

Substituted piperidinyl-tetrahydroquinolines

The invention relates to novel substituted piperidinyltetrahydroquinolines, to processes for their preparation, to their use in a method for the treatment and/or prophylaxis of diseases and to their use for preparing medicaments for the treatment and/or prophylaxis of diseases, in particular of cardiovascular disorders, diabetic microangiopathies, diabetic ulcers on the extremities, in particular for promoting wound healing of diabetic foot ulcers, diabetic heart failure, diabetic coronary microvascular heart disorders, peripheral and cardiac vascular disorders, thromboembolic disorders and ischaemias, peripheral circulatory disturbances, Raynaud's phenomenon, CREST syndrome, microcirculatory disturbances, intermittent claudication, and peripheral and autonomous neuropathies.

Adrenoreceptor α_2 receptors (α_2 -ARs) belong to the family of the G-protein-coupled receptors. They bind to the pertussis toxin-sensitive inhibitory G protein G_i and G_o and reduce adenylate cyclase activity. They are involved in the mediation of diverse physiological effects in various tissues following stimulation by endogenous catecholamines (adrenaline, noradrenaline) which are either released by synapses or reach their site of action via the blood. α_2 -AR play an important physiological role, mainly for the cardiovascular system, but also in the central nervous system. Biochemical, physiological and pharmacological studies have shown that, in addition to various α_1 -AR subtypes, there are three α_2 -AR subtypes (α_{2A} , α_{2B} and α_{2C}) in many target cells and tissues of cardiovascular relevance, which makes them attractive target proteins for therapeutic interventions. However, the elucidation of the precise physiological task of the receptor subtypes remains difficult because of a lack of highly selective ligands and/or antagonists of the respective α_2 -AR (Gyires et al., α_2 -Adrenoceptor subtypes-mediated physiological, pharmacological actions, *Neurochemistry International* 55, 447-453, 2009; Tan and Limbird, *The α_2 -Adrenergic Receptors: Adrenergic Receptors in the 21st Century/Receptors*, 2005, 241-265).

Cardiovascular changes such as, for example, the regulation of the contractility of the heart are regulated, firstly, by the central modulation of the sympathetic efferent nerves. Furthermore, the sympathetic efferent system also regulates direct effects on smooth muscle cells and the endothelial cells of the vessels. Thus, the sympathetic system is involved in the regulation of the output performance of the heart, but also in the control of local perfusion of various vascular beds. This is also controlled via α_2 -ARs involved in the regulation of the peripheral resistance. Thus, blood vessels are innervated by sympathetic nerve fibres which are located in the adventitia and whose endings are provided with varicosities for the release of noradrenalin. Released noradrenalin modulates, via the α_2 -AR in endothelial cells and smooth muscle cells, the respective local vascular tone.

In addition to the effects on the sympathetic efferent nerves, the peripheral cardiovascular function are also regulated by pre- and postsynaptic α_2 -AR. Smooth muscle cells and endothelial cells express

SUBSTITUTED PIPERIDINYL-TETRAHYDROQUINOLINES AND THEIR USE AS
ALPHA-2C ADRENORECEPTOR ANTAGONISTS

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Cardiovascular changes such as, for example, the regulation of the contractility of the heart are regulated, firstly, by the central modulation of the sympathetic efferent nerves. Furthermore, the sympathetic efferent system also regulates direct effects on smooth muscle cells and the endothelial cells of the vessels. Thus, the sympathetic system is involved in the regulation of the output performance of the heart, but also in the control of local perfusion of various vascular beds. This is also controlled via α_2 -ARs involved in the regulation of the peripheral resistance. Thus, blood vessels are innervated by sympathetic nerve fibres which are located in the adventitia and whose endings are provided with varicosities for the release of noradrenalin. Released noradrenalin modulates, via the α_2 -AR in endothelial cells and smooth muscle cells, the respective local vascular tone.

In addition to the effects on the sympathetic efferent nerves, the peripheral cardiovascular function are also regulated by pre- and postsynaptic α_2 -AR. Smooth muscle cells and endothelial cells express

in which

R¹ and R² together with the nitrogen atom to which they are attached form an azetidine,

where the azetidine has two substituents which, together with the carbon atom of the azetidine to which they are jointly attached, form an oxetane,

and

R⁵ represents C₁-C₄-alkyl, preferably methyl or ethyl,

and the salts thereof, the solvates thereof and the solvates of the salts thereof.

9. Compound of the formula (I) as defined in any of Claims 1 to 6 for use in the treatment and/or prevention of diseases.
10. Compound of the formula (I) as defined in any of Claims 1 to 6 for use in ~~a method for the~~ treatment and/or prophylaxis of primary and secondary forms of diabetic microangiopathies, diabetic wound healing, diabetic ulcers on the extremities, in particular for promoting wound healing of diabetic foot ulcers, diabetic retinopathy, diabetic nephropathy, diabetic erectile dysfunction, diabetic heart failure, diabetic coronary microvascular heart disorders, peripheral and cardial vascular disorders, thromboembolic disorders and ischaemias, peripheral circulatory disturbances, Raynaud's phenomenon, CREST syndrome, microcirculatory disturbances, intermittent claudication, and peripheral and autonomous neuropathies.
11. Medicament comprising a compound of the formula (I) as defined in any of Claims 1 to 6 in combination with one or more inert non-toxic pharmaceutically suitable auxiliaries.
12. Medicament comprising a compound of the formula (I) as defined in any of Claims 1 to 6 in combination with one or more further active compounds selected from the group consisting of lipid metabolism-modulating active compounds, antidiabetics, hypotensive agents, agent which lower the sympathetic tone, perfusion-enhancing and/or antithrombotic agents and also antioxidants, aldosterone and mineralocorticoide receptor antagonists, vasopressin receptor antagonists, organic nitrates and NO donors, IP receptor agonists, positive inotropic compounds, calcium sensitizers, ACE inhibitors, cGMP- and cAMP-modulating compounds, natriuretic peptides, NO-independent stimulators of guanylate cyclase, NO-independent activators of guanylate cyclase, inhibitors of human neutrophil elastase, compounds which inhibit the signal transduction cascade, compounds which modulate the energy metabolism of the heart, chemokine receptor antagonists, p38 kinase inhibitors, NPY agonists, orexin agonists, anorectics, PAF-AH inhibitors, antiphlogistics, analgesics, antidepressives and other psychopharmaceuticals.

13. Medicament according to Claim 11 or 12 for use in the treatment and/or prophylaxis of primary and secondary forms of diabetic microangiopathies, diabetic wound healing, diabetic ulcers on the extremities, in particular for promoting wound healing of diabetic foot ulcers, diabetic retinopathy, diabetic nephropathy, diabetic erectile dysfunction, diabetic heart failure, diabetic coronary microvascular heart disorders, peripheral and cardiac vascular disorders, thromboembolic disorders and ischaemias, peripheral circulatory disturbances, Raynaud's phenomenon, CREST syndrome, microcirculatory disturbances, intermittent claudication, and peripheral and autonomous neuropathies.
14. ~~Method~~ The use of the compound of the formula (I) as defined in any of Claims 1 to 6 in the manufacture of a medicament for the treatment and/or prophylaxis of primary and secondary forms of diabetic microangiopathies, diabetic wound healing, diabetic ulcers on the extremities, in particular for promoting wound healing of diabetic foot ulcers, diabetic retinopathy, diabetic nephropathy, diabetic erectile dysfunction, diabetic heart failure, diabetic coronary microvascular heart disorders, peripheral and cardiac vascular disorders, thromboembolic disorders and ischaemias, peripheral circulatory disturbances, Raynaud's phenomenon, CREST syndrome, microcirculatory disturbances, intermittent claudication, and peripheral and autonomous neuropathies ~~in humans and animals by administration of an effective amount of at least one compound of the formula (I) as defined in any of Claims 1 to 6 or of a medicament as defined in any of Claims 11 to 13.~~
15. Adrenoreceptor α_2C receptor antagonists for use in ~~a method for~~ the treatment and/or prophylaxis of comorbidities and/or sequelae of diabetes mellitus, diabetic heart disorders, diabetic coronary heart disorders, diabetic coronary microvascular heart disorders, diabetic heart failure, diabetic cardiomyopathy and myocardial infarction, diabetic microangiopathy, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, diabetic erectile dysfunction, diabetic ulcers on the extremities, diabetic foot syndrome, for promoting diabetic wound healing, and for promoting wound healing of diabetic foot ulcers.