697 – 704), autism (Hollander et al., Neuropsychopharm., 28, 2008, 193 – 98), stress, including post traumatic stress disorder (PTSD) (Pitman et al., Psychiatry Research, 48, 107 – 117), anxiety, including anxiety disorders and depression (Kirsch et al., J. Neurosci., 25, 49, 11489 – 93, Waldherr et al., PNAS, 104, 2007, 16681 – 84), surgical blood loss or control of post-partum haemorrhage (Fujimoto et al., Acta Obstet. Gynecol., 85, 2006, 1310 -14), labor induction and maintenance (Flamm et al., Obstet. Gynecol., 70, 1987, 70 – 12), wound healing and infection, mastitis and placenta delivery, and osteoporosis. Additionally, oxytocin agonists may be useful for the diagnosis of both cancer and placental insufficiency.

Furthermore, the Articles "Intranasal Oxytocin blocks alcohol withdrawal in human subjects" (Alcohol Clin Exp Res, Vol, No. 2012) and "Breaking the loop: Oxytocin as a potential treatment for drug addiction" (Hormones and Behavior, 61, 2012 , 331- 339) propose to treat alcohol withdrawel and drug addiction with a oxytocin agonist.

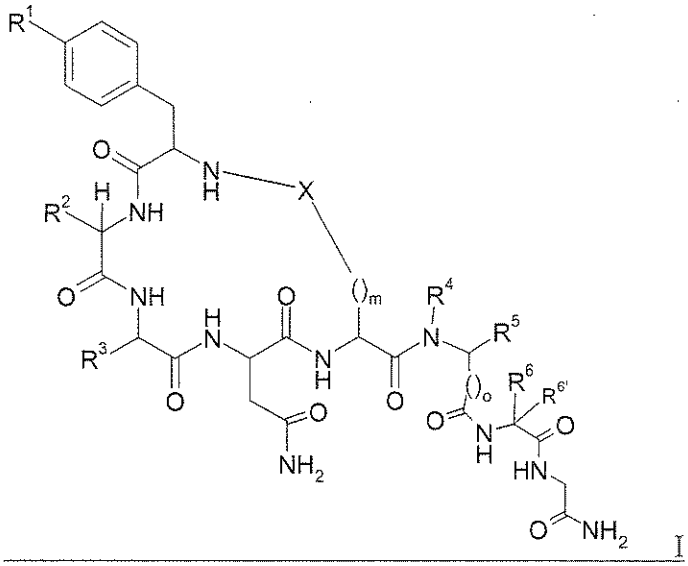
Oxytocin and its receptors exists in areas of the brain implicated in the symptoms of schizophrenia, such as the nucleus accumbens and the hippocampus. The oxytocin receptor agonists may be used for the treatment of autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, Alzheimer's disease, psychiatric disorders, memory loss and metabolic diseases (WO2012/016229).

Objects of the ~~present invention~~ embodiments disclosed herein are novel compounds of formula I and the use of compounds of formula I and their pharmaceutically acceptable salts for the treatment of CNS diseases related to the oxytocin receptor, which diseases are autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory loss, alcohol withdrawel,drug addiction and for the treatment of Prader-Willi Syndrom.

Further objects are the preparation of novel compounds of formula I and medicaments, containing them.

The present ~~invention~~ disclosure may provide selective, efficacious compounds, providing alternatives and/or improvements in the treatment of certain CNS diseases including autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory loss, alcohol withdrawel, drug addiction and for the treatment of Prader-Willi Syndrom. -

In one aspect, there is provided a compound of formula



I

wherein

wherein

R^1 is hydroxy or amino;

R^2 is *sec*-butyl or isobutyl;

R^3 is lower alkyl, lower alkyl substituted by hydroxy, $-(CH_2)_2C(O)-NH_2$, $-(CH_2)_3-NH_2$ or $-CH_2$-five membered aromatic heterocyclic group;

R^4 is hydrogen or lower alkyl;

R^5 is hydrogen or lower alkyl; or

R^4 and R^5 may form together with the N and C atom to which they are attached a pyrrolidine ring, optionally substituted by hydroxy or halogen, a piperidine ring or an azetidine ring;

R^6 is hydrogen, lower alkyl, lower alkyl substituted by hydroxy, $-(CH_2)_2C(O)OH$, $-(CH_2)_2C(O)NH_2$, benzyl optionally substituted by amino or hydroxy, $-CH_2$-five membered aromatic heterocyclic group, indolyl, $-CH_2$-cycloalkyl, cycloalkyl, $-(CH_2)_2$-S-lower alkyl or is $-(CH_2)_{1-4}-NH_2$;

$R^{6'}$ is hydrogen or lower alkyl; or

R^6 and $R^{6'}$ are together cycloalkyl;

X is –C(O)-CHR-NR'-C(O)- ;

R/R' are independently from each other hydrogen or lower alkyl;

m is 2;

o is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomers thereof.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutical acceptable carrier and/or adjuvant.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutical acceptable carrier and/or adjuvant for use in the treatment of autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory loss, alcohol withdrawel, drug addiction and for the treatment of Prader-Willi Syndrom.

In another aspect, there is provided a compound as defined herein for use as therapeutic active substances.

In another aspect, there is provided a compound as defined herein for use as therapeutic active substances in the treatment of autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory loss, alcohol withdrawel, drug addiction and for the treatment of Prader-Willi Syndrom.

In another aspect, there is provided use of a compound as defined herein in the preparation of medicaments for the therapeutic and/or prophylactic treatment of autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory loss, alcohol withdrawel, drug addiction and for the treatment of Prader-Willi Syndrom.

It has been shown that the present peptides have a very good selectivity to the vasopressin receptors V1a and V2 as shown in the table. This may have a major advantage for use as medicament to avoid side effects. These physiological effects may be considered to be

6. A pharmaceutical composition comprising a compound according to any one of claims 1 –5 and a pharmaceutical acceptable carrier and/or adjuvant.

7. A pharmaceutical composition comprising a compound according to any one of claims 1–5 and a pharmaceutical acceptable carrier and/or adjuvant for use in the treatment of autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory loss, alcohol withdrawel, drug addiction and for the treatment of Prader-Willi Syndrom.

8. A compound according to any one of claims 1–5 for use as therapeutic active substances.

9. A compound according to any one of claims 1–5 for use as therapeutic active substances in the treatment of autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory loss, alcohol withdrawel, drug addiction and for the treatment of Prader-Willi Syndrom.

10. The use of a compound according to any one of claims 1–5 ~~for~~ in the preparation of medicaments for the therapeutic and/or prophylactic treatment of autism, stress, including post traumatic stress disorder, anxiety, including anxiety disorders and depression, schizophrenia, psychiatric disorders and memory loss, alcohol withdrawel, drug addiction and for the treatment of Prader-Willi Syndrom.