A61P 31/48 (2006.01) A61P 25/08 (2006.01)

Title: USE OF 8-ALPHA-ERGOLINES FOR THE TREATMENT OF TRAUMATIC BRAIN DISORDERS

Abstract: The present invention relates to 8-α-ergoline derived compounds and salts, enantiomers, mixtures of enantiomers, diastereomers, mixtures of diastereomers, hydrates, solvates and racemates and/or pharmaceutically acceptable salts of these compounds for use in pharmaceutical compositions together with pharmaceutically acceptable carriers, excipients and/or diluents. Said 8-α-ergoline derived compounds are useful for the preparation of pharmaceutical compositions for the treatment and/or prophylaxis of epileptic seizures, increased cranial pressure and brain edema in the acute or rehabilitation phase of a brain injury.
1. Use of the compounds of the general formula (I)

\[
R^1\text{ and } R^4 \text{ represent independently from each other } -H, \text{ -CHO, -COCH}_3, \text{ -COC}_2H_5, \text{ -COC}_3H_7, \text{ -CO-CyClO-C}_3H_5, \text{ -COC(CH}_3)_2, \text{ -COC(CH}_3)_3, \text{ -COOH, -COOCH}_3, \text{ -COOC}_2H_5, \text{ -COOC}_3H_7, \text{ -COO-CyClO-C}_3H_5,
\]

\[
-R^8\text{ -R}^{43}; \text{ a linear or branched, saturated or unsaturated alkyl residues with 1 - 10 carbon atoms, which can be substituted with one or more of the residues } R^8 - R^{43}; \text{ a linear or branched, saturated or unsaturated -CO-alkyl residue with 1 - 10 carbon atoms, which can be substituted with one or more of the residues } R^8 - R^{43}; \text{ a linear or branched, saturated or unsaturated -NH-CO-alkyl residue with 1 - 10 carbon atoms, which can}
\]

wherein

\[
R^1 \text{ and } R^4 \text{ represent independently from each other -H, -CHO, -COCH}_3, \text{ -COC}_2H_5, \text{ -COC}_3H_7, \text{ -CO-CyClO-C}_3H_5, \text{ -COC(CH}_3)_2, \text{ -COC(CH}_3)_3, \text{ -COOH, -COOCH}_3, \text{ -COOC}_2H_5, \text{ -COOC}_3H_7, \text{ -COO-CyClO-C}_3H_5,
\]

\[
-R^8\text{ -R}^{43}; \text{ a linear or branched, saturated or unsaturated alkyl residues with 1 - 10 carbon atoms, which can be substituted with one or more of the residues } R^8 - R^{43}; \text{ a linear or branched, saturated or unsaturated -CO-alkyl residue with 1 - 10 carbon atoms, which can be substituted with one or more of the residues } R^8 - R^{43}; \text{ a linear or branched, saturated or unsaturated -NH-CO-alkyl residue with 1 - 10 carbon atoms, which can}
\]

AMENDED SHEET (ARTICLE 19)
be substituted with one or more of the residues R8 - R43; a linear or branched, saturated or unsaturated -NH-CO- NH-alkyl residue or -NH-CO- N(dialkyl residue) with alkyl residues with 1 - 10 carbon atoms, which can be substituted with one or more of the residues R8 - R43; an aryl residue or cycloalkyl residue or bicyclic or tricyclic carbocycle, which can be substituted with one or more of the residues R8 - R43; a heteroaryl residue or heterocyclyl residue or a bicyclic or tricyclic saturated or unsaturated heterocycle, which can be substituted with one or more of the residues R8 - R43;

R6 represents one of the residues -H, -F, -Cl, -Br, -I, -CN or -NO2;

R6 - R45 represent independently from each other -H, -OH, -OCH3,
-OC2H5, -OC3H7, -O-cyclo-C3H5, -OCH(CH3)2, -OC(CH3)3, -OC4H9,
-OPh, -OCH2Ph, -OCPh3, -SH, -SCH3, -SC2H5, -SC3H7,
-S-Cyclo-C3H5, -SCH(CHa)2, -SC(CH3)3, -NO2, -F, -Cl, -Br, -I, -N3,
-CN, -OCN, -NCO, -SCN, -NCS, -CHO, -COCH3, -CO2H5,
-COC(CH3)2, -COO-Ch(CH3)3, -COOH, -COCH3,
-COOC(CH3)3, -COOC2H5, -COOC3H7, -COO-cyclo-C3H5, -COOCH(CH3)2,
-COOC(CHs)3, -COOC2H5, -COOC3H7, -COO-cyclo-C3H5,
-OOC-CH(CH3)2, -OOC-C(CH3)3, -CONH2, -CONHCH3, -CONH2H5,
-CONHC3H7, -CONHCyclo-C3H5, -CONH[CH(CH3)2], -CONHz[CH(CH3)3],
-CON(C2H5)2, -CON(C3H7)2, -CON(cyclo-C3H5)2,
-CON[CH(CH3)2], -CON[C(CH3)3], -NH2, -NHCH3, -NHC2H5, -NHC3H7,
-NH-cyclo-C3H5, -NHCH(CH3)2, -NHC(CHs)3, -N(CH3)2, -N(C2H5)2, -N(C3H7)2,
-N(cyclo-C3H5), -N[N(CH3)2], -N[N(CHs)3], -SOCH3, -SOC2H5, -SOC3H7,
-SO-Cyclo-C3H5, -SOCH(CH3)2, -SOC(CH3)3, -SO2CH3, -SO2C2H5,
-SO2C3H7, -SO2CyCIO-CsH5, -SO2C2H5, -SO2C3H7, -SO3H,
-SO3C3H7, -SO3C2H5, -SO3C3H7, -SO3CyC3H5, -SO3CH(CH3)2,
-SO3C2H5, -SOSz(C2H5), -OCF3, -OC2F5, -OCOOCH3, -OCOO2H5,
-O-COO-cyclo-C3H5, -O-COOCH(CHs)2, -O-COOCH(CH3)3,
-NH-CO-NH2, -NH-CO-NHC3H7, -NH-CO-NHC2H5, -NH-CO-NHC3H7,
-NH-CO-NH-Cyclo-C3H5, -NH-CO-NH[CH(CH3)2], -NH-CO-NH[C(CH3)3],
-NH-CO[N(CH3)2], -NH-CO-N(C2H5)2, -NH-CO-N(C3H7)2,
-NH-CO-N([Cyclo-C3Hs]2), -NH-CO-N[CH(CH3)2], -NH-CO-N[C(CH3)2],
-NH-CS-NH2, -NH-CS-NHC3H7, -NH-CS-NHC2H5, -NH-CS-NHC3H7,
-NH-CS-NH-Cyclo-C3H5, -NH-CS-NH[CH(CHs)2], -NH-CS-NH[C(CH3)3],
-NH-CS-N(C2H5)2, -NH-CS-N(C3H7)2,
-NH-CS-N(cyclo-C3Hs)2, -NH-CS-N[CH(CH3)2], -NH-CS-N[C(CH3)2],
-NH-C(=NH)-NH2, -NH-C(=NH)-NHC3H7, -NH-C(=NH)-NHC2H5,
-NH-C(=NH)-NHC3H7, -NH-C(=NH)-NH[CH(CH3)2], -NH-C(=NH)-NHC3H7.
-NH-C(=NH)-N(CH₃)₂, -NH-C(=NH)-N(C₂H₅)₂, -NH-C(=NH)-N(C₃H₇)₂,
-NH-C(=NH)-N(cyclo-C₃H₅)₂, ... 2 and R 3 represent independently from each other -H, - R 6 , -NH-CO — NH-alkyl residue o r -NH-CO — N(dialkyl residue);

5 -COOH

-CONHC

salts,

2. Use of the compounds of the general formula (I) wherein
R¹ and R⁴ represent independently from each other -H, -CHO, -COCH₃,

25 -COC₂H₅, -COC₃H₇, -CO-cyclo-C₃H₅, -COCH(CH₃)₂, -COC(CH₃)₂,

-CONHC₃H₇, -COOH , -COOCH₃, -COOC₂H₅, -COOC₃H₇, -COO-cyclo-C₃H₅,

-CONHC₃H₇, -CONHC₃H₇, -CONHC₃H₇, -CONHC₃H₇,

30 -CON(C₃H₅)₂, -CON[C(CH₃)₃]₂, -SO₃-C₂H₅, -SO₃-C₃H₇, -SO₃-cyclo-C₃H₅,

-SO₃CH(CH₃)₂, -SO₃CH(CH₃)₂, -SO₃CH(CH₃)₂, -SO₃CH(CH₃)₂,

-CH₂Br, -CH₂Br, -CH₂Br, -CH₂Br,

-C₄H₉, -CH₂CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH₂CH(CH₃)₂,

-cyclo-C₃H₅, -CyClO-C₄H₇, -CyClO-C₅H₇, -CyClO-C₆H₁₁,

n represents an integer from 1 to 10; as well as

salts, enantiomers, mixtures of enantiomers, diastereomers, mixtures of diastereomers, hydrates, solvates and racemates of the afore-mentioned compounds for the preparation of a pharmaceutical composition for the treatment and/or prophylaxis of brain disorder wherein the brain disorder is characterized by increased cranial pressure or neural edema.
alkyl and dialkyl represent independently of each other -CH₂F, -CH₂CH₂F,
-CH₂CHF₂, -CH₂CF₃, -CH₂CH₂Cl, -CH₂CH₂Br, -CH₂CH₂I, -CH₃, -C₂H₅,
-C₃H₇, -CH(CH₃)₂, -C(CH₃)₃, -C₄H₉, -CH₂-CH(CH₃)₂, -CH(CH₃)-C₂H₅,
-C₆H₁₁, -C₆H₁₃, -C₁H₁₅, -C₈H₁₇, -cyclo-C₃H₅, -cyclo-C₄H₇, -cyclo-C₅H₉,
-cyclo-C₇H₁₅, -Ph, -CH₂-Ph, -Ph₃, -CH=CH₂, -CH₂=CH=CH₂, -C(CH₃)=CH₂,
-CH=CH-C₂H₅, -C₂H₄-CH=CH₂, -CH=C(CH₃)₂, -C≡CH, -C≡C-CH₃ and -CH₂-C≡CH;
R⁶ represents one of the residues -H or -Br;
R⁶ - R⁴⁵ represent independently from each other -H, -OH, -OCH₃,
-OC₂H₅, -OC₃H₇, -O-cyclo-C₃H₅, -OCH(CH₃)₂, -O(CH₃)₃, -OC₄H₉,
-OPh, -OCH₂Ph, -OCPh₃, -SH, -SCH₃, -SC₂H₅, -SC₃H₇,
-S-cyclo-C₃H₅, -SCH(CH₃)₂, -SC(CH₃)₃, -NO₂, -F, -Cl, -Br, -I, -N₃,
-CN, -OCN, -NCO, -SCN, -NCS, -CHO, -COCH₃, -COC₂H₅,
-COC₃H₇, -CO-Cyclopentyl-C₄H₉, -COCH(CH₃)₂, -COOC(CH₃)₃, -COOH, -COCN,
-COOCH₃, -COOCH₂H₅, -COOCH₃H₇, -COO-cyclo-C₃H₅, -COOCH(CH₃)₂,
-COOOC(CH₃)₂, -OOC-CH₃, -OOC-C₂H₅, -OOC-C₃H₇, -OOC-cyclo-C₃H₅,
-CONH₃H₂, -CONH-cyclo-C₃H₅, -CONH(CH(CH₃)₂)₂, -CONH(C(CH₃)₂),
-CON(C₃H₇)₂, -CON(C₂H₅)₂, -CON(C₃H₇)₂, -CON(cyclo-C₃H₅)₂,
-CON[CH(C₃H₇)₂], -CON[CH(CH₃)₂], -NH₂, -NHCH₃, -NHC₂H₅, -NHC₃H₇,
-NH-Cyclopentyl-C₃H₅, -NHCH(CH₃)₂, -NHC(CH₃)₃, -N(CH₃)₂, -N(C₂H₅)₂,
-N(C₃H₇)₂, -N(cyclo-C₃H₅)₂, -N[C(CH₃)₃], -N(C₃H₇)₂,
-N(Cyclopentyl-C₄H₉), -SO₂CH₃, -SO₂CH₂CH₃, -SO₂CH₂CH₂CH₃, -SO₂CH₃,
-SO₂H, -SO₂H₂, -SO₂-Cyclopentyl-C₃H₅, -SO₂CH₂CH₃, -SO₂CH₂CH₂CH₃,
-SO₂CH₄, -SO₂COOCH₃, -S₀₂C(CH₃)₂, -S₀₂C₂CH₃, -SO₃H,
-SO₃H₂, -SO₃H₃, -SO₃C₂H₅, -SO₃C₃H₇, -SO₃-Cyclopentyl-C₃H₅, -SO₃CH(CH₃)₂,
-SO₃CH(CH₃)₃, -OC₃H₇, -OC₂F₅, -OC₂F₆, -OC₂F₇, -OC₂F₈,
-O-Cyclopentyl-C₃H₅, -O-Cyclopentyl-C₄H₉, -O-Cyclopentyl-C₅H₉,
-O-Cyclopentyl-C₇H₁₅, -O-Cyclopentyl-C₈H₁₇, -O-Cyclopentyl-C₉H₂₁,
-O-Cyclopentyl-C₁₀H₂₁, -O-Cyclopentyl-C₁₁H₂₃, -O-Cyclopentyl-C₁₂H₂₅,
-NH-Cyclopentyl-C₃H₅, -NH-Cyclopentyl-C₄H₉, -NH-Cyclopentyl-C₅H₉,
-NH-Cyclopentyl-C₇H₁₅, -NH-Cyclopentyl-C₈H₁₇, -NH-Cyclopentyl-C₉H₂₁,
-NH-Cyclopentyl-C₁₀H₂₁, -NH-Cyclopentyl-C₁₁H₂₃, -NH-Cyclopentyl-C₁₂H₂₅,
-NH-Cyclopentyl-C₁₃H₂₇, -NH-Cyclopentyl-C₁₄H₂₉, -NH-Cyclopentyl-C₁₅H₃₁,
-NH-Cyclopentyl-C₁₆H₳₃, -NH-Cyclopentyl-C₁₇H₳₅, -NH-Cyclopentyl-C₁₈H₳₇,
-NH-Cyclopentyl-C₁₉H₳₉, -NH-Cyclopentyl-C₂₀H₂₁, -NH-Cyclopentyl-C₂₁H₂₃,
-NH-Cyclopentyl-C₂₂H₂₅, -NH-Cyclopentyl-C₂₃H₂₇, -NH-Cyclopentyl-C₂₄H₂₉,
-NH-Cyclopentyl-C₂₅H₳₁, -NH-Cyclopentyl-C₂₆H₳₃, -NH-Cyclopentyl-C₂₇H₳₅,
-NH-Cyclopentyl-C₂₈H₳₇, -NH-Cyclopentyl-C₂₉H₳₉, -NH-Cyclopentyl-C₃₀H₳₁, -NH-Cyclopentyl-C₃₁H₳₃,
-NH-Cyclopentyl-C₃₂H₳₅, -NH-Cyclopentyl-C₃₃H₳₇, -NH-Cyclopentyl-C₃₄H₳₉,
-NH-Cyclopentyl-C₃₅H₳₁, -NH-Cyclopentyl-C₃₆H₳₃, -NH-Cyclopentyl-C₃₇H₳₅,
-NH-Cyclopentyl-C₃₈H₳₇, -NH-Cyclopentyl-C₃₉H₳₉, -NH-Cyclopentyl-C₄₀H₳₁,
-NH-Cyclopentyl-C₄₁H₳₃, -NH-Cyclopentyl-C₄₂H₳₅, -NH-Cyclopentyl-C₄₃H₳₇,
-NH-Cyclopentyl-C₄₄H₳₉, -NH-Cyclopentyl-C₄₅H₳₁, -NH-Cyclopentyl-C₄₆H₳₃,
-NH-Cyclopentyl-C₄₇H₳₅, -NH-Cyclopentyl-C₄₈H₳₇, -NH-Cyclopentyl-C₄₉H₳₉,
-NH-Cyclopentyl-C₅₀H₳₁, -NH-Cyclopentyl-C₅₁H₳₃, -NH-Cyclopentyl-C₅₂H₳₅,
-NH-Cyclopentyl-C₅₃H₳₇, -NH-Cyclopentyl-C₅₄H₳₉, -NH-Cyclopentyl-C₅₅H₳₁,
-NH-Cyclopentyl-C₅₆H₳₃, -NH-Cyclopentyl-C₅₇H₳₅, -NH-Cyclopentyl-C₅₈H₳₇,
-NH-Cyclopentyl-C₅₉H₳₉, -NH-Cyclopentyl-C₆₀H₳₁, -NH-Cyclopentyl-C₆₁H₳₃,
-NH-Cyclopentyl-C₆₂H₳₅, -NH-Cyclopentyl-C₆₃H₳₇, -NH-Cyclopentyl-C₆₄H₳₉,
-NH-Cyclopentyl-C₆₅H₳₁, -NH-Cyclopentyl-C₆₆H₳₃, -NH-Cyclopentyl-C₆₇H₳₅,
-NH-Cyclopentyl-C₆₈H₳₇, -NH-Cyclopentyl-C₆₉H₳₉, -NH-Cyclopentyl-C₇₀H₳₁,
-NH-Cyclopentyl-C₇₁H₳₃, -NH-Cyclopentyl-C₇₂H₳₅, -NH-Cyclopentyl-C₇₃H₳₇,
-NH-Cyclopentyl-C₇₄H₳₉, -NH-Cyclopentyl-C₇₅H₳₁, -NH-Cyclopentyl-C₇₆H₳₃,
-NH-Cyclopentyl-C₇₇H₳₅, -NH-Cyclopentyl-C₇₈H₳₇, -NH-Cyclopentyl-C₇₉H₳₉,
-NH-Cyclopentyl-C₈₀H₳₁, -NH-Cyclopentyl-C₈₁H₳₃, -NH-Cyclopentyl-C₈₂H₳₅,
-NH-Cyclopentyl-C₈₃H₳₇, -NH-Cyclopentyl-C₈₄H₳₉, -NH-Cyclopentyl-C₈₅H₳₁,
-NH-Cyclopentyl-C₈₆H₳₃, -NH-Cyclopentyl-C₈₇H₳₅, -NH-Cyclopentyl-C₈₈H₳₇,
-NH-Cyclopentyl-C₈₉H₳₉, -NH-Cyclopentyl-C₉₀H₳₁, -NH-Cyclopentyl-C₉₁H₳₃,
-NH-Cyclopentyl-C₉₂H₳₅, -NH-Cyclopentyl-C₉₃H₳₇, -NH-Cyclopentyl-C₉₄H₳₉,
-NH-C(=NH)-N[C(CH3)3]2, -0-CO-NH2, -0-CO-NHCH3, -0-CO-NHC2H5, -0-CO-NHC3H7, -0-CO-NH-CyCIo-C3H5, from intramuscular injection, continuous intravenous infusion, or continuous subcutaneous infusion.

-0-CO-OCH(3)2, -0-CO-OC(CH3)3, -CH2F, -CH2Cl, -CH2Br, -CH2I, -CH2-CH2F, -CH2CHF2, -CH2-CF3, -CH2CH2Cl, -CH2CH2Br, -CH2CH2I, -CH3, -C2H5, -C3H7, -CH(CH3)2, -C(CH3)3, -C4H9, -CH2-CH(CH3)2, -CH(CH3)-C2H5, -C5H11, -Ph, -CH2-Ph, -CPh3, -CH=CH2, -CH2-CH=CH2, -C(CH3)=CH2, -CH=CH-CH3, -C2H4-CH=CH2, -CH=C(CH3)2, -C≡CH, -C≡C-CH3, -CH2-CH2=C-

X represents a single bond or a double bond;
n represents an integer from 1 to 10.

3. Use according to claim 1, wherein the compound of the general formula (I) is selected from the group comprising: 8-α-ergoline, 8-α,1,6-dimethyl-ergoline, 8-α-1-methylergoline, 8-α-6-methylergoline, 8-α-10-methoxyergoline, lisuride, d-isolysergic acid, d-isolysergic acid amide, d-isolysergic acid di-ethylamide, proterguride and terguride.

4. Use according to claim 1, wherein the compound of the general formula (I) is selected from the group comprising: lisuride, terguride and proterguride.

5. Use according to one of claims 1 to 4, wherein the brain disorder is selected from acute traumatic brain injury, severe acute traumatic brain injury, neural edema and increased cranial pressure associated with traumatic brain injury.

6. Use according to one of claims 1 to 5, wherein the brain edema occurs during the acute phase of a brain injury event.

7. Use according to one of claims 1 to 5, wherein the increased cranial pressure occurs during the acute phase of a brain injury event.

8. Use according to one of claims 1 to 7, wherein the pharmaceutical composition is suitable for parenteral, transdermal, oral, low dose intravenous, or subcutaneous administration, or intramuscular injection, continuous intravenous infusion, or continuous subcutaneous infusion.
9. Use according to claim 8 wherein the continuous intravenous infusion or continuous subcutaneous infusion is administered by a perfusor system or a programmable minipump.

10. Use according to claim 8 wherein the pharmaceutical composition is suitable for transdermal administration via transdermal patch as a longterm chronic therapy.

11. Use according to any one of claims 8 to 10, wherein the compound of the general formula (I) is administered in a dosage corresponding to an effective concentration in the range of 0.5 - 25 µg/kg body weight.

12. Use according to claim 11, wherein the dosage is infused during acute brain injury continuously over a period from 24 hours to 4 weeks and in the case of epileptic seizures and symptomatic epilepsy as a chronic longterm therapy.