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(54) Titre : ENANTIOMERE 4R,5S DE 2-(5-METHYL-2-OXO-4-PHENYL-PYRROLIDIN-1-YL)-ACETAMIDE AYANT UNE ACTIVITE NOOTROPIQUE

(54) Title: 4R,5S-ENANTIOMER OF 2-(5-METHYL-2-OXO-4-PHENYL-PYRROLIDIN-1-YL)-ACETAMIDE WITH NOOTROPIC ACTIVITY

(57) Abrégé/Abstract:
The invention relates to the 5S,4R-enantiomer of 2-(5-methyl-2-oxo-4-phenyl- pyrrolidin-1-yl)-acetamide with cognition enhancing activity of high pharmacological value and to its preparation method which includes the synthesis of 5S-methyl-4R-phenylpyrrolidin-2-one, its N-alkylation with ethyl haloacetate and the treatment of intermediate ethyl 2-(5S-methyl-2-oxo-4R-phenyl-pyrrolidin-1-yl)-acetate with ammonia.

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(54) **Title**: 4R,5S-ENANTIOMER OF 2-(5-METHYL-2-OXO-4-PHENYL-PYRROLIDIN-1-YL)-ACETAMIDE WITH NOOTROPIC ACTIVITY

(57) **Abstract**: The invention relates to the 5S,4R-enantiomer of 2-(5-methyl-2-oxo-4-phenyl- pyrrolidin-1-yl)-acetamide with cognition enhancing activity of high pharmacological value and to its preparation method which includes the synthesis of 5S-methyl-4R-phenylpyrrolidin-2-one, its N-alkylation with ethyl haloacetate and the treatment of intermediate ethyl 2-(5S-methyl-2-oxo-4R-phenyl-pyrrolidin-1-yl)-acetate with ammonia.

4*R*,5*S*-Enantiomer of 2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide with nootropic activity

Technical Field

[0001] This invention relates to preparation and medical use of 4*R*,5*S*-enantiomer of 2-(5-methyl-2-oxo-4-phenylpyrrolidin-1-yl)-acetamide for use as nootropic medicament.

Background Art

[0002] It is known that cognition enhancing drugs facilitate attention abilities and acquisition, storage and retrieval of information and attenuate the impairment of cognitive functions associated with head traumas, stroke, age and age-related pathologies.

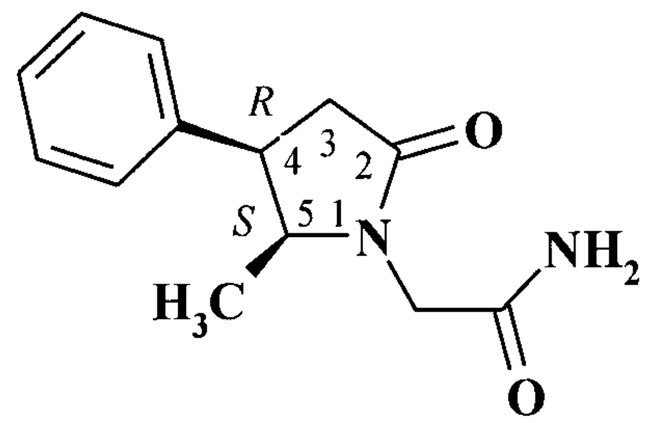
[0003] Racemic molecule of 2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide, a piracetam structural derivative, was mentioned in 2001 (M. V. Berestovitskaya, M. M. Zobachova, B. M. Novikov, O. S. Vasil'eva, N. V. Usik, S. M. Aleksandrova, I. N. Turenkov. International Conference on the Synthesis of Nitrogen Heterocycles, Moscov, Oct. 9-12, 2001, vol. 1, pp. 229-233). However there is no data on the chemical structure and biological properties of this compound provided.

[0004] **EP 2013166** B (AKCIJU SABIEDRIBA OLAINFARM) 10.03.2010 disclosed *R*-enantiomer of *N*-carbamoylmethyl-4-phenyl-2-pyrrolidinone being different from the present one only in that 5-methyl group is lacking with neurotropic activity.

Summary of invention

[0005] According to the current invention, the pharmacological studies of racemic 2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide, containing two chiral centers in positions 4 and 5 of the pyrrolidone ring, unexpectedly revealed its rather promising cognition enhancing properties. However, when we have prepared separate 4*R*,5*S*-enantiomer of 2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide and subjected it to nootropic investigation, it surprisingly and unexpectedly appeared to be much more pharmacologically active in comparison to the parent racemic compound.

[0006] According to the current invention, we describe a method of preparation of 4*R*,5*S*-enantiomer of 2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide of Formula 1 with cognition enhancing properties of high pharmacological value:



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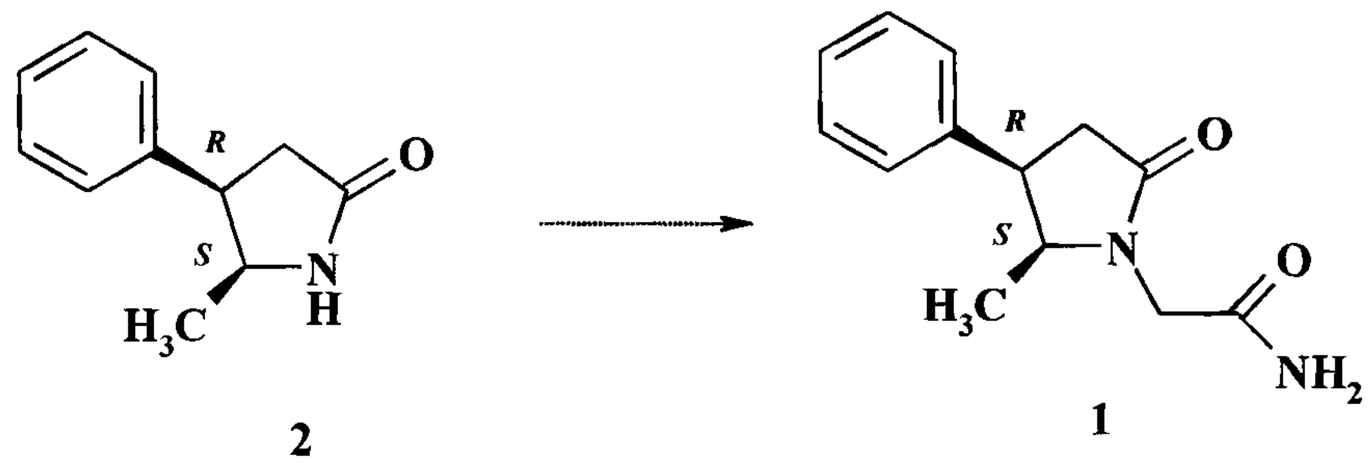
which is a new chemical compound with nootropic activity.

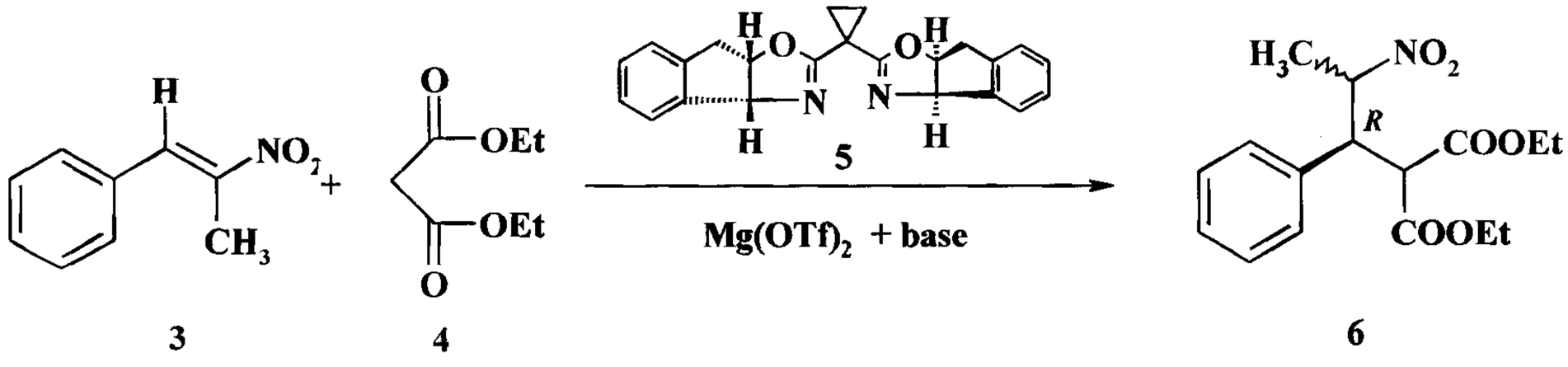
[0007] According to the current invention, the chemical scheme of 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide (**1**) preparation includes the synthesis of 4*R*,5*S*-enantiomer of 5-methyl-4-phenylpyrrolidin-2-one (**2**) and the insertion of acetamide group in position 1 of the pyrrolidone ring:



2 1

[0008] Methods of racemic 5-methyl-4-phenylpyrrolidin-2-one preparation and its separation into enantiomeric mixture of *eritro*- and *treo*-isomres were documented in literature (Colonge J., Pouchol J.M., *Bull. Soc. Chim.*, **1962**, 598-603; Langlois M.. et. al. *Bull. Soc. Chim.*, **1971**, 2976-2982; Lesniak S., Pasternak B., *Tetrahedron Lett.*, 2005, **46**, 3093-3095). However, no written evidence about the resolution of racemic 5-methyl-4-phenylpyrrolidin-2-one into separate enantiomers or their direct synthesis from chiral or non-chiral chemical substances have been found.

[0009] According to the current invention, this problem was solved by asymmetric Michael addition of 2-nitroprop-1-enylbenzene (**3**) to diethyl malonate (**3**) in the presence of complex catalyst consisting of chiral 2,2'-cyclopropylidene-bis-oxazoline **5**, magnesium triflate and organic base leading to the formation of diethyl 2-[2(*R*,*S*)-nitro-1*R*-phenylpropyl]-malonate diastereoisomeric mixture (**6**)



3 4 6

[0010] The obtained intermediate **6** was converted into 5*S*-methyl-4*R*-phenylpyrrolidin-2-one (**2**) by the sequence of following steps (see scheme below):

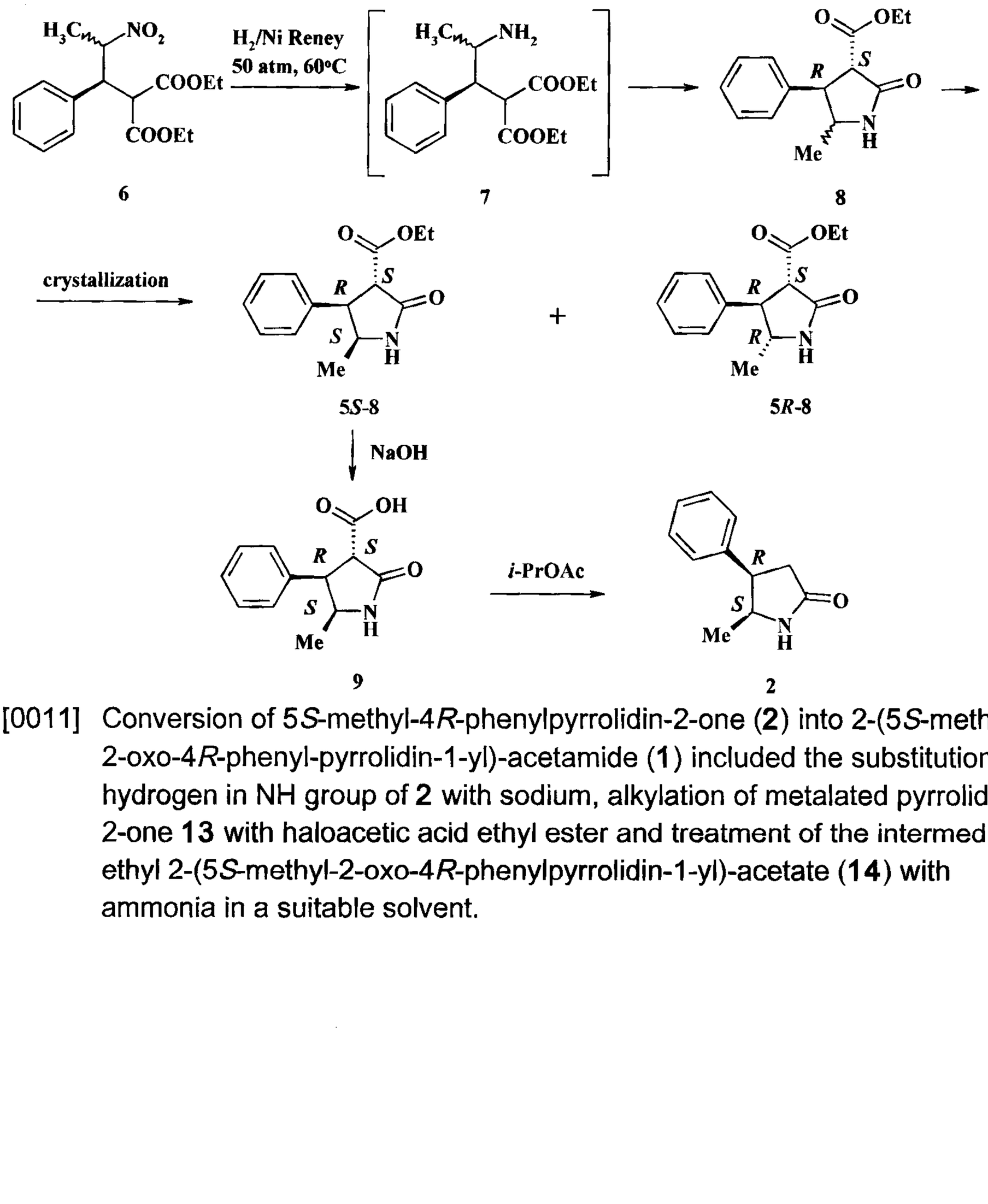
a) the addition of 2-nitroprop-1-enylbenzene to diethyl malonate in the presence of complex catalysts consisting of chiral 2,2'-cyclopropylidene-bis-oxazoline, magnesium triflate and organic base;
b) the conversion of diethyl 2-(2-nitro-1*R*-phenylpropyl)malonate into enantiomeric 5*S*-methyl-4*R*-phenylpyrrolidin-2-one by the hydrogenation of diethyl 2-(2-nitro-1*R*-phenylpropyl)malonate in the presence of Ni Reney, resolution of the diastereoisomeric mixture of

ethyl 5-methyl-2-oxo-4*R*-phenylpyrrolidin-3*S*-carboxylate into separate 5*S*,4*R*- and 5*R*,4*S*-enantiomers, decarboxylation of ethyl 5*S*-methyl-2-oxo-4*R*-phenylpyrrolidin-3*S*-carboxylate;

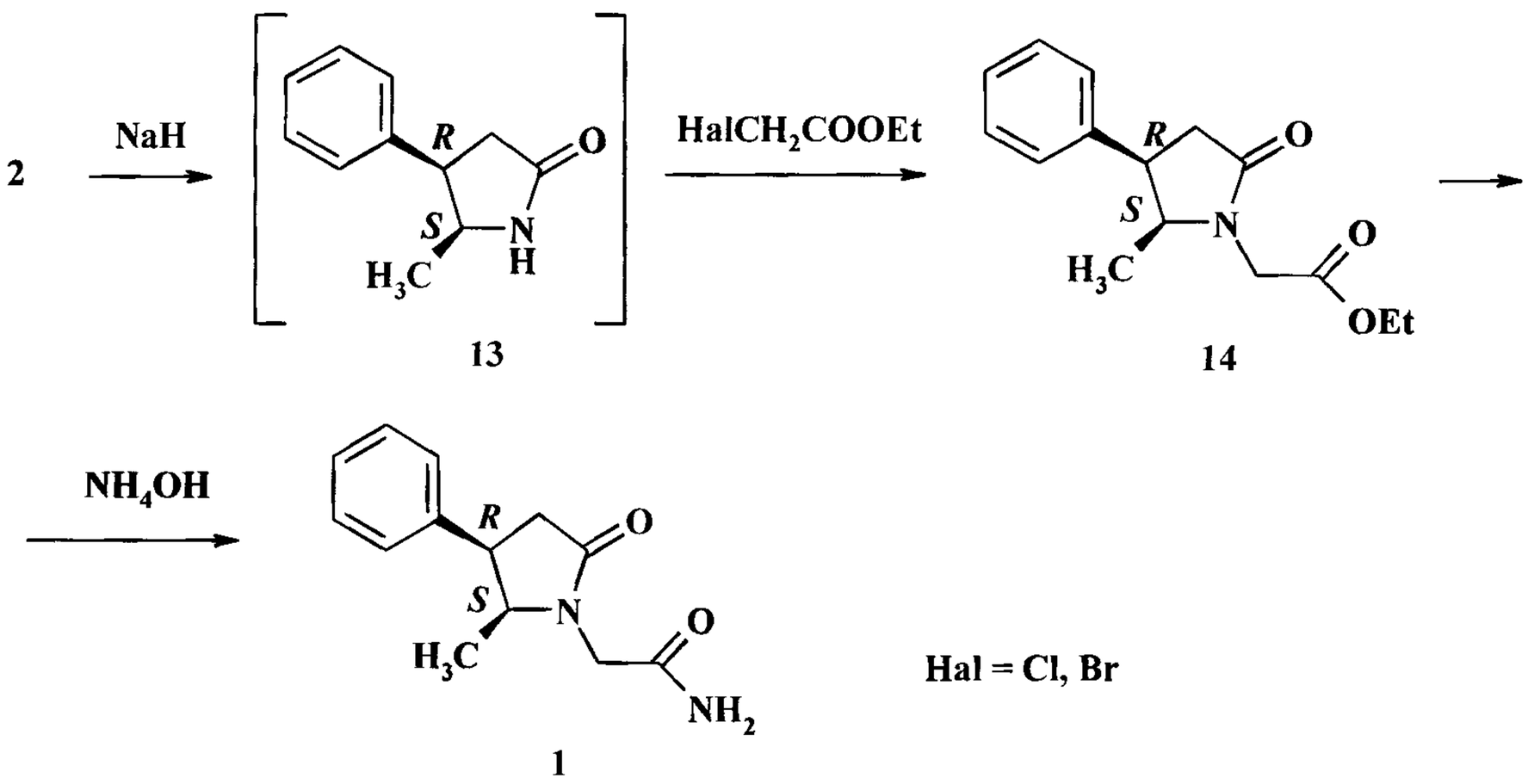
c) the substitution of hydrogen in the amide group of 5*S*-methyl-4*R*-phenylpyrrolidin-2-one with sodium ion in a suitable organic solvent.

d) the N-alkylation of N-metalated 5*S*-methyl-4*R*-phenylpyrrolidin-2-one with haloacetic acid esters in a suitable organic solvent;

e) the amidation of ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate with ammonia in a suitable solvent.



[0011] Conversion of 5*S*-methyl-4*R*-phenylpyrrolidin-2-one (**2**) into 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide (**1**) included the substitution of hydrogen in NH group of **2** with sodium, alkylation of metalated pyrrolidin-2-one **13** with haloacetic acid ethyl ester and treatment of the intermediate ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenylpyrrolidin-1-yl)-acetate (**14**) with ammonia in a suitable solvent.



[0012] According to the current invention, comparative pharmacological evaluation of 2-(4*R*-phenyl-2-oxopyrrolidin-1-yl)acetamide), *racemic* 2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide and 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide, employing standard passive avoidance test, proved the high effectiveness of the optically active 2-(5*S*-methyl-2-oxo-4*R*-phenylpyrrolidin-1-yl)-acetamide (1) as enhancer of learning memory.

[0013] Therefore, 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide may be used as a highly effective agent for use as medicament with nootropic activity.

Description of embodiments

[0014] The scope of the invention should not be limited to the working examples, which are for demonstration purposes. One skilled in the art can practice the invention based on the disclosures in the present patent application.

[0015] The following examples are illustrating but not restricting the present invention.

[0016] Examples

[0017] Example 1

[0018] The solution of (3a*R*,3'a*R*,8a*S*,8'a*S*)-2,2'-cyclopropylidenebis-[3a,8a]-dihydro-8H-indeno-[1,2-d]-oxazole (420 mg, 1.18 mM) in chloroform (hydrocarbon stabilized) (5 ml), magnesium triflate (378 mg, 0. 1.18 mM) and water (25 μL) were added into 250 ml reaction flask at room temperature and mixture was stirred under argon for 1 hour. Molecular sieves (1.0 g) and 1,4-dioxane (30 ml) were added to the obtained mixture, and stirred for additional 30 min. Obtained suspension was diluted with 45 ml of chloroform solution containing diethylmalonate (1.67 g, 10.2 mM), 2-nitroprop-1-enylbenzene (1.63 g, 10.0 mM) and morpholine (46 μL). Reaction mixture was stirred at room temperature. Conversion and selectivity were determined by chiral HPLC analysis [Chiralpak IC, 4.6x250 mm, 1.0 ml/min, eluent i-PrOH-Hexane (1:9)] each 24 hours. After

completion of reaction, the reaction mixture was diluted with hexane (50 ml), stirred for 20 min. and the solid was filtered off. The filtrate was washed with 5% aqueous HCl (2x50 ml), brine (2x50 ml), dried over anhydrous Na_2SO_4. The drying reagent was removed by filtration and the solution was concentrated under reduced pressure. The residue was purified by column chromatography on silica with ethylacetate/hexane (1:10) collecting fractions with R_f 0.28. Yield 87% (2.8 g). Obtained low-melting yellow solid, according to chiral HPLS is the mixture of eritro- and treo-isomers of diethyl 2-(2-nitro-1*R*-phenylpropyl)-malonate in ratio 3:1. Optical purity: 93%.

[0019] ^{1}H NMR ($CDCl_3$), δ, ppm (J, Hz): 0.85 (2.25 H, t, J=7.0 eritro-$CH_2\underline{CH_3}$); 0.93 (0.75 H, t, J=7.0 treo-$CH_2\underline{CH_3}$); 1.15-1.27 (3H, m, $CH_2\underline{CH_3}$); 1.29 (0.75 H, d, J=6.8, treo-$C\underline{H_3}CNO_2$); 1.37 (2.25 H, d, J=6.8, eritro-$C\underline{H_3}CNO_2$); 3.63-3.93 (3H, m, $\underline{CH_2}CH_3$, COC$\underline{H}$CO); 4.07-4.29 (3H, m, $\underline{CH_2}CH_3$, PhC$\underline{H}$,); 4.29-5.06 (0.25H, m, treo-C$\underline{H}NO_2$); 5.07-5.16 (0.75H, m, eritro-C$\underline{H}NO_2$); 6.99-7.28 (5H, m, C_6H_5).

[0020] Example 2

[0021] The substitution of morpholine in example 1 by N-methylmorpholine resulted in the formation of diethyl 2-(2-nitro-1*R*-phenylpropyl)-malonate as a mixture of eritro- and treo-isomers 3:1. Optical purity: 94%. Yield 85%.

[0022] Example 3.

[0023] The substitution of morpholine in example 1 by the mixture of morpholine (46 μL) and tetra-methylguanidine (46 μL) resulted in the formation of diethyl 2-(2-nitro-1*R*-phenylpropyl)-malonate as a mixture of eritro- and treo-isomers 3:1. Optical purity: 95%. Yield 87%.

[0024] Example 4

[0025] The stirring suspension of diethyl 2-(2-nitro-1*R*-phenylpropyl)-malonate (2.34 g, 7.22 mM) in ethanol (50 ml) and 1 ml of 50% Ni Reney slurry in water was hydrogenated at 50 °C and 50 atm for 18 hours. After completion of reaction, the reaction mixture was cooled, the catalyst was filtered off and washed with 30 ml of ethanol. Filtrate was concentrated under reduced pressure. The residue was purified by liquid column chromatography on silica gel with CH_2Cl_2/EtOH (10:1 → 1:10) collecting fractions with R_f 0.28. Yield 80% (1.43 g). Obtained white solid according to ^{1}H NMR spectra is the mixture of eritro- and treo-isomers of ethyl 5-methyl-2-oxo-4*R*-phenylpyrrolidin-3*S*-carboxylate in ratio 17:3. Yield 80% (1.43 g).

[0026] ^{1}H NMR ($CDCl_3$), δ, ppm (J, Hz): 0.76 (2.55 H, d, J=6.3 eritro-5-CH_3); 1.18-1.23 (3.45 H, m, treo-5-CH_3 and $CH_2\underline{CH_3}$); 3.73 (1H, d, J=9.0, 3-H); 4.02-4.22 (4H, m, $\underline{CH_2}CH_3$, 4-H, 5-H); 6.23 (1H, br. s, NH); 7.09-7.33 (5H, m, C_6H_5).

[0027] Recrystallization of the obtained product from ethanol resulted in the isolation of 785 mg of 5*S*-methyl-4*R*-phenyl-2-pyrrolidinone-3*S*-carboxylate. M. p. 141-143 °C.

[0028] Anal. Calculated for $C_{14}H_{17}NO_3$ (247.30) C 68.00; H 6.93; N 5.66.

[0029] Found: C 67.93; H 6.87; N 5.64.

[0030] ^{1}H NMR ($CDCl_3$), δ, ppm (J, Hz): 0.76 (3 H, d, J=6.3 eritro-5-CH_3); 1.18-1.23 (3 H, m, $CH_2\underline{CH_3}$); 3.73 (1H, d, J=9.0, 3-H); 4.02-4.22 (4H, m, $\underline{CH_2}CH_3$, 4-H, 5-H); 6.23 (1H, br. s, NH); 7.09-7.33 (5H, m, C_6H_5).

[0031] Example 5

[0032] Potassium hydroxide (672 mg, 12 mM) was added to the solution of ethyl 5*S*-methyl-4*R*-phenyl-2-pyrrolidinone-3*S*-carboxylate (900 mg, 4.00 mM) in methanol (50 ml) and obtained mixture was refluxed for 3 hours. The reaction mixture was cooled and evaporated under reduced pressure. The residue was dissolved in 20 ml of water, water solution was washed with ethylacetate (3x30 ml) adjusted to pH 2 with diluted HCl and evaporated under reduced pressure. Obtained residue was suspended in EtOH/CH_2Cl_2 (1:1) solution, stirred for 1 hour, filtered and filtrate evaporated under reduced pressure. The residue was dissolved in the solution of iso-propylacetate (40 ml) and para-toluenesulfonic acid (100 mg). Obtained mixture was refluxed for 24 hours, cooled and concentrated under reduced pressure. The residue was purified by liquid column chromatorgaphy on silca gel with CH_2Cl_2/EtOH (20:1) collecting fractions with R_f 0.40. Obtained yellow solid according chiral HPLC is the eritro-somer of 5*S*-methyl-4*R*-phenylpyrrolidin-2-one. Yield 65% (455 mg).

[0033] Anal. Calculated for $C_{11}H_{13}NO$ (175.23) C 75.40; H 7.48; N 7.99.

[0034] Found: C 75.63; H 7.55; N 8.07.

[0035] ^{1}H NMR ($CDCl_3$), δ, ppm (J, Hz): 0.75 (3.00 H, d, J=6.5 5-CH_3); 2.55-2.69 (2H, m, 3-CH_2); 3.64-3.72 (1H, m, 4-H); 3.96-4.04 (1H, m, 5-H); 6.78 (1H, br. s, NH); 7.07-7.33 (5H, m, C_6H_5).

[0036] Example 6

[0037] The substitution of potassium hydroxide in example 5 by sodium hydroxide resulted in the formation of the 5*S*-methyl-4*R*-phenyl-2-pyrrolidinone. Yield 62%.

[0038] Example 7

[0039] The solution of 5*S*-methyl-4*R*-phenyl-2-pyrrolidinone (351 mg, 2.00 mM) in toluene (30 ml) was added to the suspension of sodium hydride (56 mg, 2.35 mM) in toluene (30 ml). The stirred mixture was heated at 80÷90°C during 30 min and then cooled to the room temperature. Ethyl bromoacetate (368 mg, 2.20mM) was added to the reaction mixture, which was heated at 110÷120°C for 6 hours and than concentrated under reduced pressure. The residue was dissolved in toluene (30 ml). Obtained solution was washed with 5% aqueous HCl (2x50 ml), brine (2x50 ml), dried over anhydrous Na_2SO_4. The drying reagent was removed by

filtration and the solution was concentrated under reduced pressure. The residue was purified by column chromatography on silica with CH_2Cl_2/MeOH (20:1). Fractions with R_f 0.48 were collected and evaporated under reduced pressure, giving ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate (381 mg, 73%) as colorless oil.

[0040] ^{1}H NMR ($CDCl_3$), δ, ppm (J, Hz): 0.72 (3.00 H, d, J=6.6 5-CH_3); 1.23 (3H, t, J=7.0, $CH_2\underline{CH_3}$); 2.60-2.91 (2H, d, J=8.5, 3-CH_2); 3.65-3.74 (1H, m, 4-H); 3.66 (2H, d, J=17.7, NCH_2COO); 4.01-4.10 (1H, m, 5-H); 4.10-4.20 (2H, m, $\underline{CH_2}CH_3$); 4.38 (1H, d, J=17.7, NCH_2COO); 7.09-7.31 (5H, m, C_6H_5).

[0041] Example 8

[0042] The substitution of sodium hydride in example 7 by sodium ethylate resulted in the formation of ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate with yield 68%.

[0043] Example 9

[0044] The substitution of ethyl bromoacetate in example 7 by ethyl chloroacetate resulted in formation of ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate with yield 70%.

[0045] Example 10

[0046] The substitution of toluene in example 7 by hexane resulted in the formation of ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate with yield 71%.

[0047] Example 11

[0048] The substitution of toluene in example 7 by benzene resulted in the formation of ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate with yield 70%.

[0049] Example 12

[0050] The substitution of toluene in example 7 by 1,4-dioxane resulted in the formation of ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate with yield 72%.

[0051] Example 13

[0052] The substitution of toluene in example 7 by dichloromethane resulted in the formation of ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate with yield 67%.

[0053] Example 14

[0054] The solution of ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate (350 mg, 1.34 mM) in methanol (30 ml) was saturated with gaseous ammonia for 5 hours. Reaction mixture was concentrated under reduced pressure and residue was purified by column chromatography with CH_2Cl_2/EtOH (20:1). Fractions with R_f 0.32 were collected and evaporated under reduced pressure, giving 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide (249 mg, 80%) as white solid recrystallized from water. M.p. 169-171°C.

[0055] Calculated for $C_{13}H_{16}N_2O_2$ (232.28) C 67.22; H 6.94; N 12.06.

[0056] Found: C 67.31; H 6.99; N 12.10.

[0057] ^{1}H NMR ($CDCl_3$), δ: 0.77 (3.00 H, d, J=6.6 5-CH_3); 2.62-2.81 (2H, m, 3-CH_2); 3.66-3.75 (1H, m, 4-H); 3.75 (1H, d, J=16, NCH_2COO); 3.98-4.08 (1H, m, 5-H); 4.04 (1H, d, J=16, NCH_2COO); 5.48 and 6.29 (2H, br.s, br.s, NH_2); 7.07-7.32 (5H, m, C_6H_5).

[0058] Example 15

[0059] The substitution of gaseous ammonia in example 13 by the 25% aqueous ammonium resulted in the formation of 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide with 78% yield.

[0060] Example 16

[0061] The substitution of methanol in example 13 by the ethanol resulted in the formation of 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide with 81% yield.

[0062] Example 17

[0063] The substitution of methanol in example 13 by the n-propanol resulted in the formation of 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide with 77% yield.

[0064] Example 18

[0065] Racemic 2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide was prepared by N-methycarbamoylation of 5-methyl-4-phenylpyrrolidin-2-one

[0066] ^{1}H NMR ($CDCl_3$), δ: 0.77 (1.50 H, d, J=6.6 eritro-5-CH_3); 1.23 (1.50 H, d, J=6.3 treo-5-CH_3); 2.53-2.86 (2H, m, 3-CH_2); 3.66-3.75 (1H, m, 4-H); 3.75 (0.5H, d, J=16, eritro-NCH_2COO); 3.86 (0.5H, d, J=16, treo-NCH_2COO); 3.95 (0.5H, d, J=16, treo-NCH_2COO); 3.98-4.08 (1H, m, 5-H); 4.04 (0.5H, d, J=16, erito-NCH_2COO); 5.48 and 6.29 (2H, br.s, br.s, NH_2); 7.07-7.32 (5H, m, C_6H_5).

[0067] **Biological tests**

[0068] Learning and memory

[0069] **Passive avoidance test** was performed in a shuttle-box apparatus (Ugo Basile, Italy) with two communicating compartments of equal size (20x10 x16 cm) and a stainless steel grid floor (bars spaced 0.7 cm apart). The right-hand compartment (shock compartment) was painted black to obtain a dark chamber. The left-hand compartment was painted white and illuminated by a bulb (100 W) installed on the top of plexiglass cover. These compartments were separated by a guillotine door (5x4 cm). On day 1 (training trial), mice were placed in the illuminated compartment and the door between the two compartments was opened 60 s later. When mice entered the dark compartment with all four feet, the door automatically closed and an inescapable electrical foot shock (0.1 mA; 3 s) was delivered through the grid floor. Latency to cross into the dark compartment (training latency) was automatically measured. The retention test was performed 24 hours later (day 2). Mice were placed into the light (safe) compartment, with access to the dark one (within 10 s) for a period

of 300 s (cut-off time). The latency to cross into the dark compartment with all four feet was automatically measured (retention latency).

[0070] Effects of 2-(4*R*-phenyl-2-oxopyrrolidin-1-yl)acetamide), *racemic* 2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide and 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide on retention of passive avoidance response (memory) in ICR male mice.

[0071] Data presented in Table 1 demonstrate effects of, 2-(4*R*-phenyl-2-oxopyrrolidin-1-yl)acetamide), *racemic* 2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide and 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide on memory in the passive avoidance task in mice.

Table 1

Effects of administrated compounds on memory in the passive avoidance task in mice

Compounds	**Latent time, s**
Control (Saline)	62,7±6,2
2-(4*R*-phenyl-2-oxopyrrolidin-1-yl)acetamide	94,9±27,6
2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide *racemic*	74,2±19,9
2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide	170,6±41,9*#$

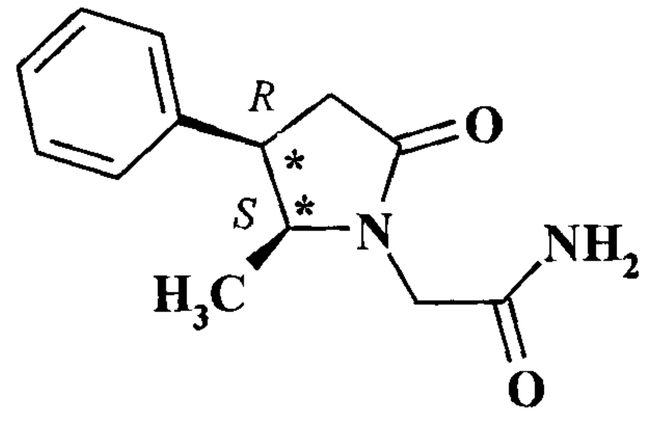
The compounds were administered intraperitoneally at the dose of 46 μmol/kg 60 min before the training trial (day 1). The saline control group was run concurrently with the drug-treated groups. The statistical analysis was performed by Student's t-test. Data represent mean ± S.E.M

*$p < 0.05$, #$p < 0.05$, $ $p < 0.05$ versus saline control group, 2-(4*R*-phenyl-2-oxopyrrolidin-1-yl)acetamide-treated group and *racemic* 2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide-treated group, respectively; $n \geq 10$

[0072] As it is presented in *Table 1*, 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide treatment at the dose of 46 μmol/kg induced a statistically significant effect on memory.

Claims

1. 2-(5*S*-Methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide (I).



I

2. 2-(5*S*-Methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide for use as a medicament.
3. 2-(5*S*-Methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide for use as a nootropic medicament.
4. 2-(5*S*-Methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide for use as cognition enhancer.
5. 2-(5*S*-Methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetamide for use in treating of cognitive deficits.
6. A process of preparation of a compound (I) according to the claim 1, which includes following steps:
   a) the addition of 2-nitroprop-1-enylbenzene to diethyl malonate in the presence of complex catalysts consisting of magnesium triflate and organic base;
   b) the conversion of diethyl 2-(2-nitro-1*R*-phenylpropyl)malonate into enantiomeric 5*S*-methyl-4*R*-phenylpyrrolidin-2-one by the hydrogenation, wherein hydrogen pressure is between 3 and 60 atm, in the presence of Ni Reney, resolution of the diastereoisomeric mixture of ethyl 5-methyl-2-oxo-4*R*-phenylpyrrolidin-3*S*-carboxylate into separate 5*S*,4*R*- and 5*R*,4S-enantiomers, decarboxylation of ethyl 5*S*-methyl-2-oxo-4*R*-phenylpyrrolidin-3*S*-carboxylate;
   c) the substitution of hydrogen in the amide group of 5*S*-methyl-4*R*-phenylpyrrolidin-2-one with sodium ion in a suitable organic solvent.
   d) the *N*-alkylation of *N*-metalated 5*S*-methyl-4*R*-phenylpyrrolidin-2-one with haloacetic acid esters in a suitable organic solvent;
   e) the amidation of ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate with ammonia in a suitable solvent.
7. A process according to claim 6 wherein in step a) organic base is selected from the group, containing morpholine, N-methylmorpholine, 1,1,3,3-tetramethylquanidine and their mixtures.
8. A process according to claim 6 wherein in step b) temperature of decarboxylation of 5*S*-methyl-2-oxo-4*R*-phenylpyrrolidin-3*S*-carboxylate in iso-propyl acetate solution in the presence of para-toluenesulfonic acid is between 50° and 88°C.

9. A process according to claim 6 wherein in step c) sodium ion is introduced in the amide group of 5*S*-methyl-4*R*-phenylpyrrolidin-2-one by sodium hydride or sodium ethylate.
10. A process according to claim 6 wherein in step d) haloacetic acid ester is selected from the group of bromoacetic acid ester or chloroacetic acid ester.
11. A process according to claim 6 wherein in step e) amidation of ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate is realized in aqueous ammonia or its mixture with a suitable organic solvent.
12. A process according to claim 6 wherein in step e) amidation of ethyl 2-(5*S*-methyl-2-oxo-4*R*-phenyl-pyrrolidin-1-yl)-acetate is realized in a suitable organic solvent by its saturation with gaseous ammonia.
13. A process according to claim 11 or 12 wherein the organic solvent used for reactions is selected from group containing methanol, ethanol, propanol, chloroform, methylene chloride, ethyl acetate and 1,4-dioxane.