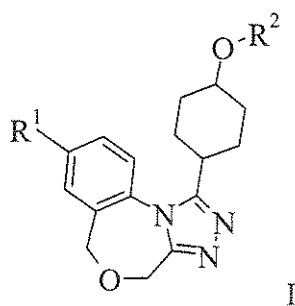


The V1a receptor is also mediating the cardiovascular effects of vasopressin in the brain by centrally regulating blood pressure and heart rate in the solitary tract nucleus (Michelini and Morris (1999). *Ann N Y Acad Sci.* **897**, 198-211, "Endogenous vasopressin modulates the cardiovascular responses to exercise"). In the periphery it induces the contraction of vascular smooth muscles and chronic inhibition of the V1a receptor improves hemodynamic parameters in myocardial infarcted rats (Van Kerckhoven, et al. (2002). *Eur J Pharmacol.* **449**, 135-41, "Chronic vasopressin V(1A) but not V(2) receptor antagonism prevents heart failure in chronically infarcted rats"). Hence, V1a antagonists with improved penetration through the blood-brain barrier are expected to be of advantage.

A vasopressin V1a receptor antagonist was shown to be effective in reducing dysmenorrhea in the clinic (Brouard, et al. (2000). *Bjog.* **107**, 614-9, "Effect of SR49059, an orally active V1a vasopressin receptor antagonist, in the prevention of dysmenorrhoea"). V1a receptor antagonism has also been implicated in the treatment of female sexual dysfunction (Aughton, et al. (2008). *Br J Pharmacol.* doi:10.1038/bjp.2008.253, "Pharmacological profiling of neuropeptides on rabbit vaginal wall and vaginal artery smooth muscle in vitro"). In a recent study V1a receptor antagonists were suggested to have a therapeutic role in both erectile dysfunction and premature ejaculation (Gupta, et al. (2008). *Br J Pharmacol.* **155**, 118-26, "Oxytocin-induced contractions within rat and rabbit ejaculatory tissues are mediated by vasopressin V(1A) receptors and not oxytocin receptors").

Summary

In one aspect, there is provided a compound of formula I.



wherein

R¹ is halogen, and

R² is selected from the group consisting of

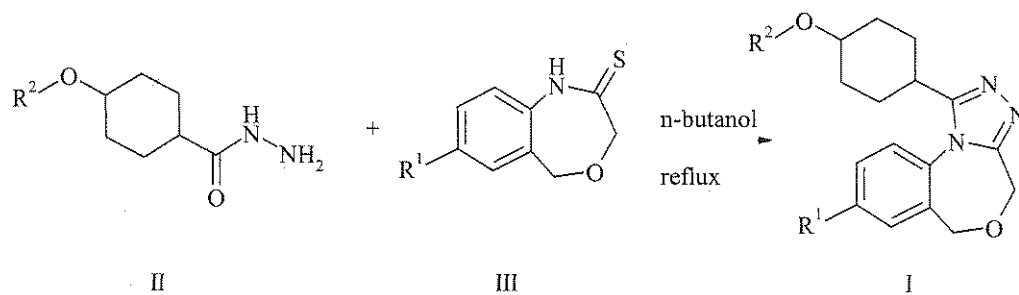
- i) heteroaryl, unsubstituted or substituted by 1 to 3 substituents individually selected from the group consisting of OH, halogen, cyano, C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, halogen-C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl and hydroxy-C₁₋₆-alkyl;
- ii) aryl, unsubstituted or substituted by 1 to 3 substituents individually selected from the group consisting of OH, halogen, cyano, C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, halogen-C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl and hydroxy-C₁₋₆-alkyl;

- iii) C₃₋₇-cycloalkyl, unsubstituted or substituted by 1 to 3 substituents individually selected from the group consisting of OH, halogen, cyano, C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen-C₁₋₆-alkyl, halogen-C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl and hydroxy-C₁₋₆-alkyl; and
- iv) C₁₋₆-alkyl, unsubstituted or substituted by 1 to 3 substituents individually selected from the group consisting of OH, halogen, cyano, C₁₋₆-alkoxy and halogen-C₁₋₆-alkoxy;

or pharmaceutically acceptable salts thereof,

wherein the term "heteroaryl", refers to an aromatic carbocyclic group having a single 4 to 8 membered ring or multiple condensed rings containing 6 to 14 ring atoms and containing 1, 2 or 3 heteroatoms individually selected from N, O and S, in which at least one heterocyclic ring is aromatic.

In another aspect, there is provided a process for preparing a compound of formula I as defined above, which process comprises reacting a compound of formula II with a compound of formula III to a compound of formula I



wherein R¹ and R² are as defined above.

In another aspect, there is provided a compound of formula I as defined above for use as therapeutically active substance.

In another aspect, there is provided a compound of formula I as defined above for the use as therapeutically active substance for the therapeutic and/or prophylactic treatment of diseases and disorders which are associated with V1a receptor antagonism.

In another aspect, there is provided a compound of formula I as defined above for the use as therapeutically active substance acting peripherally and centrally in the conditions of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

In another aspect, there is provided a pharmaceutical composition comprising a compound of formula I as defined above and a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable auxiliary substance.

In another aspect, there is provided the use of a compound of formula I as defined above for the manufacture of a medicament for acting peripherally and centrally in the conditions of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

Detailed description of the invention

Object of the present invention is a compound of formula I and their pharmaceutically acceptable salts thereof, the preparation of the above mentioned compounds, medicaments containing them and their manufacture as well as the use of the above mentioned compounds in the therapeutic and/or prophylactic treatment of diseases and disorders which are associated with modulation of the V1a receptor, and in particular with V1a receptor antagonism. A further object of the invention is to provide selective inhibitors of the V1a receptor, since selectivity for the V1a receptor is expected to afford a low potential to cause unwanted off-target related side effects such as discussed above.

Present compounds are useful as therapeutics acting peripherally and centrally in the conditions of dysmenorrhea, male or female sexual dysfunction, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior. Particular indications with regard to the present invention are the treatment of anxiety, depressive disorders, obsessive compulsive disorder, autistic spectrum disorders, schizophrenia, and aggressive behavior.

The following definitions of the general terms used in the present description apply irrespectively of whether the terms in question appear alone or in combination with other groups.