like.

The term "(C_1-C_6)alkoxy(C_1-C_6)alkyl", as employed herein as such or as part of another group, refers to at least one (C_1-C_6)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein. Representative examples of (C_1-C_6)alkoxy(C_1-C_6)alkyl include,

but are not limited to methoxymethyl, ethoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, 3,3-dimethoxypropyl, 2,4-dimethoxybutyl and the like.

The term "hydroxy(C_1-C_6)alkoxy", as employed herein as such or as part of another group, refers to a hydroxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkoxy group, as defined herein.

The term "hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, as employed herein, refers to a hydroxy(C_1-C_6)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein.

The term "carbamoyl", as employed herein as such or as part of another group, refers to a -CONH2 group.

The term "mono- or di(C_1-C_6)-alkylcarbamoyl", as employed herein, refers to one or two (C_1-C_6)alkyl group(s), as defined herein, appended to the parent molecular moiety through a -HNCO- or -NCO- group. Representative examples of mono- or di(C_1-C_6)-alkylcarbamoyl include, but are not limited to N-methylcarbamoyl, *N*-ethylcarbamoyl, *N*-propylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl and the like.

The compounds of formula I, as well as the pharmaceutically acceptable salts and esters thereof, are referred to below as the compounds of the invention, unless otherwise indicated.

The invention includes within its scope all the possible stereoisomers of the compounds, including geometric isomers, e.g. Z and E isomers (*cis* and *trans* isomers), and optical isomers, e.g. diastereomers and enantiomers. Furthemore, the invention includes in its scope both the individual isomers and any mixtures thereof, e.g. racemic mixtures. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical isomers, e.g. enantiomers, from the mixture thereof the conventional resolution methods, e.g. fractional crystallisation, may be used.

Pharmaceutically acceptable salts, e.g. acid addition salts with both organic and inorganic acids are well known in the field of pharmaceuticals. Non-limiting examples of these salts include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates and ascorbates. Pharmaceutically acceptable esters, when applicable, may be prepared by known methods using pharmaceutically acceptable acids that are conventional in the field of pharmaceuticals and that retain the pharmacological properties of the free form. Non-limiting examples

of those esters include esters of aliphatic or aromatic alcohols, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl esters.

The compounds of formula (I), their production and their action as alpha2C antagonists for the treatment of diseases or conditions of the peripheric or central nervous systemare disclosed in WO-A 03/082866 in general and especially the compounds specifically are an explicit part of the description of the present invention and are hereby incorporated by reference.

The term effective amount as used herein refers to an amount of a compound of formula (I) that is effective for treatment and/or prophylaxis of sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

The present invention relates to (alpha-2C) antagonists, in particular the arylquinolizine of formula (I), for the use in a method for the treatment and/or prophylaxis of sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

The present invention further relates to the use of compounds of formula (I) for the manufacture of medicaments for the treatment and/or prophylaxis of sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

A further subject of the present invention is the use of a combination of one or more compounds of the formula (I) with one or more other active compounds in a method for the treatment and/ or prophylaxis sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

A further subject of the present invention is a pharmaceutical composition comprising at least one compounds of the formula (I) in combination with one or more inert non-toxic pharmaceutically suitable excipients for use in a method for the treatment and/ or prophylaxis sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

The present invention further relates to pharmaceutical composition comprising a combination with one or more other active compounds in combination with one or more inert non-toxic pharmaceutically suitable excipients for use in a method for the treatment and/ or prophylaxis sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

The present invention is also directed to a method for the treatment and/or prophylaxis of sleep-related breathing disorders, by administering systemically and/or locally a therpeutically effective amount of at least one compound of formula (I) or a medicament comprising at least one compound od formula (I) in combination with a inert, non-toxic, pharmaceutically accepable additive.

A further subject of the present invention is a combination of one or more compounds of the formula (I) with one or more other active compounds for use in a method for the treatment and/ or prophylaxis sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

Arylquinolizine of formula (I) according to the invention can be used alone or, if required, in combination with one or more other pharmacologically active substances, provided that this combination does not lead to undesirable and unacceptable side effects. Preferred examples of combination suitable for the purpose to treat sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring, include:

- respiratory stimulants such as, by way of example and with preference, theophylline, doxapram, nikethamide or caffeine;
- psychostimulants such as, by way of example and with preference, modafinil or armodafinil;
- amphetamines and amphetamine derivatives such as, by way of example and with preference, amphetamine, metamphetamine or methylphenidate;
- serotonin reuptake inhibitors such as, by way of example and with preference, fluoxetine, paroxetine, citalopram, escitalopram, sertraline, fluvoxamine or trazodone;
- serotonin precursors such as, by way of example and with preference, L-tryptophan;
- selective serotonin noradrenaline reuptake inhibitors such as, by way of example and with preference, venlafaxine or duloxetine;
- noradrenergic and specific serotonergic antidepressants such as, by way of example and with preference, mirtazapine;
- selective noradrenaline reuptake inhibitors such as, by way of example and with preference, reboxetine or atomoxetine;
- tricyclic antidepressants such as, by way of example and with preference, amitriptyline, protriptyline, doxepine, trimipramine, imipramine, clomipramine or desipramine;
- muscarinic receptor antagonists, by way of example and with preference oxybutynin;
- GABA agonists such as, by way of example and with preference, baclofen;
- glucocorticoids such as, by way of example and with preference, fluticasone, budesonide, beclometasone, mometasone, tixocortol or triamcinolone;

- cannabinoid receptor agonists;
- carboanhydrase inhibitors such as, by way of example and with preference, acetazolamide, methazolamide or diclofenamide;
- opioid and benzodiazepine receptor antagonists such as, by way of example and with preference, flumazenil, naloxone or naltrexone;
- cholinesterase inhibitors such as, by way of example and with preference, neostigmine, pyridostigmine, physostigmine donepezil, galantamine or rivastigmine;
- appetite suppressants such as, by way of example and with preference, sibutramin, opiramate, phentermine, lipase inhibitors or cannabinoid receptor antagonists;
- mineralocorticoid receptor antagonists.

A preferred subject of the present invention is a combination of one or more compounds of the formula (I) with one or more other active compounds selected from the groups consisting of muscarinic receptor antagonists, mineralocorticoid receptor antagonists, diuretics, corticosteroids for use in a method for the treatment and/ or prophylaxis sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a muscarinic receptor antagonist, by way of example and with preference oxybutynin.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a mineralocorticoid receptor antagonist, by way of example and with preference spironolactone, eplerenone or finerenone.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a diuretic, by way of example and with preference furosemide, bumetanide, torsemide, bendroflumethiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichlormethiazide, chlorthalidone, indapamide, metolazone, quinethazone, acetazolamide, dichlorphenamide, methazolamide, glycerol, isosorbide, mannitol, amiloride or triamterene.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a corticosteroid, by way of example and with preference prednisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone, beclomethasone, flunisolide, budesonide or fluticasone.

If required, arylquinolizine of formula (I) according to the invention can also be employed in conjunction with the use of one or more medical technical devices or auxiliaries, provided this does not lead to unwanted and unacceptable side-effects. Medical devices and auxiliaries suitable for such a combined application are, by way of example and with preference:

- devices for positive airway pressure ventilation such as, by way of example and with preference, CPAP (continuous positive airway pressure) devices, BiPAP (bilevel positive airway pressure) devices and IPPV (intermittent positive pressure ventilation) devices;
- neurostimulators of the Nervus hypoglossus;
- intraoral auxiliaries such as, by way of example and with preference, protrusion braces;
- nasal disposable valves;
- nasal stents.

Arylquinolizine of formula (I) according to the invention can act systemically and/or locally. For this purpose, they can be administered in a suitable manner, for example by the oral, parenteral, pulmonal, intrapulmonal (inhalative), nasal, intranasal, pharyngeal, lingual, sublingual, buccal, rectal, dermal, transdermal, conjunctival or otic route, or as an implant or stent.

A further subject of the present invention is a pharmaceutical composition comprising a compound of the formula (I) for the systemically and/or locally administration by the oral, parenteral, pulmonal, intrapulmonal (inhalative), nasal, intranasal, pharyngeal, lingual, sublingual, buccal, rectal, dermal, transdermal, conjunctival or otic route, or as an implant or stent. The preferred administration is the oral route.

For these administration routes, the compounds according to the invention can be administered in suitable administration forms.

For oral administration, administration forms which function according to the state of the art, releasing the compounds according to the invention rapidly and/or in a modified manner, which contain the compounds according to the invention in crystalline and/or amorphized and/or dissolved form, such as for example tablets (uncoated or coated tablets, for example with gastric juice-resistant or delayed dissolution or insoluble coatings, which control the release of the compound according to the invention), tablets rapidly disintegrating in the oral cavity or films/wafers, films/lyophilisates, capsules (for example hard or soft gelatine capsules), dragees, granules, pellets, powders, emulsions, suspensions, aerosols or solutions are suitable.

Parenteral administration can be effected omitting an absorption step (e.g. intravenous, intra-arterial, intracardial, intraspinal or intralumbar administration) or involving absorption (e.g. intra-muscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal administration). Suitable administration forms for parenteral administration include injection and infusion preparations in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

For the other administration routes, for example inhalation formulations (including powder inhalers and nebulisers), nasal drops, solutions or sprays, tablets for lingual, sublingual or buccal administration, tablets, films/wafers or capsules, suppositories, oral or ophthalmic preparations, vaginal capsules, aqueous suspensions (lotions, shakable mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (e.g. plasters), milk, pastes, foams, dusting powders, implants or stents are suitable.

Oral or parenteral administration, in particular oral and intravenous administration, are preferred.

The compounds according to the invention can be converted into the stated administration forms. This can be effected in a manner known per se by mixing with inert, non-toxic, pharmaceutically suitable additives. These additives include carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersants or wetting agents (for example sodium dodecylsulphate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g. antioxidants such as for example ascorbic acid), colourants (e.g. inorganic pigments such as for example iron oxides) and flavour or odour correctors.

In general, to achieve effective results in parenteral administration it has been found advantageous to administer quantities of about 0.001 to 10 mg/kg, preferably about 0.01 to 1 mg/kg body weight. In oral administration, the dosage is about 0.01 bis 100 mg/kg, preferably about 0.01 to 20 mg/kg and quite especially preferably 0.1 to 15 mg/kg body weight.

Nonetheless it can sometimes be necessary to deviate from the said quantities, namely depending on body weight, administration route, individual response to the active substance, nature of the preparation and time or interval at which administration takes place. Thus in some cases it can be sufficient to manage with less than the aforesaid minimum quantity, while in other cases the stated upper limit must be exceeded. In the event of administration of larger quantities, it may be advisable to divide these into several individual administrations through the day.

The following practical examples illustrate the invention. The invention is not limited to the examples.

Examples

A. Experimental Methods

Advantageous pharmacological properties of the compounds of the present invention can be determined by the following methods.

The therapeutic potential of the compounds of formula (I) according to the present invention in sleep apnea has been assessed preclinically in a pig model of obstructive sleep apnea (OSA).

Using negative pressure, it is possible to induce collapse and thus obstruction of the upper respiratory tract in anaesthetized, spontaneously breathing pigs (Wirth K.J. et al., Sleep 36(5) (2013) pp. 699-708).

German Landrace pigs are used for the model. The pigs are anaesthetized and tracheotomized. Two tracheal are inserted into the trachea, one into the rostral part and the other into the caudal part of the trachea. Using a connection piece, the rostral cannula is connected to a tube to the negative pressure device and to the distal tracheal cannula. The distal tracheal cannula is additionally connected to a tube with an open end to atmosphere via a connection piece that served for free tracheal breathing, circumventing the upper airway. By appropriate opening and clamping of those tubes breathing can be switched from nasal breathing to breathing through the caudal tracheal cannula, circumventing the upper airway, and the (isolated) upper airway can be connected to the negative pressure device, causing airflow in the inspiratory direction.

At certain points in time, the collapsibility of the upper respiratory tract is tested by having the pig breathe via the caudal cannula and applying negative pressures of -50, -100 and -150 cm water head (cm H_2O) to the upper respiratory tract. This causes the upper respiratory tract to collapse, which manifests itself in an interruption of the airflow and a pressure drop in the tube system. This test is conducted prior to the administration of the test substance and at certain intervals after the administration of the test substance. An appropriately effective test substance can prevent this collapse of the respiratory tract in the inspiratory phase.

In this OSA pig model, systemic application of the α2-Adrenoceptor subtype C (alpha-2C) antagonists of formula (I) (1S,12bS)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-[1]benzofuro[2,3-a]quinolizine with i.v. bolus injection of 0.3 mg/kg followed by an i.v. infusion of 0.1 mg/kg/h for four hours inhibited upper airway collapsibility at all negative pressures of -50, -100 and -150 cm for more than 6 hours (see **Table 1, 2** and **3** and **Figure 1**).

Figure 1:

Effect of i.v. bolus injection of 0.3 mg/kg followed by an i.v. infusion of 0.1 mg/kg/h for four hours of the α2-Adrenoceptor subtype C (alpha-2C) antagonists of formula (I) (1S,12bS)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-[1]benzofuro[2,3-a]quinolizine given at time point 0 min on upper airway collapsibility at different levels of negative pressure. Percentages of pigs with no collapse are given. Mean values.

Table 1: I.v. bolus injection of 0.3 mg/kg followed by an i.v. infusion of 0.1 mg/kg/h of (1S,12bS)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-[1]benzofuro[2,3-a]quinolizine inhibits upper airway collapsibility at negative pressures of -50 cm head (cm H_2O)

Time, min	Percent pigs without collaps -50 cm H_2O, %
0	0
10	100
60	100
120	100
180	100
240	100
300	100

Table 2: I.v. bolus injection of 0.3 mg/kg followed by an i.v. infusion of 0.1 mg/kg/h of (1S,12bS)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-[1]benzofuro[2,3-a]quinolizine inhibits upper airway collapsibility at negative pressures of -100 cm head (cm H_2O)

Time, min	Percent pigs without collaps -100 cm H_2O, %
0	0
10	100
60	100
120	100
180	100
240	100
300	100

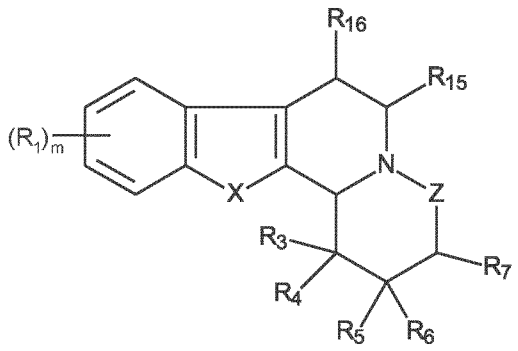
Table 3: I.v. bolus injection of 0.3 mg/kg followed by an i.v. infusion of 0.1 mg/kg/h of (1S,12bS)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-[1]benzofuro[2,3-a]quinolizine inhibits upper airway collapsibility at negative pressures of -150 cm head (cm H_2O)

Time, min	Percent pigs without collaps -150 cm H_2O, %
0	0
10	100
60	100
120	100
180	100
240	100
300	100

From the above mentioned data it can be deducted that the α2-Adrenoceptor subtype C (alpha-2C) antagonists of formula (I) are suitable to treat sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

Claims

1. Compounds of formula (I)



(I)

wherein

X is CR_2R_2', O, S or NR_2;

Z is $–CHR_8-(CH_2)n-$ or a single bond;

R_1 is is hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C=O)-, CO-, CN, NO_2, NH_2, mono- or di(C_1-C_6)alkylamino or carboxyl;

R_2 and R_2' are independently H, hydroxy or (C_1-C_6)alkyl or R_2 and R_2' form, together with the carbon ring atoms to which they are attached, a carbonyl group;

R_3 is H, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, aryloxy, aryl(C_1-C_6)alkoxy, aryloxy(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, NH_2, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl, carboxyl or (C_1-C_6)alkyl-S-(C_1-C_6)alkyl, wherein the said (C_3-C_7)cycloalkyl or aryl is unsubstituted or substituted with 1or 2 substituents each independently being hydroxy, (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, NH_2, CN or NO_2, or one of R_3 or R_4 and R_6 together form a bond between the ring atoms to which they are attached;

R_4 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl;

R_5 is H, hydroxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, aryloxy, aryl(C_1-C_6)alkoxy, aryloxy(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C1-C6)alkyl-CO-O-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl, carboxyl or (C_1-C_6)alkyl-S-(C_1-C_6)alkyl, wherein the said (C_3-C_7)cycloalkyl or aryl is unsubstituted or substituted with 1 or 2 substituents each independently being hydroxy, (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, NH_2, CN or NO_2, or R_4 and R_5 form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring unsubstituted or substituted with 1 to 3 substituent(s) R_9 each independently being hydroxy, (C_1-C_6)alkyl, halogen, NH_2, NO_2, (C_3-C_7)cycloalkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino, mono- or di(C_1-C_6)alkylamino (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, carboxyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, carbamoyl mono- or di(C_1-C_6)alkylcarbamoyl or oxo;

R_6 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl or R_6 forms a bond between the ring atom to which it is attached and the ring atom to which R_7 is attached;

R_7 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl;

R_8 is H, hydroxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_1-C_6)alkoxy(C_1-C_6)alkyl or, only when n is 0, R_7 and R_8 form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring unsubstituted or substituted with 1 to 3 substituent(s) R_{10} each independently being hydroxy, (C_1-C_6)alkyl, halogen, NH_2, NO_2, (C_3-C_7)cycloalkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, carboxyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl or oxo;

R_{15} is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or

di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkyl-CO-, (C_1-C_6)alkyl-CO-O-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-CO-(C_1-C_6)alkoxy(C_1-C_6)alkyl, carbamoyl, mono- or di(C_1-C_6)alkylcarbamoyl or carboxyl;

R_{16} is H or (C_1-C_6)alkyl;

R_7 and R_8 are attached to the carbon ring atoms, which are adjacent;

m is 0 to 2; and

n is 0 or 1,

or a pharmaceutically acceptable salt or ester thereof, for the use in a method for the treatment and/or prophylaxis of sleep-related breathing disorders, preferably obstructive and central sleep apneas and snoring.

2. Compounds according to claim 1, wherein the compound is 1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (1β-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-1- yl)-methanol, 1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, (1α-Methyl-1,2,3,4,6,7, 12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, 1,2,3,4,4aβ,5,6,7,8, 13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno-[1,2-*c*]phenanthrene, 1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cβ-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene or 3,4,4aβ,5,6,7,8,13,13bβ,13cα-decahydro-2H-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-one.

3. Compounds according to claim 1, wherein the compound is 1α-Methyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ol, (1α-Methyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (-)-(1α-Methyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (+)-(lα-Methyl-1,3,4,5,6,11-bßhexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, lα-Isopropyl-1,3,4,5,6,11b-Hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ol, 1α-Ethyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ol, (lα-Ethyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, 5,6,7,7aß,8,9,10,11,11aß,11bα-Decahydro-12-oxa-6a-aza-indeno[l,2-*a*]fluorene, 1-Methyl-lα,3,4,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (1-Hydroxymethyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl]-methanol, 1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (-)-1-Methoxymethyl-la-methyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (+)-1-Methoxymethyl-lα-methyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, 2,3,4,4aß,5,6,7,8,13bß,13cß-Decahydro-1H-13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene, 2,3,4,4aß,5,6,7,8,13bα,13cß-

Decahydro-1H-13-oxa-6a-aza-indeno[1,2-*c*]phenanthrene, 1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-carboxylic acid ethyl ester, 1-Ethoxymethyl-lα-methyl-1,3,4,5,6,11bß-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, (-)-(1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-l-yl)-methanol, (+)-(1α-Methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-yl)-methanol, 1α-Ethyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-carboxylic methyl ester, 1-Methoxymethyl-lα-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (-)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene, (+)-1-Methoxymethyl-1α-methyl-1,3,4,5,6,11bα-hexahydro-2H11-oxa-4a-aza-benzo[*a*]fluorene, (1α-Ethyl-1,3,4,5,6,11bα-hexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluorene-1-yl)-methanol, acetic acid 1α-Methyl-1,3,4,5,6,11bßhexahydro-2H-11-oxa-4a-aza-benzo[*a*]fluoren-1-ylmethyl ester, (1α-Methyl-1,2,3,4,6,7,12,12bα-octahydroindeno[2,1-*a*]quinolizin-1-yl)-methanol or (-)-(1S,12bS)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-[1]benzofuro[2,3-a]quinolizine.

4. Compounds according to claim 1, wherein the compound is 1α-Ethyl-12-methyl-1,2,3,4,6,7,12bß-octahydroindolo[2,3-*a*]quinolizin-1-ol or 1α-Ethyl-12-ethyl-1,2,3,4,6,7,12bß-octahydroindolo[2,3-*a*]quinolizin-1-ol.

5. Compounds according to claim 1, wherein the compound is 2,3,4,4aß,5,6,7,8,13,13bß-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cß-ol, (-)-2,3,4,4aß,5,6,7,8,13,13bß-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cß-ol, (+)-2,3,4,4aß,5,6,7,8,13,13bßdecahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cß-ol, (2,3,4,4aß,5,6,7,8,13,l3bß-Decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthrenyl)-13cß-methanol, 5,6,7,7a,11,11b,12-Decahydro-6a,12-diaza-indeno[1,2-*a*]fluoren11a-ol, 3,4,4aß,5,6,7,8,13,13bß,13cα-decahydro-2H-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-one, 1,2,3,4,5,6,7,8,13,13b-decahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene, acetic acid 1α,2,3,4,4aß,5,6,7,8,13,13bß,13cα-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-yl ester or acetic acid 1ß,2,3,4,4aß,5,6,7,8,13,13bß,13c*α*-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthren-1-yl ester.

6. Compounds according to claim 1, wherein the compound is 2ß-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine, 2α-methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine, 1*a*-Ethyl-2α-methyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-1-ol, 1α-Isopropyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-l-ol, (-)-1α-isopropyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-1-ol, (+)-1α-isopropyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-l-ol, 1ß-Isopropyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-

a]quinolizine, (1α-Isopropyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α-n-Propyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 2-(1α,2,3,4,6,7,12,12bß-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-butan-2-ol, 1-(1,2α,3,4,6,7,12,12bα-Octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-1-ol, 2-(1α,2,3,4,6,7,12,12bß-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-propan-2-ol, 1-*s*-Butyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-l-ol, 1-Cyclohexyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-1-ol, 9-Fluoro-la-isopropyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-l-ol, (1α-Methyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (-)-(1α-Methyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-a]quinolizin-1-yl)-methanol, (+)-(1α-Methyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α-Ethyl-1,4,6,7,12,12bß-hexahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, 3ß,4α-Dimethyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizine, (1,2α,3,4,6,7,12,12bα-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (1,2α,3,4,6,7,12,12bß-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol, (2α-Ethyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol, (1-αEthyl-1,2,3,4,6,7,12,12bß-octahydroindolo[2,3-*a*]quinolizin-1-ylmethoxy)-acetic acid ethyl ester, 1-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-ethanone, 1-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-ethanol, 2-(2α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, 2-(3-ethyl-1,2α,3α,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (3-ethyl-2-methyl-1α,2ß,3ß,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-l-yl)-methanol, 3-ethyl-1,2-dimethyl-1α,2ß,3ß,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizine, 1,2-dimethyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizin-lß-ol, (1-ethyl-2-methyl-1ß,2ß,3ß,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-3-yl)-methanol or 1-ß-Hydroxymethyl-1-methyl-1,2,3,4,6,7,12,12bß-octahydro-indolo[2,3-*a*]quinolizine-6ß-carboxylic acid methyl ester.

7. Compounds according to claim 1, wherein the compound is (-)-(1S,12bS)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-[1]benzofuro[2,3-a]quinolizine.

8. Use of a compound according to claims 1 to 7, wherein the sleep-related breathing disorders are obstructive and central sleep apneas and snoring.

9. Combination of one or more compounds of the formula (I) with one or more other active compounds for use according to any of claims 1 to 8.

10. Pharmaceutical composition comprising at least one compounds of the formula (I) according to any of claims 1 to 7 in combination with one or more inert non-toxic pharmaceutically suitable excipients for use according to any of claims 1 to 8.

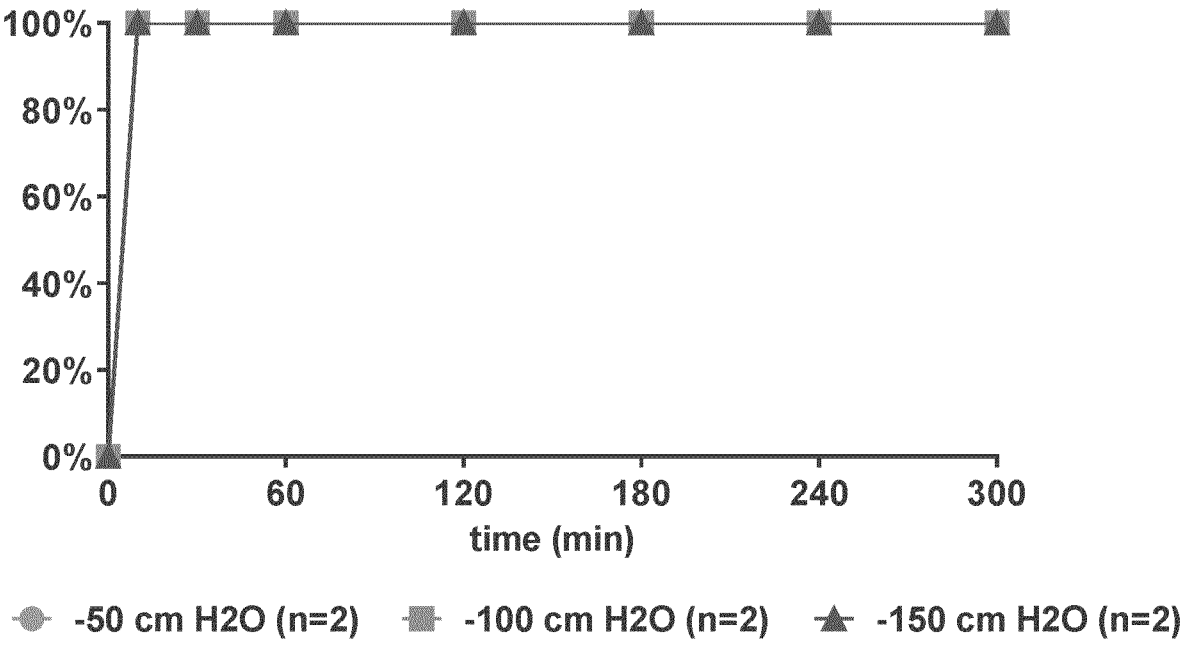
11. Pharmaceutical composition comprising a combination according to claim 8 in combination with one or more inert non-toxic pharmaceutically suitable excipients for use according to any of claims 1 to 8.

12. Method for the treatment and/or prophylaxis of sleep-related breathing disorders, by administering systemically and/or locally a therpeutically effective amount of at least one compound according to any of claims 1 to 7 or a medicament comprising at least one compound according to any of claims 1 to 7 in combination with a inert, non-toxic, pharmaceutically accepable additive.

13. Method according to claim 12 wherein the medicament further comprises at least one further active compound selected from the group consisting of of muscarinic receptor antagonists, mineralocorticoid receptor antagonists, diuretics, corticosteroids .

14. A medicament, comprising a compound of the formula (I) as defined in any of claims 1 to 7 in combination with one or more further active ingredients selected from the group consisting of muscarinic receptor antagonists, mineralocorticoid receptor antagonists, diuretics, corticosteroids.

Fig. 1:


100%
80%
60%
40%
20%
0%
0
60
120
180
240
300
time (min)
-50 cm H2O (n=2)
-100 cm H2O (n=2)
-150 cm H2O (n=2)