(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 June 2017 (29.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/108441 A1

(51) International Patent Classification:
A61K 45/06 (2006.01) *A61K 31/505* (2006.01)
A61K 31/27 (2006.01) *A61K 31/55* (2006.01)
A61K 31/445 (2006.01) *A61P 25/28* (2006.01)

(21) International Application Number:
PCT/EP2016/080362

(22) International Filing Date:
9 December 2016 (09.12.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
15202028.5 22 December 2015 (22.12.2015) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2017/108441 A1

(54) Title: TREATMENT OF COGNITIVE IMPAIRMENT WITH CGC STIMULATOR

(57) Abstract: The present invention is directed to the treatment of cognitive impairment. More in particular, the present invention is directed to the treatment of cognitive impairment associated with aging, Alzheimer's disease or schizophrenia. More in particular, it provides a composition comprising an sGC stimulator for use in the treatment of cognitive impairment in a mammal in need of such treatment, wherein the treatment comprises administering to a mammal suffering from cognitive impairment an sGC stimulator selected from the group consisting of Riociguat,its active metabolite M1, a pharmaceutically acceptable salt of Riociguat and a pharmaceutically acceptable salt of M1, wherein the sGC stimulator is administered at a daily dose of between 0. and 1.0 mg.

TREATMENT OF COGNITIVE IMPAIRMENT WITH CGC STIMULATOR

Field of the invention

The present invention is directed to the treatment of cognitive impairment. More in particular, the present invention is directed to the treatment of cognitive impairment associated with aging, Alzheimer's disease or schizophrenia.

Background of the invention

Society is faced with an increasing number of aged people. Thus, there will be an increase in cognitive impairments in the population in the near future. In addition, the cognitive demands of today's society increase due to the increased flow of information via internet, television and cell phones in daily life as well as at work. Suboptimal cognitive function and cognitive impairments heavily affect daily life of the individual and the quality of life (Mattson et al, Physiol Rev, 2000 Vol. 82, pp 637-672). This will be especially present in patients with pronounced cognitive decline as in dementia and Alzheimer's disease, but also depression and schizophrenia (Blaney, Psychol Bull, 1986, pp 229-246. Frith, Br Med Bull, 1996, Vol 52, pp 618-626). Therefore, there is a clear and increasing need for strategies and therapeutics to counteract cognitive decline that may eventually increase the individual quality of life.

There is a recent publication indicating that an increased activity of soluble guanylate cyclase (sGC) improves cognitive function in aged rats back to that of the level of adult rats (Komsuoglu Celikyurt et al, Med. Sci. Monit. Basic Res., 2014, Vol 20, pp 130-137). In that study, the drug YC-1 was used, which is an activator of sGC. The natural activator of sGC is the molecule nitric oxide (NO). YC-1, which is a relatively non-specific drug, mimics the action of NO; so NO does not need to be present for YC-1 to be effective.

It is an object of the present invention to find a drug for the improved treatment of cognitive impairment.

Summary of the invention

We found that the sGC stimulator Riociguat (BAY 63-2521) or its active metabolite M1 (BAY60-4552), previously described for the treatment of pulmonary hypertension, was capable of treating cognitive impairment when administered in a specific dose range.

The invention therefore relates to a composition comprising an sGC stimulator for use in the treatment of cognitive impairment in a mammal in need of such treatment, wherein the treatment comprises administering to a mammal suffering from cognitive impairment an sGC stimulator selected from the group consisting of Riociguat, its active metabolite M1, a pharmaceutically acceptable salt of Riociguat and a pharmaceutically acceptable salt of M1, wherein the sGC stimulator is administered at a daily dose of between 0.1 and 1.0 mg.

We also found that the action of the sGC stimulator could be improved when administered in combination, either sequentially or simultaneously with an acetylcholinesterase inhibitor.

Hence, in a further embodiment, the invention relates to a pharmaceutical composition, comprising a sGC stimulator, an acetylcholinesterase inhibitor and a pharmaceutically acceptable carrier.

Legend to the figures

Figure 1 is a graph showing the average discrimination index (d2) value and SEM of the 24h interval OLT performance of mice after different doses of riociguat. The d2 is indicated on the y-axis and the different doses of riociguat are shown on the x-axis. Hash signs indicate a difference from zero (one-sample t-test: ###: $p < 0.001$). A difference from the vehicle condition is indicated with asterisks (post-hoc Dunnett's t-test: ***: $p<0.001$).

Figure 2 is a graph showing the average d2 value and SEM of the 1h interval OLT performance of mice after biperiden and riociguat administration. Biperiden was always given at a dose of 3 mg/kg. The discrimination index (d2) is indicated on the y-axis and the different treatment conditions are shown on the x-axis. Hash signs indicate a difference from zero (one sample t-test: ##: $p<0.01$; ###: $p<0.001$). A difference from the biperiden + vehicle condition is indicated with asterisks (post-hoc Dunnett's t-test: *: $p<0.05$; **: $p<0.01$).

Figure 3 is a graph showing the average percentages of alternations and SEM of the y-maze continuous alternation performance after biperiden and riociguat administration. The mean alternation % is indicated on the y-axis and the different treatment conditions are shown on the x-axis. Biperiden was always given at a dose of 3 mg/kg. Hash signs indicate a difference from chance level, i.e. 50% (one-sample t-test: #: $p<0.05$; ##: $p<0.01$; ###: $p<0.001$). A difference from the biperiden + vehicle condition is indicated with asterisks (post-hoc Dunnett's t-test: *: $p<0.05$; **: $p<0.01$).

Figure 4 is a graph showing the average d2 value and SEM of the 24h interval

OLT performance of mice after sub-efficacious doses of riociguat and/or donepezil. The discrimination index (d2) is indicated on the y-axis and the different treatment conditions are shown on the x-axis. Hash signs indicate a difference from zero (one-sample t-test: ##: $p < 0.01$). A difference from the vehicle + vehicle condition is indicated with asterisks (post-hoc Dunnett's t-test: *: $p<0.05$).

Detailed description of the invention

As a model system, we employed the object location task (OLT) as described in example 2 wherein mice were treated with the sGC stimulator Riociguat (BAY 63-2521). In contrast to an sGC activator, a stimulator of sGC is dependent on NO being present and modulates the action of available NO on sGC.

The model system provides an index d2, which is a relative measure of discrimination corrected for exploratory activity. The d2 index can range from -1 to 1. A significant positive difference from zero, i.e. chance level, indicates that the mice remembered the object locations from a previous encounter, and a difference from the vehicle condition signifies an actual memory improvement.

Table 1 summarizes the results of the 24h inter-trial interval OLT per treatment condition. There were no differences in exploration time between treatment conditions for both T1 (e1: $F_{4,68}= 0.71$, n.s.) and T2 (e2: $F_{4,68}= 1.67$, n.s.). When provided with a vehicle treatment, the mice were not able to remember the object locations after 24h as is indicated with a d2 value that is not different from chance level (zero) as measured with a one-sample t-test.

When given a dose between 0.01 and 0.3 mg/kg riociguat, the OLT performance was higher than chance level, in particular for a dose of 0.03 mg/kg ($p<0.001$), indicating well-functioning spatial memory. Higher or lower doses were not able to increase the performance significantly higher than chance level. Figure 1 gives a visual representation of the OLT performance in healthy mice.

A one-way ANOVA comparing the d2 value of every group showed a significant difference between group performance ($F_{4,68}=4.19$; $p<0.01$). The post-hoc Dunnett's t-test comparing every condition to vehicle treatment showed that a dose of 0.03 mg/kg riociguat significantly enhanced mice OLT performance ($p<0.01$).

Table 1. Mean values in seconds of the different 24h interval OLT measures. SEM in brackets.

Dose riociguat	e1 (SEM)	E2 (SEM)	d2 (SEM)	N
Vehicle	25.73 (3.17)	17.76 (2.52)	-0.01 (0.07)	14
0.01 mg/kg	27.65 (3.17)	15.23 (1.85)	0.05 (0.07)	15
0.03 mg/kg	30.04 (4.44)	22.80 (2.49)	0.38 (0.05) ###	14
0.1 mg/kg	21.77 (2.66)	17.09 (1.67)	0.15 (0.07)	15
0.3 mg/kg	26.20 (4.25)	21.52 (3.35)	0.09 (0.09)	15

Table 1 shows the mean exploration times in T1 (e1) and T2 (e2) and discrimination performance (d2) of the different treatment conditions. N indicates the number of animals tested. The Standard Error of the Mean (SEM) is presented between brackets. One sample t-tests were performed on the d2 measures. A significant difference from zero (one-sample t-test; indicated by hashes; ###: $p<0.001$) indicates that the animals remembered the location of the object from T1.

We also tested whether riociguat could have a beneficial effect on cognition in an OLT model wherein a memory deficit had been induced by biperidin. Therein, the muscarinic M1 receptor antagonist biperiden was used to induce a memory deficit and riociguat's ability to attenuate this memory deficit in the OLT was tested. Biperiden was given intraperitoneally (I.P.) 30 minutes before the task at a dose of 0 (vehicle) or 3 mg/kg.

The results of riociguat in combination with a biperiden-induced memory deficit with a 1h inter-trial interval OLT are summarized in table 2. No significant differences were found between the exploration times of the different conditions for T1 (e1: $F_{5,76}=0.55$, n.s.) and T2 (e2: $F_{5,76}=1.78$, n.s.).

After a 1h interval, vehicle + vehicle treated mice were able to remember the location of the objects, indicated by the significant difference of the d2 value from chance level measured with a one-sample t-test ($p<0.001$). When given biperiden + vehicle the mice performance was not different from chance level indicating a spatial memory impairment due to 3 mg/kg biperiden administration.

One-sample t-tests comparing every biperiden + riociguat treatment to chance level showed that both biperiden + 0.03 mg/kg and biperiden + 0.1 mg/kg riociguat treated mice recognized the locations of the object after 1 hour ($p<0.001$ and $p<0.01$, respectively).

Table 2. Mean values of the different 1h interval OLT measures. SEM in brackets.

Condition	e1 (SEM)	e2 (SEM)	d2 (SEM)	N
vehicle + vehicle	24.06 (3.1)	21.69 (3.33)	0.39 (0.07)###	14
3 mg/kg biperiden + vehicle	24.28 (2.68)	17.19 (2.11)	-0.04 (0.07)	14
biperiden + 0.01 mg/kg	23.68 (5.23)	20.34 (2.17)	0.08 (0.09)	13
biperiden + 0.03 mg/kg	18.00 (2.78)	19.03 (2.35)	0.37 (0.07)###	14
biperiden + 0.1 mg/kg	26.05 (4.25)	18.16 (2.64)	0.25 (0.07) ##	13
biperiden + 0.3 mg/kg	22.99 (4.09)	29.30 (5.64)	0.06 (0.1)	14

Table 2 shows the mean exploration times in T1 (e1) and T2 (e2) and discrimination performance (d2) of the different treatment conditions. The Standard Error of the Mean (SEM) is presented between brackets. N indicates the number of animals tested. One sample t-tests were performed on the d2 measures. A significant difference from zero (one-sample t-test; indicated by hashes; ##: $p<0.01$; ###: $p<0.001$) indicates that the animals remembered the location of the object from T1.

To evaluate the performance difference between all treatment groups, a one-way ANOVA was performed over the d2 values of every condition. The one-way ANOVA revealed a significant difference between the different conditions ($F_{5,76}=5.213$; $p<0.001$). Next, every treatment group was compared to the biperiden + vehicle group with a post-hoc Dunnett's t-test, and the latter showed a significant difference for the vehicle + vehicle condition ($p<0.01$) confirming that when treated with biperiden mice perform significantly lower than vehicle treated animals. Furthermore, Dunnett's t-tests showed that biperiden + 0.03 mg/kg riociguat ($p<0.01$) and biperiden + 0.1 mg/kg riociguat ($p<0.05$) treated mice performed significantly higher as biperiden + vehicle treated animals. This indicates that at doses of 0.03 and 0.1 mg/kg riociguat is able to completely attenuate a biperiden induced memory deficit. These results are graphically illustrated in Figure 2.

In addition, we tested whether riociguat was able to treat cognitive impairment in mice with a biperiden-induced memory deficit in the y-maze continuous alternation task:

Table 3 summarizes the results of riociguat on spatial working memory after a biperiden-induced memory deficit in the y-maze continuous alternation task. Mean alternation % was compared to 50% alternations (chance level) by one sample t-tests. Vehicle + vehicle ($p<0.001$), biperiden + 0.01 ($p=0.001$), biperiden + 0.03 ($p<0.001$) and biperiden + 0.1 mg/kg riociguat ($p<0.05$) treated animals showed significantly higher performances than chance level, indicating a well-functioning working memory. Biperiden + vehicle and biperiden + 0.3 mg/kg riociguat did not show a difference from chance level which indicates impaired working memory in these treatment conditions.

Table 3. Mean alternation values of the y-maze alternation task.

Condition	Alternations %	SEM	N
vehicle + vehicle	66.12 ###	2.61	9
3 mg/kg biperiden + vehicle	54.23	2.15	9
biperiden + 0.01 mg/kg	56.82 ##	1.35	9
biperiden + 0.03 mg/kg	65.04 ###	2.62	9
biperiden + 0.1 mg/kg	57.58 #	2.57	9
biperiden + 0.3 mg/kg	53.96	3.42	9

Table 3 shows the mean percentages of alternations and their Standard Error of the Mean (SEM) for every treatment condition. One sample t-tests were performed on the alternation percentages. N indicates the number of animals tested. A significant difference from 50% (one sample t-test; indicated by hashes; #: $p<0.05$; ##: $p<0.01$; ###: $p<0.001$) indicates that the animals have well-functioning spatial working memory.

A one-way ANOVA comparing the performance between the different treatment groups showed a significant effect ($F_{5,48}=4.441$; $p<0.01$). Dunnett's t-tests comparing the groups to the biperiden + vehicle treatment showed that both the vehicle + vehicle ($p=0.008$) and biperiden + 0.03 mg/kg riociguat ($p<0.05$) treated mice performed significantly higher. This indicates that a dose of 0.03 mg/kg riociguat is able to fully restore a biperiden-induced (working) memory deficit up to the level of performance of vehicle treated animals. Doses of 0.01 mg/kg and 0.1 mg/kg riociguat were able to show a functioning working-memory but do not show a significant difference from the biperiden + vehicle condition, therefore these doses have an intermediate effect on spatial working memory performance after a biperiden induced memory deficit. These results are graphically depicted in Figure 3.

From the results of the OLT and y-maze alternation experiments it can be concluded that riociguat can enhance spatial memory performance up to a dose of 0.1 mg/kg. In particular a dose of 0.03 mg/kg riociguat is able to enhance spatial memory in healthy mice and restore spatial memory performance to the level of vehicle in a pharmacological model of memory impairment.

Based on the above results in several animal model tests, it may reasonably be assumed that riociguat will work in an equivalent way in humans. This may be tested in one or more of the tests according to examples 6 – 11. These experiments will show that in healthy adult subjects riociguat is effective on memory performance.

Such a study may be conducted according to a double-blind, placebo controlled, 6 period cross-over design. Twenty healthy subjects, both males and females within the age range of 18-40 years may be included in the study. All subjects may be randomized in a double blind fashion to 1 of 6 treatment sequences, each sequence consisting of the following periods: A) Placebo + placebo; B) placebo + riociguat 0.5 mg; C) placebo + riociguat 1.0 mg; D) biperiden 2 mg + placebo; E) biperiden 2 mg + riociguat 0.5 mg and F) E) biperiden 2 mg + riociguat 1.0 mg, according to a computer-generated allocation schedule in a cross-over design. Between each of the six treatment sequences there may be a 5 days washout period.

Cognitive status may be quantified using a computerized cognitive battery, a validated tool for measuring the cognitive impairment in humans. The battery may consist of: Verbal learning task (VLT), visual N-back task, spatial memory task, attention network test and simple and choice reaction time test (examples 6 – 11, see Table 4).

Table 4. Overview of the testing day for each treatment period

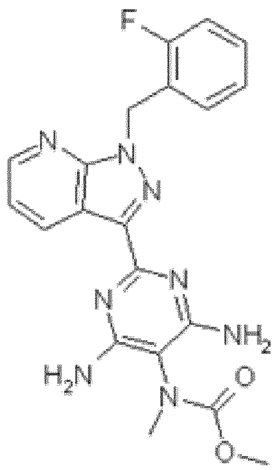
Time (min);Relative to dosing	Activity
-10	Questionnaires
0	Dosing (Biperiden: 0, or 2 mg)
30	Dosing (Riociguat: 0, 0.5 or 1 mg)
100	VLT immediate recall, 3 trials (10 min)
110	SMT immediate
125	n-Back
140	Break | questionnaires
145	VLT delayed recall and recognition
155	SMT delayed recognition
160	ANT
175	Simple and choice reaction time task

Based on the formula for dose translation from animals to humans as described by Reagan-Shaw and colleagues (Reagan-Shaw et al, FASEB J, 2007, Vol 22 pp 659-661), especially a daily dose of between 0.1 and 1 mg, in particular about 0.5 mg riociguat may be most effective in restoring memory performance to the level of placebo in a pharmacological model of memory impairment. A dose of 0.2, such as 0.3 or 0.4 mg per day may also be effective, as well as a daily dose of 0.6, 0.7, 0.8 or 0.9 mg per day.

Hence, the invention relates to a composition comprising an sGC stimulator for use in the treatment of cognitive impairment in a mammal in need of such treatment, wherein the treatment comprises administering to a mammal suffering from cognitive impairment an sGC stimulator selected from the group consisting of Riociguat, its active metabolite M1, a pharmaceutically acceptable salt of Riociguat and a pharmaceutically acceptable salt of M1, wherein the sGC stimulator is administered at a daily dose of between 0.1 and 1.0 mg.

The term riociguat refers to a known sGC stimulator with the chemical name Methyl N-[4,6-Diamino-2-[1-[(2-fluorophenyl)methyl]-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl]-N-methyl-carbaminate (Mitteldorf et al, Chem. Med. Chem. 2009, Vol 4 pp 853-865). Riociguat (BAY 63-2521, trade name Adempas™) is a novel drug (by Bayer) that is a stimulator of soluble guanylate cyclase (sGC). Clinical trials have looked at riociguat as a new approach to treat two forms of pulmonary hypertension (PH): chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). Riociguat constitutes the first drug of a novel class of sGC stimulators.

The structural formula of riociguat is:



Riociguat (BAY63-2521) has an active metabolite (M1 or BAY60-4552) with similar pharmacologic activity but approximately 10 fold lower potency.

In a preferred embodiment, the invention relates to a composition for use in the treatment of cognitive impairment as described above wherein the daily dose is between 0.1 and 0.5 mg.

In a further preferred embodiment, the invention relates to a composition for use in the treatment of cognitive impairment as described above wherein the cognitive impairment is mild cognitive impairment.

In a further preferred embodiment, the invention relates to a composition for use in the treatment of cognitive impairment as described above wherein the cognitive impairment is associated with Alzheimer’s disease, schizophrenia or aging in a mammal.

The terms ‘treating cognitive impairment’ or ‘treatment of cognitive impairment’ refer to Inhibiting, i.e., arresting further development of the pathology and/or symptomatology, or ameliorating, i.e., reversing the pathology or symptomatology, of the disease and its progression. For example, this can include the following: arresting or delaying the decline, or providing improvement in: a) memory (short-term and/or long term), b) decision making, c) executive functions (e.g., reasoning, problem-solving, planning), d) language skills (e.g., naming, fluency, expressive speech, and comprehension), e) visuospatial skills, and f) attentional control.

The term ‘mammal’ has its ordinary meaning and includes, e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swine and monkey, with preference given to humans.

The phrase 'cognitive impairment' refers to any decline in one or more of memory functions, decision making, executive functions, language skills, visuospatial skills, or attentional control.

Cognitive impairment may be associated with aging as well as with a variety of disorders. Disorders, including Mild Cognitive Impairment (MCI) associated with Alzheimer's disease, cognitive impairment associated with Alzheimer's disease, cognitive impairment associated with Schizophrenia (CIAS), cognitive impairment associated with Vascular disease, cognitive impairment associated with Parkinson's disease, cognitive impairment associated with Huntington's disease, cognitive impairment due to stroke, cognitive impairment due to attention deficit disorder, cognitive impairment due to depression, frontotemporal dementia due to motor neuron disease, and post-operative cognitive decline (POCD) in the elderly. Also patients with Subjective Cognitive Decline (SCD) (Jessen et al, Alz Dem, 2014, Vol. 10, pp 844-852) are included as they have a self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event. Clinical judgment must be used to make these distinctions between normal cognition, SCD, MCI or Alzheimer's disease. Inclusion criteria for patients with SCD (based on Jessen et al, Alz Dem, 2014, Vol. 10, pp 844-852) are: 1) being referred to a clinician for the evaluation of cognitive complaints; 2) Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event; and 3) Normal age-, gender-, and education- adjusted performance on standardized cognitive tests.

Inclusion criteria for the MCI patients are: 1) Referred to a clinician for the evaluation of cognitive problems, and 2) Patients have to fulfill the criteria based on Albert et al. (Albert et al, Alz Dem, 2011, Vol 7, pp 270-279) or the new DSM-V criteria for mild neurocognitive disorder (NCD): a) Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains, being between 1-2 standard deviations (SD) below average. The evidence should consist of concern of the individual, a knowledgeable informant, or the clinician that there's been a mild decline in cognitive functioning; and a modest impairment in cognitive performance, documented by standardized neuropsychological testing. b) The cognitive deficits do not interfere with capacity for independence in everyday activities. c) The cognitive deficits do not occur exclusively in context of delirium, and are not better explained by another mental disorder. These inclusion criteria will allow the use of different internationally used MCI criteria.

'Concurrent administration' (also including 'concomitant administration') means that both the sGC stimulator and the acetylcholinesterase inhibitor (a) are administered to the mammal in need of the treatment in a single dosage form for simultaneous, concomitant administration or (b) are administered to the mammal in need of the treatment in two separate dosage forms, and the two separate dosage forms are administered immediately one after the other. In this context, the two separate dosage forms are administered immediately one after the other, if the dosages are administered within between 0 and 15 minutes of each other; or more preferably within between 0 and 5 minutes of each other; or most preferably within between 0 and 1 minute of each other.

'Sequential administration' (also including 'administering sequentially'), as used herein, means that the sGC stimulator is administered to the mammal in need of the treatment in one dosage form and the acetylcholinesterase inhibitor is administered to the mammal in need of the treatment in another separate dosage form, wherein the second dosage form is administered to the mammal in need of the treatment while the first dosage form still has an effect on the mammal being treated. In a preferred embodiment of the invention, the first and the second dosage form are administered within such a time interval that the effect of the combined treatment on the mammal being treated is synergistic. In this context, the two separate dosage forms are considered to be administered sequentially, if the two dosage forms are administered at least 15 but no more than 240 minutes apart, preferably between 15 and 120 minutes apart, and more preferable between 15 and 60 minutes apart.

We also observed a synergistic effect of a combination of riociguat and the acetylcholinesterase inhibitor donepezil with regard to cognitive improvement on natural spatial memory in the Object Location Task (OLT) in male C57BL/6 mice (see example 12)

The results of the combined treatment conditions of sub-efficacious doses of riociguat and donepezil using a 24h inter-trial interval OLT are summarized in Table 5.

There were no differences in exploration time between treatment conditions for both T1 (e1: $F_{3,34}$=1.114, n.s.) and T2 (e2: $F_{3,34}$=0.2933, n.s.). When given a combination of riociguat and donepezil the mice were able to remember the object locations after 24h, as shown by a one-sample t-test comparing the d2 value with chance level ($p<0.01$), while the mice treated with sub-efficacious doses of riociguat and donepezil alone did not show any object location memory. A one-way ANOVA comparing the treatment groups mean performance showed a significant treatment effect ($F_{3,34}$=3.116; $p<0.05$) and the post-hoc Dunnett's t-test revealed that the donepezil + riociguat treatment differed significantly from vehicle + vehicle treatment ($p<0.05$). Figure 4 gives a graphical representation of these findings.

These results indicate that while sub-efficacious doses of donepezil and riociguat alone do not have any effect on memory performance in healthy mice, when given in combination they are fully effective in preventing natural forgetting.

Table 5. Mean values (± SEM) of the different 24h interval OLT measures after combined treatments

Dose	e1 (SEC)	e2 (SEC)	d2	N
Vehicle (saline) + vehicle (tylose)	24.65 (6.42)	21.16 (3.14)	0.02 (0.11)	9
Vehicle (saline) + 0.01 mg/kg riociguat	26.06 (2.88)	21.21 (2.44)	0.11 (0.11)	10
0.1 mg/kg donepezil + vehicle (tylose)	34.93 (6.4)	18.34 (2.33)	0.01 (0.06)	9
0.1 mg/kg donepezil + 0.01 mg/kg riociguat	23.15 (3.66)	19.28 (2.41)	0.39 (0.11) ##	10

Table 5 displays the mean exploration times in T1 (e1) and T2 (e2) and discrimination performance (d2) of the different treatment conditions. The Standard Error of the Mean (SEM) is presented between brackets. One sample t-tests were performed on the d2 measures. A significant difference from zero (one-sample t-test; indicated by hashes; ##: $p<0.01$) indicates that the animals remembered the location of the object from T1.

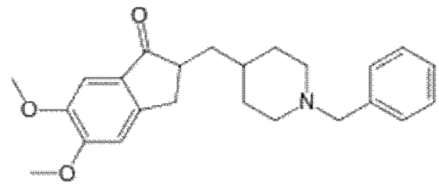
Hence, the invention also relates to a composition for use in the treatment of cognitive impairment as described above, wherein the treatment additionally comprises administering an acetylcholinesterase inhibitor to a mammal suffering from cognitive impairment.

In a preferred embodiment, the invention relates to a composition for use in the treatment of cognitive impairment as described above wherein the composition comprises an sGC stimulator and an acetylcholinesterase inhibitor.

In a further preferred embodiment, the invention relates to a composition for use in the treatment of cognitive impairment according to claim 5 or 6 wherein the acetylcholinesterase inhibitor is selected from the group consisting of donepezil, a pharmaceutical acceptable salt of donepezil, galantamine, a pharmaceutically acceptable salt of galantamine, rivastigmine, and a pharmaceutically acceptable salt of rivastigmine.

Donepezil is marketed under the trade name Aricept, and is a medication used is in the palliative treatment of Alzheimer's disease. Donepezil is used to improve cognition and behavior of people with Alzheimer's, but does not slow the progression of or cure the disease.

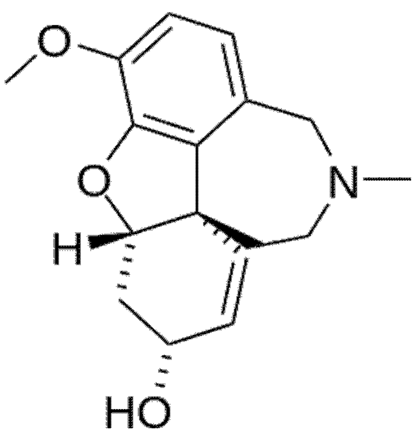
It was developed by Eisai and Pfizer and is sold as a generic by multiple suppliers. Donepezil acts as a centrally acting reversible acetylcholinesterase inhibitor.



Donepezil

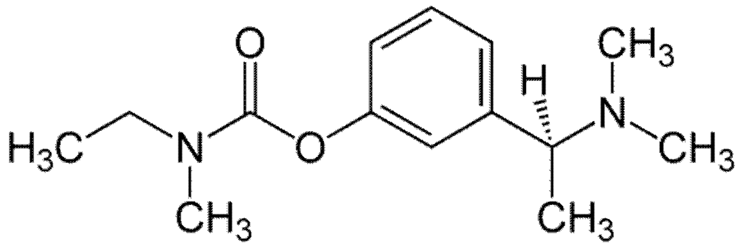
Galantamine (also called Nivalin, Razadyne, Razadyne ER, Reminyl or Lycoremine) is used for the treatment of mild to moderate Alzheimer's disease and various other memory impairments, in particular those of vascular origin. It is an alkaloid that is obtained synthetically or from the bulbs and flowers of Galanthus caucasicus (Caucasian snowdrop, Voronov's snowdrop), Galanthus woronowii (Amaryllidaceae) and related genera like Narcissus (daffodil), Leucojum aestivum (snowflake), and Lycoris including Lycoris radiata (Red Spider Lily).

Galantamine has the following structural formula:



Rivastigmine (sold under the trade name Exelon) is a parasympathomimetic or cholinergic agent for the treatment of mild to moderate dementia of the Alzheimer's type and dementia due to Parkinson's disease. The drug can be administered orally or via a transdermal patch; the latter form reduces the prevalence of side effects which typically include nausea and vomiting.

Rivastigmine has the following structural formula:



In a further preferred embodiment, the invention relates to a composition for use in the treatment of cognitive impairment as described above wherein the sGC stimulator and the acetylcholinesterase inhibitor are administered in one single dosage form.

Examples

Example 1: Cognitive Improvement Effects of Riociguat on Spatial Memory in Mice

The objective of this study was to evaluate the cognitive improvement effects of riociguat on spatial memory employing the Object Location Task (OLT) and Y-maze continuous alternation task in male C57BL/6 mice.

It was first tested if Riociguat enhances natural memory in the OLT. Then, the muscarinic M1 receptor antagonist biperiden was used to induce a memory deficit and riociguat's ability to attenuate this memory deficit in the OLT was tested. Finally, riociguat was tested for its effects on working memory in the Y-maze continuous alternation task.

In total 40 male C57BL/6 mice were supplied by Charles River (Sulzfeld, Germany) and tested between 4-5 months of age. Average body weight at the beginning of the study was 28.0 g. All animals were housed individually in standard green line Tecniplast IVC cages on sawdust bedding. The animals were housed on a reversed 12/12-h light/dark cycle (lights on from 19:00h to 07:00h) and received food and water ad libitum.

Both riociguat and biperiden were dissolved in 99.6% ethanol and further diluted in 0.5% methylcellulose (vehicle). Riociguat (MW: 422.42) was used as a free base and biperiden (MW: 311.46) was used as a HCl salt. Both compounds were supplied by Beijing Mesochem Technologies CO (Beijing, China).

Doses of 0 (vehicle), 0.01, 0.03, 0.1 and 0.3 mg/kg of riogicuat were administrated orally (P.O.) 30 minutes in advance for both the OLT and the Y-maze alternation task. Biperiden was given intraperitoneally (I.P.) 30 minutes before the task at a dose of 0 (vehicle) or 3 mg/kg.

Example 2: The object location task (OLT):

The OLT apparatus consisted of a circular arena, 40 cm in diameter. The back half of the 40 cm high wall was made of white polyvinyl chloride (PVC) and the front was made of transparent PVC. Two objects were placed in symmetrical positions at the mid-line between the black and transparent halves of the arena, about 5 cm away from wall. Four different sets of objects were available and presented to the animals in a balanced manner to avoid learning or place biases:

(1) a cone made of brass (maximal diameter 2.5 cm and total height 9.5 cm), (2) a massive metal cube (2.5 cm × 5 cm × 7.5 cm) with two holes (diameter 1.5 cm) and water, (3) a white polyvinyl chloride cube with rounded edges and a circular base (5 cm × 5 cm × 7 cm), and (4) a massive aluminum cube with a tapering top (5 cm × 5 cm × 6.5 cm)

A test session comprised two trials, each with durations of 4 min. Prior to the trials the mice were put in an empty cage for 4 minutes to increase arousal during testing. During the learning trial (T1) the apparatus contains two identical objects placed on a horizontal line in the middle of the arena (object a1 and a2). Mice were always introduced into the apparatus with their nose towards the transparent wall segment (i.e. facing outwards to the front of the arena). Subsequently, the mice were put back in their home cage for a 1 h or 24 h interval. After the retention interval, the mice were put back into the arena for the learning trial (T2). In T2 one of the two objects from T1 is moved to a different position to the front or back of the arena. One object (a3) is the same as T1 and the other has a novel location (b), the objects orientation was kept the same over the trials. The time spent exploring each object during T1 and T2 was recorded manually on a personal computer. Exploration was defined in the following manner: directing the nose to the object at a distance of no more than 2 cm and/or touching the object with the nose. Sitting on the object was not considered as exploratory behavior. In order to avoid the presence of olfactory cues the objects were thoroughly cleaned with a 70% ethanol solution before each trial. Drug conditions were tested in semi-random order, so within one testing session, multiple treatment conditions were tested. The person conducting the experiments was always unaware of the conditions that were being tested.

Example 3: OLT statistical data analysis:

The exploration time (in seconds) of each object during T1 are presented as ‘a1’ and ‘a2’. The time spent in exploring the familiar and the moved object in T2 are represented as ‘a3’ and ‘b’, respectively. Using this information, the variables e1 and e2 were calculated wherein e1 = a1 + a2 and e2 = a3 + b.

The index d2 is a relative measure of discrimination corrected for exploratory activity and was calculated as b – a3/ e2. The d2 index can range from -1 to 1. A significant positive difference from zero, i.e. chance level, indicates that the mice remembered the object locations from T1, and a difference from the vehicle condition signifies an actual memory improvement.

From the biperiden + vehicle, biperiden + 0.1 mg/kg riociguat and biperiden + 0.3 mg/kg riociguat treatment conditions one animal had to be removed from the analysis due to insufficient exploration (<6 s in T1 or T2). One mouse died to events unrelated to the experiment, making the group distribution uneven.

One sample t-tests were used to compare the d2 index of the conditions to zero to evaluate if the mice were able to recognize the moved object. To compare the groups, a one-way ANOVA was performed between the d2 values of the conditions and when significant, post-hoc Dunnett’s t-tests were performed to compare the experimental conditions to the vehicle group for the 24h inter-trial interval OLT. Dunnett’s t-tests comparing the groups to the biperiden + vehicle condition were performed for the 1h inter-trial interval OLT with a biperiden induced memory deficit. A $p<0.05$ was considered significant.

Example 4: The y-maze continuous alternation task.

The apparatus of the y-maze continuous alternation test was made of grey Plexiglas with three arms symmetrically placed together at a 120 degrees angle. Each arm was 40 cm long, 17 cm high, 4 cm wide at the bottom and 13 cm wide at the top. At the beginning of the trial each mouse was placed in one of three arms (randomly divided and balanced), and was then allowed to freely explore the apparatus for 6 minutes. The number of entries into a different arm and the order was taken as a measurement. An entry was only counted if all four paws of the animal were placed completely inside the arm. When a mouse visited all 3 arms consecutively it made a triad. In between trials the apparatus was cleaned with a 70% ethanol solution to avoid olfactory cues.

Example 5: Y-maze continuous alternation task statistical data analysis:

To measure spatial (working) memory, the percentage of alternations was calculated by taking the number of triads and dividing it by the maximum possible alternations (total entries minus 2) and multiply this by 100. A score of 50% alternations is considered chance level, therefore a significant difference from 50% is indicative of functional working memory. A minimal of 10 arm entries per mice was considered sufficient to give a reliable score. Therefore, mice with less than 10 arm entries were excluded from the analysis. For each condition one-sample t-tests were used to compare to a score of 50%. A one-way ANOVA was performed to evaluate differences between the conditions and when significant, a Dunnett's t-test comparing the conditions to the biperiden + vehicle treatment was performed. A $p<0.05$ was considered significant.

Example 6: Verbal Learning task (VLT):

The Rey VLT as modified by Riedel and colleagues (Klaassen et al, Psychopharmacology, 1999, Vol 141, pp 279-286) is used. This modified VLT maximizes the possibility of measuring enhancement rather than only impairment, by means of prolonging the list. The test consists of a list of 30 monosyllabic words (18 nouns and 12 adjectives). The words are shown on a computer screen for 1 second. Three trials with the same item sequence are presented. Each trial ends with a free recall of the words (immediate recall). Forty-five minutes after the first exposure, the subject is asked to recall as many words as possible (delayed recall). Subsequently, a recognition test is presented, consisting of 15 former words and 15 new but comparable words (distracters). The words are shown on a computer screen for 2 seconds and subjects are asked to rate whether they were presented in the learning trial by a “yes/no” response. The inter-word interval is 2 seconds. The number of words correctly recalled will be collected during the three immediate learning trials (first, second, third and total) and delayed recall. The number of words correctly recalled in the learning trials is summed to yield the total immediate free recall score.

Example 7: Spatial memory task (SMT):

The spatial memory task assesses spatial memory and is based on the object relocation task by Postma and colleagues (Kessels et al, Behav Res Methods Instrum Comput, 1999, Vol 31, pp 423-428). It consists of one immediate and two delayed conditions. In the immediate condition, a set of 10 pictures will be presented one by one on different locations within a white square on a computer screen. All pictures are everyday, easy-to-name objects, presented in gray scale (± 3.5 x 5 cm). Each picture will be presented for 2000 msec with an interstimulus interval of 1000 msec. This will be followed by a "relocation" part, which consists of the presentation of a picture in the middle of the screen, followed by a "1" and a "2" being presented on two different locations. The participants' task is to decide where the picture was originally presented, in location "1" or location "2". The "1" and "2" will remain on the screen until the participant responds. After relocation, which is accomplished by a button press, the next picture will be presented followed by a "1/2" choice option. This continues until all 10 pictures have been relocated. Thereafter, the next set of 10 pictures will be presented. A total of 6 sets of 10 pictures are displayed. Forty-five minutes later, subjects will perform the first delayed version. The original locations are not presented again. Subjects immediately start with the relocation part of the task.

<u>Example 8: The n-backtest.</u>

The n-back task is a test appropriate to assess working memory capacity (Guerreiro and Van Gerven, Psychology and Aging, Vol 26, pp 415-426). In this test, cognitive control demands are manipulated by increasing working memory load over the range n = 0 to n = 2. In each condition, a sequence of n + 64 digits will be presented one at a time. The duration of each digit is 1500 ms and a response is required for each digit. The interval between digits will be 500 ms. In the n = 0 condition, participants are required to judge whether the current digit consists of a pre-specified digit. In the other n-back conditions (i.e., n = 1 and n = 2), participants are required to judge whether the current digit is the same as n positions back in the sequence. Stimuli consist of random numbers between 1 and 9. Visual stimuli consist of green and red digits, which are presented in the centre of the display at a size of approximately 3.6 × 2.7 cm. The order of the tasks will be counterbalanced according to a 6 x 6 Latin square, provided that the n = 2 condition is always followed by the n = 0 condition. These procedures are chosen to ensure that participants have the chance to relax between conditions of higher load and to avoid confounding practice effects. Responses will be collected by means of a response box with two buttons labelled 'yes' and 'no'. Participants respond by pressing these buttons using the left and right index fingers. There are 64 trials in each condition, which are preceded by 16 practice trials. In half of the trials, the current digit matches the n-back digit, whereas in the other half it does not. Participants will be instructed to respond as fast and accurately as possible. After each block, the participants receive feedback about their total accuracy and average reaction time over the run of 64 trials. Reaction time and accuracy will be analysed for each of the 3 conditions (0-back, 1-back, 2-back).

Example 9: Attention network test (ANT):

The ANT provides measures of three functions of attention within a single task (Fan et al, J Cogn Neurosci, 2002, Vol 14, pp 340-347). Each trial begins with the presentation of a fixation cross in the middle of the computer screen. Subjects are instructed to keep their eyes fixed on the cross throughout the test. Then, at some variable interval a cue is presented for 100 ms. Four hundred ms after the offset of the cue, a target display appears, and remains on until response (i.e., a key-press indicating the direction of the target arrow), or for 1700ms if no response is made. Interstimulus interval is 3500 ms. There are four cue conditions and three target conditions. Targets (neutral, congruent, or incongruent) can appear either above or below the fixation cross. The first three cue conditions (no cue, center cue, and double cue) provide no information about the location of the impending target. By way of contrast, spatial cues indicate with 100% validity where the impending target will appear: If the spatial cue appears above fixation, the target will also appear above fixation; and if the spatial cue appears below fixation, the target will also appear below fixation. Dependent variables are differences between reaction times reflecting efficiency of Alerting (RT no cue - RT double cue), Orienting (RT center cue - RT spatial) and executive network (RT Incongruent - RT congruent).

Example 10: Simple and choice reaction time task:

This task is divided into two parts. First the participant must react as soon as the button enlightens in the center of the respond box, by pressing that button. In the second part one of three possible buttons will light up. The participant is instructed to respond as quickly as possible. Outcome variables are reaction times (simple and choice) and movement times (simple and choice).

Example 11: Profile of Mood States (POMS)

The POMS is a self-evaluation scale for short, alternating states. The POMS consists of 72 adjectives comprising six bipolar mood factors (Energetic-Tired, Elated-Depressed, Agreeable-Hostile, Confident-Unsure, Composed-Anxious, and Clearheaded-Confused). Next to each adjective is a five-point scale. In this way, the participant can indicate in what amount these items are appropriate to his mood. For each of the six mood factors, the mean score will be calculated. This score will be compared between the baseline (t-10) and the test (t90 and t140), to examine whether the treatment induced a depressive mood (McNair et al, Manual for the Profile of Mood States, 1971).

Example 12, combination therapy

An additional batch of 40 male mice of the same age of the same supplier as mentioned in example 1 was used for the combined treatment study, with an average body weight of 28.8 g at the start of the study. Donepezil was used in the form of donepezil HCl and was dissolved in saline (0.9% NaCl) (Prickaerts et al, Neuropharmacology 2012, Vol 62 pp 1099-1110).

Donepezil was administered 30 minutes before the first trial (P.O.) of the OLT at doses of 0 (vehicle), 0.03, 0.1 and 0.3 mg/kg to find the sub-efficacious dose to be used for combination testing. 0.1 mg/kg donepezil was found to be the sub-efficacious dose, i.e. 0.3 mg/kg was the first dose showing memory improvement (data not shown). From our previous experiments as described herein, 0.01 mg/kg riociguat had been found to be the sub-efficacious dose when given 30 min before the first trial (P.O.) of the OLT with a 24h inter-trial interval. For combination treatment mice received two P.O. injections 30 minutes before testing, with either vehicle (0.5% methylcellulose or saline), riociguat or donepezil.

CLAIMS

1. A composition comprising an sGC stimulator for use in the treatment of cognitive impairment in a mammal in need of such treatment, wherein the treatment comprises administering to a mammal suffering from cognitive impairment an sGC stimulator selected from the group consisting of Riociguat, its active metabolite M1, a pharmaceutically acceptable salt of Riociguat and a pharmaceutically acceptable salt of M1, wherein the sGC stimulator is administered at a daily dose of between 0.1 and 1.0 mg.

2. A composition for use in the treatment of cognitive impairment according to claim 1 wherein the daily dose is between 0.1 and 0.5 mg.

3. A composition for use in the treatment of cognitive impairment according to claim 1 or 2 wherein the cognitive impairment is mild cognitive impairment.

4. A composition for use in the treatment of cognitive impairment according to any one of claims 1 – 3 wherein the cognitive impairment is associated with Alzheimer’s disease, schizophrenia or aging in a mammal.

5. A composition for use in the treatment of cognitive impairment according to any one of claims 1 – 4, wherein the treatment additionally comprises administering an acetylcholinesterase inhibitor to a mammal suffering from cognitive impairment.

6. A composition for use in the treatment of cognitive impairment according to claim 5 wherein the composition comprises an sGC stimulator and an acetylcholinesterase inhibitor.

7. A composition for use in the treatment of cognitive impairment according to claim 5 or 6 wherein the acetylcholinesterase inhibitor is selected from the group consisting of donepezil, a pharmaceutical acceptable salt of donepezil, galantamine, a pharmaceutically acceptable salt of galantamine, rivastigmine, and a pharmaceutically acceptable salt of rivastigmine.

8. A composition for use in the treatment of cognitive impairment according to any one of claims 5 – 7 wherein the sGC stimulator and the acetylcholinesterase inhibitor are administered in one single dosage form.

9. A composition for use in the treatment of cognitive impairment according to claim 5 wherein the sGC stimulator and the acetylcholinesterase inhibitor are administered concurrently or sequentially in two separate dosage forms.

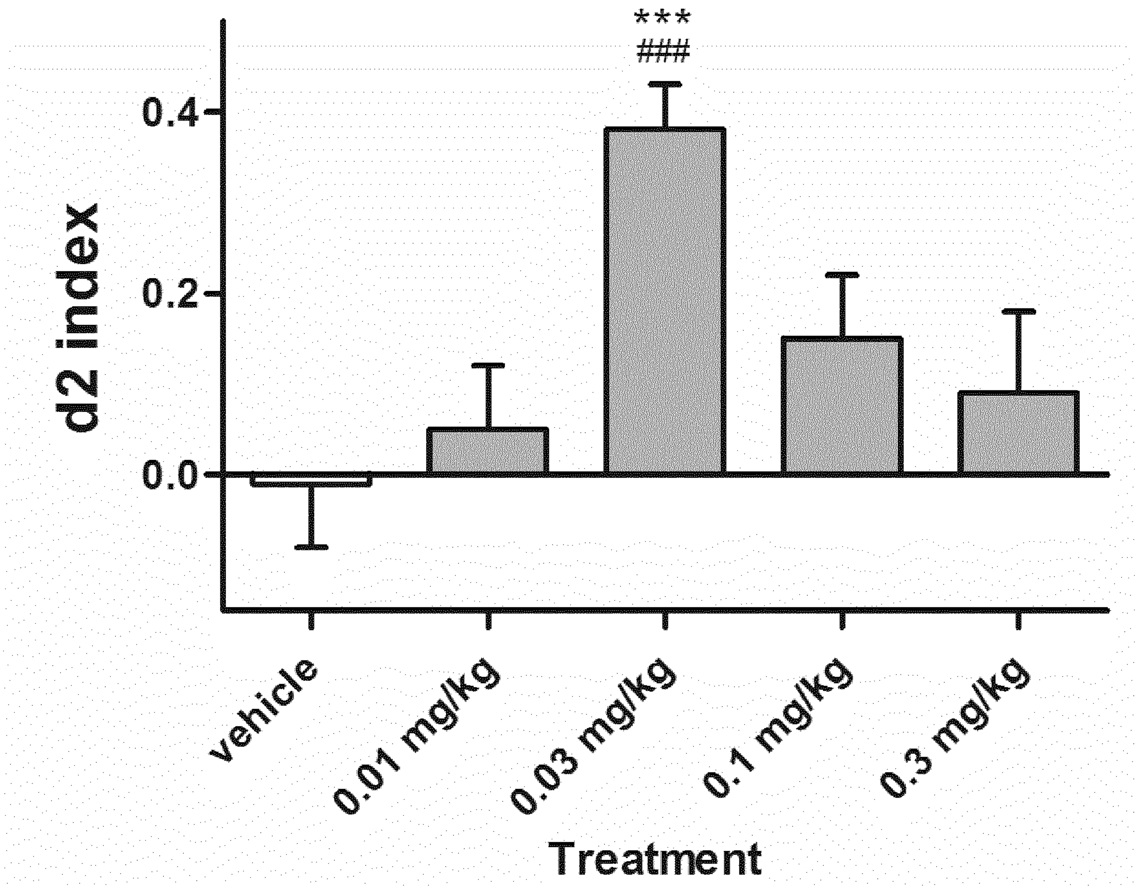
10. A pharmaceutical composition comprising a sGC stimulator, an acetylcholinesterase inhibitor and a pharmaceutically acceptable carrier wherein the sGC stimulator is selected from the group consisting of Riociguat, its active metabolite M1, a pharmaceutically acceptable salt of Riociguat and a pharmaceutically acceptable salt of M1.

11. A pharmaceutical composition according to claim 10 wherein the acetylcholinesterase inhibitor is selected from the group consisting of donepezil, a pharmaceutical acceptable salt of donepezil, galantamine, a pharmaceutically acceptable salt of galantamine, rivastigmine, and a pharmaceutically acceptable salt of rivastigmine.

12. A pharmaceutical composition according to claims 10 or 11 comprising the sGC stimulator in an amount between 0.1 and 1.0 mg in a single dosage form.

13. A pharmaceutical composition according to claim 12 comprising the sGC stimulator in an amount between 0.1 and 0.5 mg in a single dosage form.

Figure 1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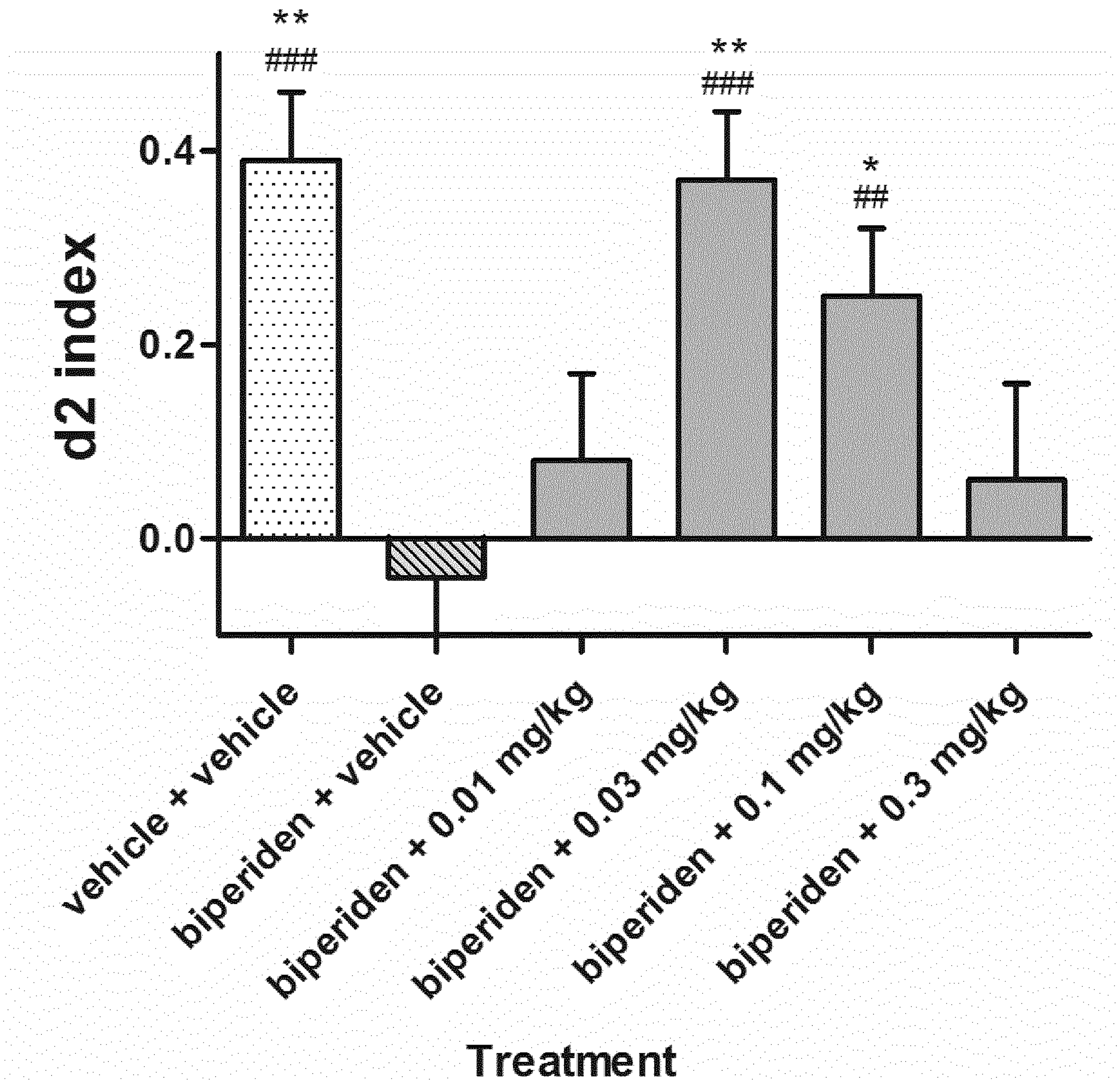
###
0.4
0.2
0.0
d2 index
vehicle
0.01 mg/kg
0.03 mg/kg
0.1 mg/kg
0.3 mg/kg
Treatment

Figure 2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##
0.4
0.2
0.0
d2 index
vehicle + vehicle
biperiden + vehicle
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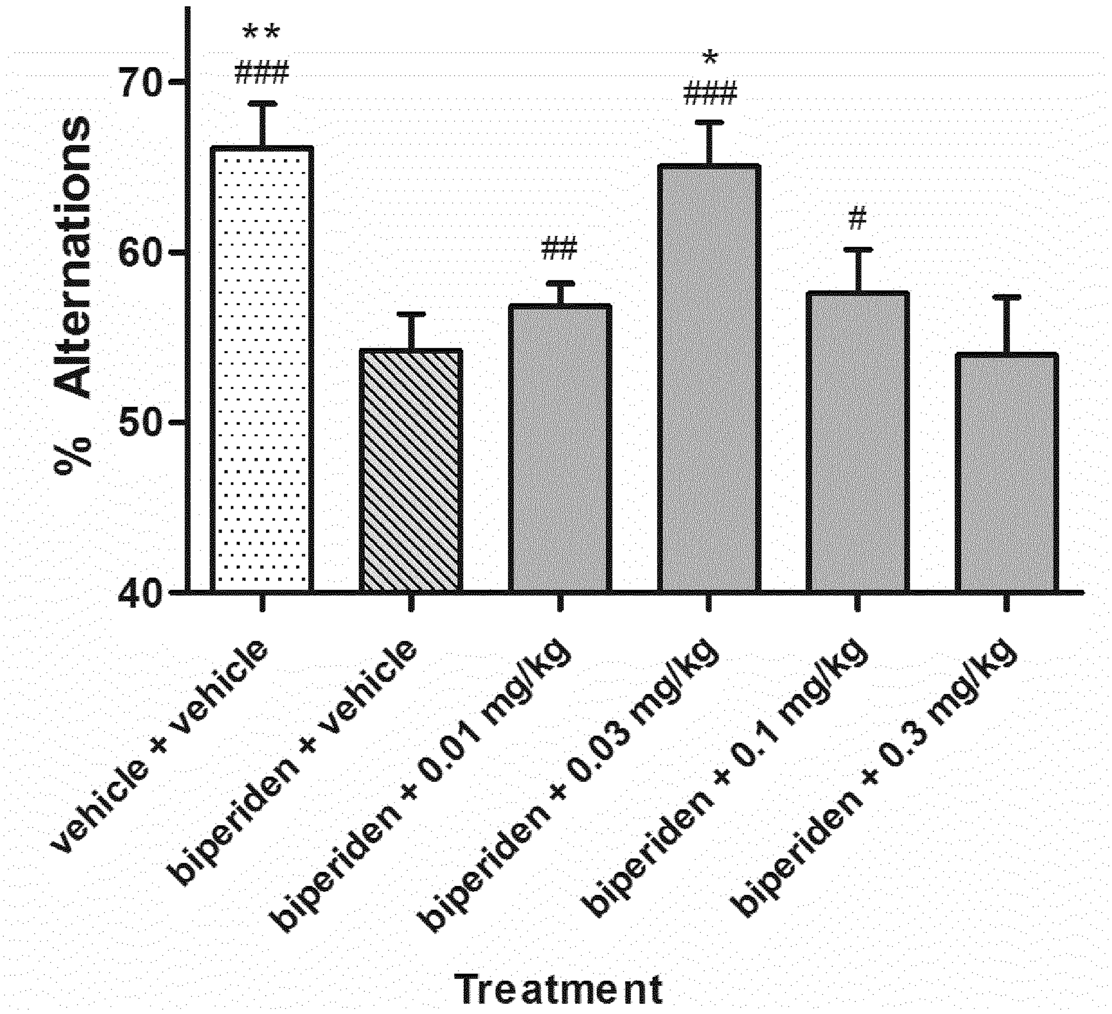
biperiden + 0.03 mg/kg
biperiden + 0.1 mg/kg
biperiden + 0.3 mg/kg
Treatment

Figure 3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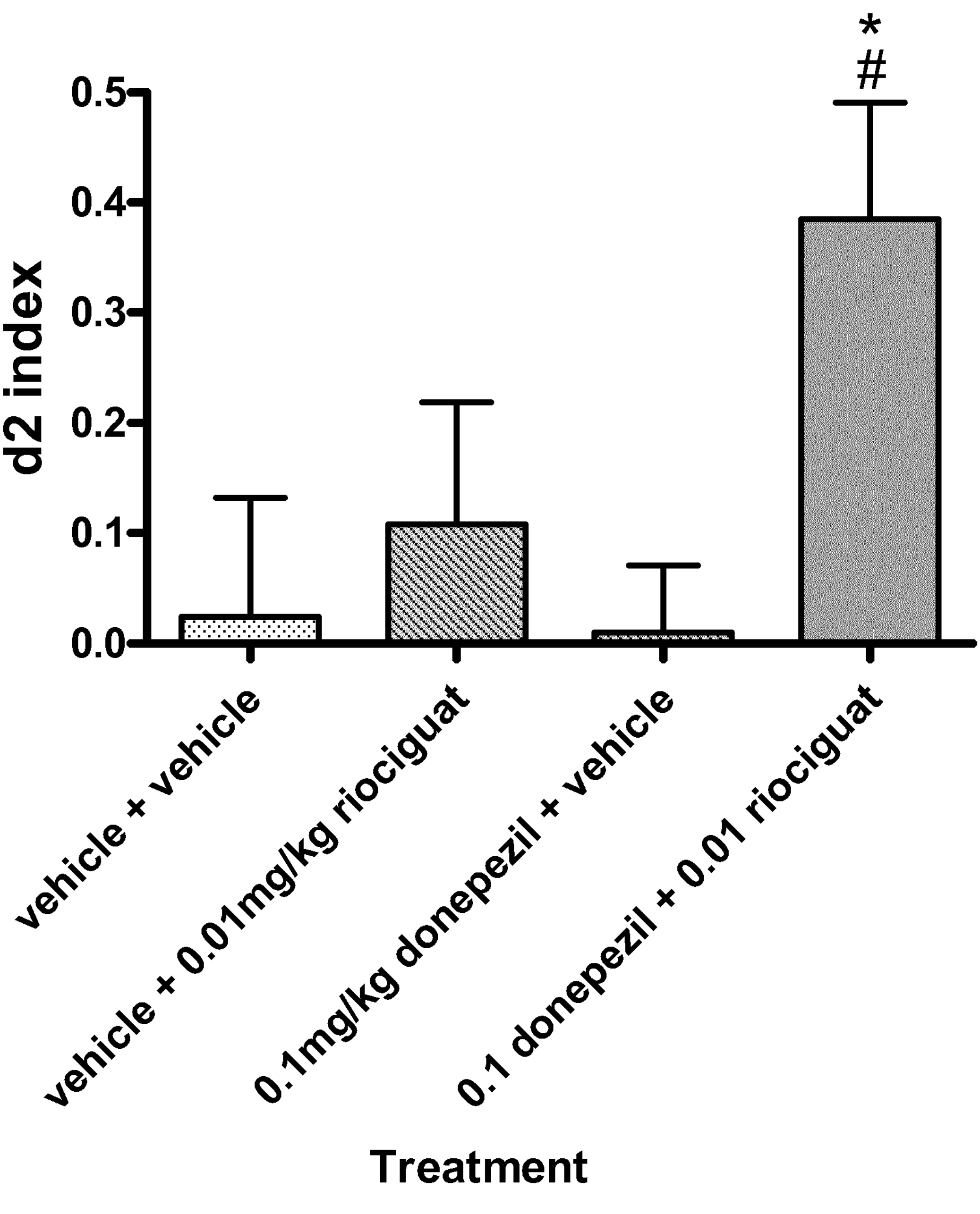
##
#
70
60
50
40
% Alternations
vehicle + vehicle
biperiden + vehicle
biperiden + 0.01 mg/kg
biperiden + 0.03 mg/kg
biperiden + 0.1 mg/kg
biperiden + 0.3 mg/kg
Treatment

Figure 4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0.5
0.4
0.3
0.2
0.1
0.0
d2 index
vehicle + vehicle
vehicle + 0.01mg/kg riociguat
0.1mg/kg donepezil + vehicle
0.1 donepezil + 0.01 riociguat
Treatment

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/080362

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/27 A61K31/445 A61K31/505 A61K31/55
A61P25/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FEYZA ARICIOGLU: "Effects of YC-1 on Learning and Memory Functions of Aged Rats", MEDICAL SCIENCE MONITOR BASIC RESEARCH, vol. 20, 1 January 2014 (2014-01-01), pages 130-137, XP055275739, DOI: 10.12659/MSMBR.891064 abstract page 131, column 2, paragraph 5 -----	1

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2017	03/02/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Strack, Eberhard

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	S. SALLOWAY ET AL: "Efficacy of donepezil in mild cognitive impairment: A randomized placebo-controlled trial", NEUROLOGY, vol. 63, no. 4, 24 August 2004 (2004-08-24), pages 651-657, XP055292493, US ISSN: 0028-3878, DOI: 10.1212/01.WNL.0000134664.80320.92 abstract -----	1
A	WO 2015/106268 A1 (IRONWOOD PHARMACEUTICALS INC [US]) 16 July 2015 (2015-07-16) claims 1,17,45 paragraph [0214] -----	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/080362

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015106268 A1	16-07-2015	EP 3094327 A1	23-11-2016
		US 2016324856 A1	10-11-2016
		WO 2015106268 A1	16-07-2015