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(54) Benævnelse: **Behandling af negative symptomer på skizofreni med (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid og farmaceutisk acceptable salte deraf**

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WO-A1-03/055878
ACKER BRAD A ET AL: "Discovery of N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]fur o[2,3-c]pyridi ne-5-carboxamide as an agonist of the alpha 7 nicotinic acetylcholine receptor: In vitro and in vivo activity", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 18, no. 12, June 2008 (2008-06), pages 3611-3615, XP002572658, ISSN: 0960-894X
WISHKA DONN G ET AL: "Discovery of N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]furo[2 ,3-c]pyridine- 5-carboxamide, an agonist of the alpha 7 nicotinic acetylcholine receptor, for the potential treatment of cognitive deficits in schizophrenia: Synthesis and structure-activity relationship", JOURNAL OF MEDICINAL CHEMISTRY, vol. 49, no. 14, July 2006 (2006-07), pages 4425-4436, XP002572659, ISSN: 0022-2623
GRAY J A ET AL: "The pipeline and future of drug development in schizophrenia.", MOLECULAR PSYCHIATRY OCT 2007, vol. 12, no. 10, October 2007 (2007-10), pages 904-922, XP002572660, ISSN: 1359-4184
FREEDMAN ROBERT ET AL: "Initial Phase 2 Trial of a Nicotinic Agonist in Schizophrenia", AMERICAN JOURNAL OF PSYCHIATRY, vol. 165, no. 8, August 2008 (2008-08), pages 1040-1047, XP055182228, ISSN: 0002-953X, DOI: 10.1176/appi.ajp.2008.07071135

DESCRIPTION

Background

[0001] Nicotinic acetylcholine receptors (nAChR) form a family of ion channels activated by acetylcholine. Functional receptors contain five subunits and there are numerous receptor subtypes. Studies have shown that central nicotinic acetylcholine receptors are involved in learning and memory. Nicotinic acetylcholine receptors of the alpha7 subtype are prevalent in the hippocampus and cerebral cortex.

[0002] WO 2003/055878 describes a variety of agonists of the alpha7 nAChR said to be useful for improving cognition. WO 2003/055878 suggests that certain agonists of the alpha7 nAChR are useful for improving perception, concentration, learning or memory, especially after cognitive impairments like those occurring for example in situations/diseases/syndromes such as mild cognitive impairment, age-associated learning and memory impairments, age-associated memory loss, Alzheimer's disease, schizophrenia and certain other cognitive disorders. Among the compounds described are (R)-7-chloro-N-(quinuclidin-3-yl)benzo [b]thiophene-2-carboxamide and pharmaceutically acceptable salts thereof.

Summary

[0003] The subject-matter as claimed is (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide or pharmaceutically acceptable salt thereof, for use in a method of treatment of an individual suffering from negative symptoms of schizophrenia wherein the (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide or a pharmaceutically acceptable salt thereof is administered to the patient at a daily dose of from 0.1 mg - 3 mg. It has been found that (R)-7-chloro-N-(quinuclidin-3-yl)benzo [b]thiophene-2- carboxamide canhaveprocognitive effects in humans atunexpectedly low doses. Thus, (R)-7- chloro-N-(quinuclidin-3-yl)benzo [b]thiophene-2-carboxamide and pharmaceutically acceptable salts thereof can be used at unexpectedly low doses improve cognition in individuals suffering from impaired cognition and in healthy individuals (i.e., individuals that are not suffering from an apparent cognitive deficit). For example, it can be used to improve cognition in patients suffering from Alzheimer's disease, schizophrenia and other disorders such as other neurodegenerative diseases (e.g., Huntington's Disease or Parkinson's Disease) and attention deficit disorder. It can be used treat certain disorders, e.g., Alzheimer's disease, schizophrenia (e.g., paranoid type, disorganized type, catatonic type, and undifferentiated type), schizophreniform disorder, schizoaffective disorder, delusional disorder, positive symptoms of schizophrenia, negative symptoms of schizophrenia at a daily dose of 3 mg, 2.70 mg, 2.50 mg,
2.25 mg, 2 mg, 1.75 mg, 1.50 mg, 1.25 mg, 1 mg, 0.7, 0.5, 0.3 mg or even 0.1 mg. The

compound can be used to improve one or more aspects of cognition, e.g., one or more of: executive function, memory (e.g., working memory), social cognition, visual learning, verbal learning and speed of processing.

[0004] Described herein are methods for treating a patient by administering a pharmaceutical composition that comprises (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide or pharmaceutically acceptable salt thereof at a daily dose of: 3 mg, 2.70 mg, 2.50 mg, 2.25 mg, 2 mg, 1.75 mg, 1.50 mg, 1.25 mg, 1 mg, 0.7 mg, 0.5 mg, 0.3 mg, or 0.1 mg. The treatment can improve one or more facets of cognition (e.g., visual motor skill, learning, delayed memory, attention, working memory, visual learning, speed of processing, vigilance, verbal learning, visual motor function, social cognition, long term memory, executive function, etc.). The methods can be used to treat: Alzheimer's disease, schizophrenia (e.g., paranoid type, disorganized type, catatonic type, and undifferentiated type), schizophreniform disorder, schizoaffective disorder, delusional disorder, positive symptoms of schizophrenia or negative symptoms of schizophrenia.

[0005] "Dose" is the amount of active pharmaceutical ingredient (API) administered to a patient. For example 1 mg dose means 1 mg of API was administered to each patient each day.

[0006] "Active Pharmaceutical Ingredient" is defined as either (R)-7-chloro-N-(quinuclidin-3-yl)bcnzo[b]thiophcnc-2-carboxamidc hydrochloride, (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide, (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride monohydrate or (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride solvate.

[0007] Where solvate represents a stoichiometric ratio of 0.1 to 10 molecules of solvent compared to (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride or (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide. Solvent molecules include but are not limited to water, methanol, 1,4 dioxane, ethanol, iso-propanol or acetone. In some cases water is the preferred solvate.

[0008] "The test compound" is defined as (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride.

[0009] "EC_{ref}" is the concentration of drug which elicits equal response in oocytes transfected with cloned human alpha7 receptor at 50 μM acetylcholine. Maximum stimulation of the cloned human alpha 7 receptor occurs at a concentration >250 μM of acetylcholine.

FIGURES

[0010]

FIGURE 1 depicts the results of a study on the effect of the test compound on P50 gating. The left panel depicts the baseline-adjusted average P50 gating ratio (T/C) as a function of group assignment [F=1.16, P=0.36]. The standard errors of each mean are noted in the legend. The bars (left to right) represent placebo, 0.3 mg test compound, and 1.0 mg test compound. The right panel depicts the baseline-adjusted average P50 difference (C-T) as a function of group assignment [F=3.97, P=0.07]. The standard errors of cach mean arc noted in the legend. The bars left to right represent placebo, 0.3 mg test compound, and 1.0 mg test compound.

FIGURE 2 depicts the results of a study on the effect of the test compound on P100 gating. The left panel depicts baseline-adjusted average N100 gating ratio (T/C) as a function of group assignment [F=3.04, P=0.10]. The standard errors of each mean are noted in the legend. The bars left to right represent placebo, 0.3 mg test compound, and 1.0 mg test compoundThe right panel depicts baseline-adjusted average N100 difference (C-T) as a function of group assignment [F=1.02, P=0.38]. The standard errors of each mean are noted in the legend. The bars left to right represent placebo, 0.3 mg test compound, and 1.0 mg test compound.

FIGURE 3 depicts that results of a study on the effect of the test compound on MMN amplitude and P00 amplitude. The left panel depicts MMN as a function of group assignment [F=4.96, P=0.02]. The standard errors of each mean are noted in the legend. The bars left to right represent placebo, 0.3 mg test compound, and 1.0 mg test compound. The right panel depicts P300 amplitude (in microvolts relative to prestimulus voltage) measured at Pz scalp in response evoked by a rare but unattended stimulus. Group assignment effect: F=6.88, P=0.008. The standard errors of each mean are noted in the legend. The bars left to right represent placebo, 0.3 mg test compound, and 1.0 mg test compound.

Detailed Description

[0011] Described below are human clinical trials demonstrating that (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide elicits positive effects on cognition at an unexpectedly low daily dose of 1 mg or less. The positive effects are observed in both patients suffering from schizophrenia and in normal subjects. Also described below are studies showing that the free concentration of (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide in humans administered at daily 1 mg dose (of (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride) is at least a an order of magnitude lower than that expected to be required to exert a positive effect on cognitive function or can improve sensory electrophysiological responses which correlate with improved cognitive and functional performance in schizophrenia patients. Also described below are studies demonstrating that that (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide has an unexpectedly long half-life in humans compared to that expected based on pre-clinical studies in animals.

[0012] Because (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide can improve cognition at an unexpectedly low free plasma concentration, it is less likely to elicit

harmful side-effects on its own and is less likely to exhibit harmful interactions with other drugs. Due to the unexpectedly low free plasma concentration required and the long half-life, (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide is expected to have special drug properties. These properties include a high margin of safety and a favorable dosing regimen (e.g., once daily dosing), both of which are highly advantageous for treating patients with cognitive defects as well as patients that arc required to take additional medications.

Effect on Cognition in Schizophrenia Patients

[0013] The studies described below demonstrate that (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride can improve sensory electrophysiological responses which correlate with improved cognitive and functional performance in schizophrenia patients. These effects were observed at a daily dose as low as 0.3 mg.

[0014] Impairment of the ability of central nervous system to inhibit irrelevant sensory information has long been used as a model for understanding the deficits of attention seen in schizophrenic patients. Two approaches to the measurement of this ability have commonly been employed (see (Heinrichs, 2004; Potter et al., 2006; Turetsky et al., 2007; Umbricht and Krljes, 2005) for reviews and meta-analyses): (1) the sensory gating paradigm in which the presentation of one stimulus normally suppresses the response elicited by a stimulus which rapidly follows it. Schizophrenic patients typically exhibit less suppression (gating) of the second response. (2) the oddball or orienting paradigm in which a rare or unexpected event elicits a diminished response in schizophrenic patients because attentional resources are inappropriately focused on less salient aspects of the environment.

[0015] Two responses arc commonly used assess brain activity: (1) the auditory P50 response elicited by the second member of a pair of clicks; and (2) the mismatch negativity (MMN) or N2 response evoked by a rarely occurring pure tone of no instructed relevance to the patient. Abnormalities in both P50 gating and the MMN have been reported in schizophrenic patients. Described below are studies assessing both of these responses in patients treated with (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride salt ("the test compound"). Also presented below are studies assessing the influence of the test compound on the N100 and P300 components of the evoked response. These components emerge after the P50 component and are as much related to attention to, and memory for, task relevant stimuli as to the neural processes by which task irrelevant stimuli are filtered (Turetsky et al., 2007; and Sandman and Patterson, 2000).

[0016] The neurobiology of P50 sensory gating is well documented in studies of human and animal subjects. Its regulation relies heavily on the integrity of the hippocampus and pathways that provide input to the hippocampus (Adler et al., 1998). For example, lesions of the cholinergic pathway originating in the medial septal nucleus disrupt the gating response, as do antagonists of low affinity nicotinic receptors. Cholinergic agonists, including nicotine itself (Adler et al., 1993; Duncan et al., 2001), have been shown to enhance P50 gating (Freedman

et al., 2001; Olincy et al., 2006).

[0017] The neurobiology of the MMN is more complex. Imaging studies suggest that the primary and secondary auditory cortices in the temporal lobe are important for its generation (Naatanen and Alho, 1995). The dorsolateral prefrontal cortex also contributes (Schall et al., 2003). The neurotransmitter systems underlying the MMN are understudied and largely unknown. Yet, as is the case for P50, nicotinic cholinergic systems appear important (Baldeweg et al., 2006; Dunbar et al., 2007).

[0018] The sensitivity of P300 and N100 to cholinergic compounds has been known for many years (Dierks et al., 1994; Kaga et al., 1992). Various cholinergic antagonists--such as scopolamine--profoundly reduce the amplitudes of these components. In contrast, the components are markedly improved in amplitude by cholinesterase inhibitors (Katada et al., 2003; Werber et al., 2001) and other compounds that enhance cholinergic activity (Easton and Bauer, 1997).

[0019] The test described above were used to study the effect of the test compound on cognition in patients suffering from schizophrenia. Prior to testing the patient were dosed with: 1 mg of the test compound daily, 0.3 mg of the test compound daily or were administered a placebo for 20 days. Subjects were tested as described below.

[0020] P50 waves were elicited by clicks, 1 msec in duration, grouped in pairs in the classic S1-S2 sequence and presented through earpieces inserted into the auditory canals. Click intensity was adjusted individually to 50 dB above the hearing threshold. The offset-to-onset time from S1 to S2 was fixed at 500 msec. The offset-to-onset time between click pairs was varied from 7-11 sec. A total of 30 pairs of clicks were presented during each of 5 or more trial blocks with a one minute rest period interposed between each block.

[0021] EEG responses to the clicks were amplified to a gain of 10K and filtered (bandpass=3-30 Hz, 12 db roll-off). They were collected from 63 tin electrodes positioned by an electrode cap (Compumedics Neuroscan, Inc.). Additional electrodes of the same type were applied to the mid-forehead (ground) and in a vertical orientation above and below the left eye. Interelectrode impedances were maintained below 10 kOhms. All recordings were made with the subject sitting upright and relaxed but awake.

[0022] The EEG and eye movement signals were sampled by an analog-to-converter programmed to retain EEG activity from 50 msec preceding to 325 msec following click onset. The sampling rate was 1000 Hz. The digitized signals were stored in a database for subsequent analysis.

[0023] The 150 sweeps of S1 and S2 responses were screened and sweeps with voltage deviations greater than 100 microvolts in the eye movement channels were rejected. The remaining accepted sweeps were formed into time point averages. While blinded to group assignment, the investigator visually examined the evoked potential waveforms at the FCz

electrode site. When possible, the investigator identified a negative trough immediately prior to the P50, the P50 itself, and the following N100 component. Admittedly, a distinct P50 component could not be visually identified in all patients at all time points. In those cases, the data were coded as missing.

[0024] P50 response amplitude was calculated as the voltage difference between the P50 peak and the preceding negative trough. The P50 gating ratio was then calculated after (Olincy et al., 2006) as the amplitude of the P50 response to the second (test) stimulus divided by the amplitude of the P50 response to the first (conditioning) stimulus. A small gating ratio is considered normal or optimal. The P50 amplitude difference (Fuerst et al., 2007) was also measured. It was the amplitude of the conditioning stimulus P50 response minus the amplitude of the test stimulus P50 response. A large P50 amplitude difference indicates normal gating.

[0025] N100 amplitude was calculated as the peak voltage of N100 minus the average voltage during the brief, 50 msec prestimulus period. As was the case for P50, N100 responses to the conditioning and test stimuli were calculated as ratios as well as differences.

[0026] The MMN and P300 components were elicited during the so-called oddball sequence. The stimulus sequence was a series of lower (500 Hz) and higher (1000 Hz) pitched pure tones presented at a rate of 1 tone per 0.6 sec. The tones were 50 msec in duration, 50 dB above hearing level, and randomly interspersed. The higher pitched tone was the oddball event. Across the series of 600 tones, it occurred at a probability of 0.2. The other tone occurred at the complementary probability of 0.8. Patients were instructed to ignore the tones and instead attend to a magazine held in the lap.

[0027] During the task, EEG and EOG activity were digitized at a rate of 500 Hz per channel for 50 msec preceding and 500 msec following stimulus onset. Trials contaminated by eyeblinks or eye movements were removed. An off-line program digitally filtered (bandpass=0.1-30 Hz, 12 db roll-off) responses to the rare and frequent events and constructed averaged event related responses for each electrode. At the FCz electrode, the MMN was measured by an automated algorithm that computed the summed amplitude, relative to the prestimulus baseline, over a 100-200 msec time window following the onsets of the rare (oddball) and frequent tones. MMN was then recalculated as the voltage difference between these responses. P300 amplitude was measured at the Pz electrode site as the peak amplitude between 250 and 500 msec following stimulus onset.

[0028] The plan for the analysis of the EEG measures was developed prior to breaking of the blind. It was based on the study design involving 3 groups (n=8 high dose, n=8 moderate dose, n=4 placebo) and 4 time points (1 predrug + 3 postdrug). The plan offered several alternative strategies based upon the completeness and quality of the recordings. Unfortunately, in the case of the P50/N100 gating study, it was necessary to discard several patients and post-treatment assignment time points from the analysis because, in those instances, a P50 waveform was not identifiable and therefore could not be measured. This problem has been acknowledged in the literature but has not been discussed as openly and frequently as a

skeptical scientist would like. For the analysis of P50 and N100, we adopted strategy 1b: "If many postdrug data points are missing/corrupted, then the remaining postdrug data points will be averaged together to create a single postdrug data point." The significant number of missing or unmeasurable P50's, unfortunately, removed another of our analysis options, wherein we hoped to focus on the subgroup of patients who showed the poorest sensory gating at baseline and might show the strongest improvement in gating after treatment. Of the 12 patients who provided valid and measurable P50 responses, 2 were in the placebo group, and 5 were in each of the two active dose groups.

[0029] Figure 1 presents the results of simple analyses of covariance wherein all time points during the treatment period with valid data were averaged together to yield a single value. This value was then adjusted by regressing it against the baseline value and estimating a new value as if all patients possessed the same baseline. Then, a simple F test was performed. In support of the assumption of no significant differences between the treatment groups at the baseline (i.e., before treatment), we conducted simple ANOVAs evaluating the effect of treatment on all of the evoked potential components discussed presently. In no case did treatment significantly affect the baseline value. The left panel of Figure 1 shows a non-significant [F=1.16, P=0.36] reduction (i.e., normalization) of the P50 gating ratio among patients receiving the 1.0 mg dose of the test compound. In contrast, the right panel of Figure 1 shows the P50 amplitude difference score-a metric with superior reliability. It likewise shows normalization at the high dose. However, in this case, the change approaches statistical significance [F=3.97, P=0.07].

[0030] Figure 2 presents an identical analysis of the N100 gating ratio and amplitude difference. Here, the gating ratio demonstrates a more reliable effect of the medication [F=3.04, P=0.10] than docs the amplitude difference [F=1.02, P=0.38]. In the left panel of Figure 2 normalization is suggested by a lower score. In the right panel of Figure 2, normalization is indicated by the opposite direction of change.

[0031] MMN and P300 amplitude reflect activation of multiple precortical and cortical pathways sensitive to stimulus novelty, short term memory, and attention. MMN was calculated as the voltage difference over 100-200 msec post-stimulus onset between the responses to the rare and frequent stimuli. A more negative MMN suggests normal cognitive function. P300 is not entirely independent of MMN. P300 was calculated as the peak amplitude relative to the average voltage of the waveform during the 50 msec prestimulus period. A more positive P300 response is indicative of improved cognitive function. P300 is maximal in amplitude when the eliciting stimulus is both rare and task relevant (i.e., attended). In the present study, the rare stimulus was not task relevant. In fact, the patient was instructed to perform no task and to ignore the stimuli. In the present study, therefore, P300 amplitude is very small in comparison to amplitudes recorded under active task conditions. The present P300 component is more similar to the small, frontally-generated P300a described by Knight and colleagues than the large, parietally-generated P300b described in most studies of attentional dysfunction in schizophrenia.

[0032] In the analysis of P50 and N100 the baseline value was the covariate and all values obtained during the treatment period were averaged together. Data loss from unidentifiable MMN and P300 components was minimal. These analyses were conducted upon data obtained from n=4 patients treated with placebo, n=7 patients treated with 0.3 mg the test compound, and n=8 patients treated with 1.0 mg the test compound.

[0033] Figure 3 shows the results of the analysis of MMN and P300 amplitudes during the oddball task. Both evoked potential components were sensitive to the test compound in the predicted direction: MMN [F=4.96, P=0.02]; P300 [F=6.88, P=0.008]. In a dose-related manner, the test compound increased MMN and P300 amplitudes.

[0034] Despite the small number of patients enrolled in this trial, the analysis revealed several significant or marginally significant results. Both the 0.3 mg and 1.0 mg doses of the test compound evoked significantly ($p<.05$) larger P300 and MMN components than were seen under the placebo condition. The effects of the test compound on an earlier component of the evoked response component (i.e., the P50) were limited to the highest, 1.0 mg, dose and were technically not significant ($p=0.1$). These results indicate that both the 0.3 mg dose and 1.0 mg dose of the test compound are anticipated to be effective in treating schizophrenia.

[0035] The relative sensitivity or insensitivity of various evoked response components to the test compound may be related to their size and reliability of measurement. In addition, sensitivity differences may relate to differences across the components in their neural generators and innervation by cholinergic afferents. Indeed, the two components (MMN and P300) which were most sensitive to the test compound are generated or modulated by frontal cortical pathways that receive input from brainstem cholinergic fibers. The P50 is, in contrast, generated subcortically.

Effect on Cognition in Normal Subjects

[0036] The impact of the test compound on cognition in normal subjects was assessed as described below. In these studies subjects were treated with the test compound dissolved in cranberry juice.

[0037] The impact of the test compound on cognition in normal subjects was assessed in a SAD (Single Ascending Dose) study with the Digit Symbol Substitution Test (DSST). Utilizing this test, the test compound was shown to have pro-cognitive effects at daily a dose as low as 1 mg. This is unexpected since acetylcholine esterase inhibitors, which indirectly activates the alpha 7 receptor by increasing acetylcholine levels, are not understood to exhibit pro-cognitive effects in normal subject and even in patients with cognitive impairment are not understood to exhibit pro-cognitive effects after a single dose. The positive effects of the test compound in the DSST indicate a beneficial effect on working memory and executive function.

[0038] In the MAD (Multiple Ascending Dose) studies cognition was assessed using tests from

the CogState battery (cogstate.com). Utilizing this test, the test compound was shown to have pro-cognitive effects at daily a dose as low as 1 mg. The CogState battery is a proprietary computerized cognitive battery of tests measure various cognitive domains including: attention, identification capability, working memory, visual memory, and executive function. In these studies the test compound was found to have a positive impact on: visual motor skills, learning, executive function, and delayed memory. The profile of the response was unique insofar as the test compound had positive effects on non-verbal learning and memory and executive function without having a stimulatory effect on attention. The magnitude of the effects were, in many cases, significant with effect sizes being > 0.4 (a threshold effect size which is commonly accepted as having clinical significance). This therapeutic profile (pro-cognitive effects on non-verbal learning and memory and executive function without a central stimulatory effect) indicates that the drug may be very beneficial in treating patients that have, as a feature of their condition, symptoms of anxiety or agitation.

(R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride shows effects at unexpectedly low dose and free plasma concentration

[0039] The studies described above demonstrate that (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride administered at a daily dose of 1.0 mg or 0.3 mg can improve cognition in patients suffering from schizophrenia and in normal subjects.

[0040] The fact that a 0.3 mg or 1.0 mg dose of (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride can elicit an effect in various measures of cognition is surprising because at these dosages the concentration of free drug is well below the Ki of the compound to bind to the alpha 7 receptor.

[0041] In order for a small molecule to exert action at its target, often a cell receptor, it must bind to its target. Thus, in general, a small molecule drug is expected to exhibit activity when the free drug concentration at the target (i.e., the concentration of drug that is free and available to bind to the target) approaches or exceeds the K_i of the drug for target. Studies have shown that in numerous cases the free drug concentration in a particular tissue is about equal to the free drug concentration in plasma (Mauer et al. 2005 and Trainor 2007). For the brain, the free plasma concentration is generally considered to represent the maximum possible free drug concentration. The free drug concentration in plasma ($[\text{free drug}]_{plasma}$) is determined by measuring the total drug concentration in the plasma ($[\text{total drug}]_{plasma}$) and the free fraction of the drug, i.e., the fraction of the drug that is not bound to plasma protein (fu_{plasma}): $[\text{free drug}]_{plasma} = [\text{total drug}]_{plasma} \times fu_{plasma}$. The total plasma drug concentration and the fraction that binds to plasma protein can both be measured using techniques known to those of skill in the art.

[0042] Studies on (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide determined that the EC_{ref} for human alpha7 receptor is approximately 0.158 μM and the K_i (rat

membrane) is approximately 10 nM. Additional studies found the following values for the free fraction of drug: Rat fu_{plasma} = 0.112, Dog fu_{plasma} = 0.107, Human fu_{plasma} = 0.129.

[0043] Multiple ascending dose (MAD) human clinical trials were conducted. The maximum plasma concentration was determined and used to calculate the maximum free drug concentration which was used to determine the maximum free drug concentration as a fraction of the EC_{ref} of the drug for human alpha7 receptor and the maximum free drug concentration as a fraction of the K_i of the drug for rat brain alpha7 receptors. The EC_{ref}, the concentration of drug which elicits equal response in oocytes transfected with cloned human alpha7 receptor at 50 μM acetylcholine (the endogenous receptor ligand), was determined to be 0.158 μM. The K_i for rat brain alpha7 receptors was determined to be 10 nM.

Table 1

Study	Day	Dose	C_{max} (ng/mL)	C_{max} total (nM)	C_{max} free (nM)	Fraction of α7 EC_{ref}	Fraction of α7 Binding K_i
SAD	1	1 mg	0.59	1.84	0.237	0.0015	0.0237
SAD	1	3.5 mg	2.06	6.42	0.828	0.0052	0.0828
MAD 1	1	1 mg	0.63	1.96	0.252	0.0016	0.0252
MAD 1	7	1 mg	2.12	6.61	0.853	0.0054	0.0853
MAD 1	14	1 mg	2.64	8.23	1.06	0.0067	0.1060
MAD 2	1	0.1 mg	0.055	0.172	0.022	0.0001	0.0022
MAD 2	21	0.1 mg	0.232	0.724	0.093	0.0006	0.0093
MAD 2	1	1 mg	0.623	1.943	0.251	0.0016	0.0251
MAD 2	21	1 mg	2.42	7.547	0.974	0.0062	0.0974
MAD 3	1	0.3 mg	0.182	0.568	0.073	0.0005	0.0073
MAD 3	21	0.3 mg	0.704	2.195	0.283	0.0018	0.0283
MAD 3	1	1 mg	0.547	1.71	0.221	0.0014	0.0221
MAD 3	21	1 mg	1.99	6.20	0.800	0.0051	0.0800

[0044] In human single and multiple ascending dose clinical trials in both healthy and schizophrenia patients a 0.3 mg daily dose and a 1.0 mg daily dose were shown to improve cognitive function or correlates of cognitive function. As can been seen from Table 1, which presents an analysis of the free drug concentration the 0.3 mg dose of (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide hydrochloride produces a maximum free plasma concentration of 0.073-0.283 nM which is 0.005 to 0.0018 of the α7 EC_{ref} and 0.0073 to 0.0283 of the α7 K_i. These values are 35-2000 times lower than would have anticipated if efficacy was to be achieved when the free plasma concentration reached the K_i or the EC_{ref} concentrations. When a similar calculation is performed for the 1.0 mg doses (free plasma of 0.237-1.06 nM) these fractional values of the K_i and EC_{ref} concentrations are 0.0015 to 0.0067 (EC_{ref}) and 0.0237 to 0.106 (K;). These values are 9.4-667 times lower than expected.

Half-life of (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide in humans

[0045] Table 2 presents half-life ($t_{½}$) data for (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide obtained from pre-clinical species as well as the half-life in humans determined in clinical trials.

Table 2

Species	Route of administration	Dose	$t_{1/2}$
Mouse	i.v.		n/a*
Rat	i.v.	1 mg/kg	2.77 h
Dog	i.v.	0.5 mg/kg	5.39
Dog	i.v.	3 mg/kg	13
Human	p.o.	1 mg	50.1-70.1
* (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide was unstable in mouse plasma and as such a half-life ($t_{1/2}$)could not be accurately calculated			

[0046] The half-life determined in rat and dog suggested a human half-life much shorter than the observed 60 hr half-life (initial allometric scaling suggested a half-life of about 8 hours). The unexpectedly long half-life in humans has several advantages. It allows for once a day dosing. The drug will also have a very small dynamic plasma range over the course of a day (about 15-20%). Thus, if a patient misses a daily dose, the plasma level and the consequent brain level will not be altered by a great degree. This means that the beneficial effects of the drug will be less dependent upon careful adherence to a specific dosing scheme. Third, long half-life and slow elimination also mean that the final dose will be lower than expected. This readily observed by looking at the C_{max} values on Day 1 versus Day 21. The C_{max} values on Day 21 are about 3.6 - 4.2 times higher than the Day1 values. This ratio will translate into a dose that is 3.6-4.2 times lower than would normally be expected due to this favorable

accumulation.

References

[0047]

Adler, L.E., Hoffer, L.D., Wiser, A., Freedman, R., 1993. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am J Psychiatry 150, 1856-1861.

Adler, L.E., Olincy, A., Waldo, M., Harris, J.G., Griffith, J., Stevens, K., Flach, K., Nagamoto, H., Bickford, P., Leonard, S., Freedman, R., 1998. Schizophrenia, sensory gating, and nicotinic receptors. Schizophr Bull 24, 189-202.

Baldeweg, T., Wong, D., Stephan, K.E., 2006. Nicotinic modulation of human auditory sensory memory: Evidence from mismatch negativity potentials. Int J Psychophysiol 59, 49-58.

Boutros, N.N., Overall, J., Zouridakis, G., 1991. Test-retest reliability of the P50 mid-latency auditory evoked response. Psychiatry Res 39, 181-192.

Dalebout, S.D., Fox, L.G., 2001. Reliability of the mismatch negativity in the responses of individual listeners. J Am Acad Audiol 12, 245-253.

de Wilde, O.M., Bour, L.J., Dingemans, P.M., Koelman, J.H., Linszen, D.H., 2007. A meta-analysis of P50 studies in patients with schizophrenia and relatives: differences in methodology between research groups. Schizophr Res 97, 137-151.

Dierks, T., Frolich, L., Ihl, R., Maurer, K., 1994. Event-related potentials and psychopharmacology. Cholinergic modulation of P300. Pharmacopsychiatry 27, 72-74.

Dunbar, G., Boeijinga, P.H., Demazieres, A., Cisterni, C., Kuchibhatla, R., Wesnes, K., Luthringer, R., 2007. Effects of TC-1734 (AZD3480), a selective neuronal nicotinic receptor agonist, on cognitive performance and the EEG of young healthy male volunteers. Psychopharmacology (Berl) 191, 919-929.

Duncan, E., Madonick, S., Chakravorty, S., Parwani, A., Szilagyi, S., Efferen, T., Gonzenbach, S., Angrist, B., Rotrosen, J., 2001. Effects of smoking on acoustic startle and prepulse inhibition in humans. Psychopharmacology (Berl) 156, 266-272.

Easton, C.J., Bauer, L.O., 1997. Beneficial effects of thiamine on recognition memory and P300 in abstinent cocaine-dependent patients. Psychiatry Res 70, 165-174.

Freedman, R., Leonard, S., Gault, J.M., Hopkins, J., Cloninger, C.R., Kaufmann, C.A., Tsuang, M.T., Farone, S.V., Malaspina, D., Svrakic, D.M., Sanders, A., Gejman, P., 2001.

Linkage disequilibrium for schizophrenia at the chromosome 15q13-14 locus of the alpha7-nicotinic acetylcholine receptor subunit gene (CHRNA7). Am J Med Genet 105, 20-22.

Fuerst, D.R., Gallinat, J., Boutros, N.N., 2007. Range of sensory gating values and test-retest reliability in normal subjects. Psychophysiology 44, 620-626.

Heinrichs, R.W., 2004. Meta-analysis and the science of schizophrenia: variant evidence or evidence of variants? Neurosci Biobehav Rev 28, 379-394.

Kaga, K., Harrison, J.B., Butcher, L.L., Woolf, N.J., Buchwald, J.S., 1992. Cat 'P300' and cholinergic septohippocampal neurons: depth recordings, lesions, and choline acetyltransferase immunohistochemistry. Neurosci Res 13, 53-71.

Katada, E., Sato, K., Sawaki, A., Dohi, Y., Ueda, R., Ojika, K., 2003. Long-term effects of donepezil on P300 auditory event-related potentials in patients with Alzheimer's disease. J Geriatr Psychiatry Neurol 16, 39-43.

Maurer, T., DeBartolo, D., Tess, D., and Scott, D., 2005. The relationship between the exposure and non-specific binding of thirty-three central nervous system drugs in mice. Drug Metabolism and Disposition 33, 175-181.

Naatanen, R., Alho, K., 1995. Generators of electrical and magnetic mismatch responses in humans. Brain Topogr 7, 315-320.

Olincy, A., Harris, J.G., Johnson, L.L., Pender, V., Kongs, S., Allensworth, D., Ellis, J., Zerbe, G.O., Leonard, S., Stevens, K.E., Stevens, J.O., Martin, L., Adler, L.E., Soti, F., Kem, W.R., Freedman, R., 2006. Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. Arch Gen Psychiatry 63, 630-638.

Potter, D., Summerfelt, A., Gold, J., Buchanan, R.W., 2006. Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. Schizophr Bull 32, 692-700.

Sandman, C.A., Patterson, J.V., 2000. The auditory event-related potential is a stable and reliable measure in elderly subjects over a 3 year period. Clin Neurophysiol 111, 1427-1437.

Schall, U., Johnston, P., Todd, J., Ward, P.B., Michie, P.T., 2003. Functional neuroanatomy of auditory mismatch processing: an event-related fMRI study of duration-deviant oddballs. Neuroimage 20, 729-736.

Trainor, G, 2007. The importance of plasma protein binding in drug discovery. Expert Opinion in Drug Discovery 2:51-64.

Turetsky, B.I., Calkins, M.E., Light, G.A., Olincy, A., Radant, A.D., Swerdlow, N.R., 2007. Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. Schizophr Bull 33, 69-94.

Umbricht, D., Krljes, S., 2005. Mismatch negativity in schizophrenia: a meta-analysis. Schizophr Res 76, 1-23.

Werber, A.E., Klein, C., Rabey, J.M., 2001. Evaluation of cholinergic treatment in demented patients by P300 evoked related potentials. Neurol Neurochir Pol 35 Suppl 3, 37-43.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO2003055878A [0002] [0002]

Non-patent literature cited in the description

- **ADLER, L.E.HOFFER, L.D.WISER, A.FREEDMAN, R.**Normalization of auditory physiology by cigarette smoking in schizophrenic patientsAm J Psychiatry, 1993, vol. 150, 1856-1861 [0047]
- **ADLER, L.E.OLINCY, A.WALDO, M.HARRIS, J.G.GRIFFITH, J.STEVENS, K.FLACH, K.NAGAMOTO, H.BICKFORD, P.LEONARD, S.**Schizophrenia, sensory gating, and nicotinic receptorsSchizophr Bull, 1998, vol. 24, 189-202 [0047]
- **BALDEWEG, T.WONG, D.STEPHAN, K.E.**Nicotinic modulation of human auditory sensory memory: Evidence from mismatch negativity potentialsInt J Psychophysiol, 2006, vol. 59, 49-58 [0047]
- **BOUTROS, N.N.OVERALL, J.ZOURIDAKIS, G.**Test-retest reliability of the P50 mid-latency auditory evoked responsePsychiatry Res, 1991, vol. 39, 181-192 [0047]
- **DALEBOUT, S.D.FOX, L.G.**Reliability of the mismatch negativity in the responses of individual listenersJ Am Acad Audiol, 2001, vol. 12, 245-253 [0047]
- **DE WILDE, O.M.BOUR, L.J.DINGEMANS, P.M.KOELMAN, J.H.LINSZEN, D.H.**A meta-analysis of P50 studies in patients with schizophrenia and relatives: differences in methodology between research groupsSchizophr Res, 2007, vol. 97, 137-151 [0047]
- **DIERKS, T.FROLICH, L.IHL, R.MAURER, K.**Event-related potentials and psychopharmacology. Cholinergic modulation of P300Pharmacopsychiatry, 1994, vol. 27, 72-74 [0047]
- **DUNBAR, G.BOEIJINGA, P.H.DEMAZIERES, A.CISTERNI, C.KUCHIBHATLA, R.WESNES, K.LUTHRINGER, R.**Effects of TC-1734 (AZD3480), a selective neuronal nicotinic receptor agonist, on cognitive performance and the EEG of young healthy male

volunteersPsychopharmacology (Berl), 2007, vol. 191, 919-929 [0047]

- **DUNCAN, E.MADONICK, S.CHAKRAVORTY, S.PARWANI, A.SZILAGYI, S.EFFEREN, T.GONZENBACH, S.ANGRIST, B.ROTROSEN, J.**Effects of smoking on acoustic startle and prepulse inhibition in humansPsychopharmacology (Berl), 2001, vol. 156, 266-272 [0047]
- **EASTON, C.J.BAUER, L.O.**Beneficial effects of thiamine on recognition memory and P300 in abstinent cocaine-dependent patientsPsychiatry Res, 1997, vol. 70, 165-174 [0047]
- **FREEDMAN, R., LEONARD, S., GAULT, J.M., HOPKINS, J., CLONINGER, C.R., KAUFMANN, C.A.**Linkage disequilibrium for schizophrenia at the chromosome 15q13-14 locus of the alpha7-nicotinic acetylcholine receptor subunit gene (CHRNA7)Am J Med Genet, 2001, vol. 105, 20-22 [0047]
- **FUERST, D.R.GALLINAT, J.BOUTROS, N.N.**Range of sensory gating values and test-retest reliability in normal subjectsPsychophysiology, 2007, vol. 44, 620-626 [0047]
- **HEINRICHS, R.W.**Meta-analysis and the science of schizophrenia: variant evidence or evidence of variants?Neurosci Biobehav Rev, 2004, vol. 28, 379-394 [0047]
- **KAGA, K.HARRISON, J.B.BUTCHER, L.L.WOOLF, N.J.BUCHWALD, J.S.**Cat 'P300' and cholinergic septohippocampal neurons: depth recordings, lesions, and choline acetyltransferase immunohistochemistryNeurosci Res, 1992, vol. 13, 53-71 [0047]
- **KATADA, E.SATO, K.SAWAKI, A.DOHI, Y.UEDA, R.OJIKA, K.**Long-term effects of donepezil on P300 auditory event-related potentials in patients with Alzheimer's diseaseJ Geriatr Psychiatry Neurol, 2003, vol. 16, 39-43 [0047]
- **MAURER, T.DEBARTOLO, D.TESS, D.SCOTT, D.**The relationship between the exposure and non-specific binding of thirty-three central nervous system drugs in miceDrug Metabolism and Disposition, 2005, vol. 33, 175-181 [0047]
- **NAATANEN, R.ALHO, K.**Generators of electrical and magnetic mismatch responses in humansBrain Topogr, 1995, vol. 7, 315-320 [0047]
- **OLINCY, A.HARRIS, J.G.JOHNSON, L.L.PENDER, V.KONGS, S.ALLENSWORTH, D.ELLIS, J.ZERBE, G.O.LEONARD, S.STEVENS, K.E.**Proof-of-concept trial of an alpha7 nicotinic agonist in schizophreniaArch Gen Psychiatry, 2006, vol. 63, 630-638 [0047]
- **POTTER, D.SUMMERFELT, A.GOLD, J.BUCHANAN, R.W.**Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophreniaSchizophr Bull, 2006, vol. 32, 692-700 [0047]
- **SANDMAN, C.A.PATTERSON, J.V.**The auditory event-related potential is a stable and reliable measure in elderly subjects over a 3 year periodClin Neurophysiol, 2000, vol. 111, 1427-1437 [0047]
- **SCHALL, U.JOHNSTON, P.TODD, J.WARD, P.B.MICHIE, P.T.**Functional neuroanatomy of auditory mismatch processing: an event-related fMRI study of duration-deviant oddballsNeuroimage, 2003, vol. 20, 729-736 [0047]
- **TRAINOR, G**The importance of plasma protein binding in drug discoveryExpert Opinion in Drug Discovery, 2007, vol. 2, 51-64 [0047]
- **TURETSKY, B.I.CALKINS, M.E.LIGHT, G.A.OLINCY, A.RADANT, A.D.SWERDLOW, N.R.**Neurophysiological endophenotypes of schizophrenia: the viability of selected

candidate measuresSchizophr Bull, 2007, vol. 33, 69-94 [0047]

- **UMBRICHT, D.KRLJES, S.**Mismatch negativity in schizophrenia: a meta-analysisSchizophr Res, 2005, vol. 76, 1-23 [0047]
- **WERBER, A.E.KLEIN, C.RABEY, J.M.**Evaluation of cholinergic treatment in demented patients by P300 evoked related potentialsNeurol Neurochir Pol, 2001, vol. 35, 337-43 [0047]

Patentkrav

1. (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf eller en farmaceutisk sammensætning, der omfatter (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf, til anvendelse i en fremgangsmåde til behandling af en person, der lider af negative symptomer på skizofreni, hvor (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf administreres til patienten ved en daglig dosis på fra 0,1 mg til 3 mg.

2. (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf eller en farmaceutisk sammensætning, der omfatter (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf, til anvendelse ifølge krav 1, hvor den daglige dosis er fra 0,3 mg til 3 mg.

3. (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf eller en farmaceutisk sammensætning, der omfatter (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf, til anvendelse ifølge krav 2, hvor den daglige dosis er fra 1 mg til 3 mg.

4. (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf eller en farmaceutisk sammensætning, der omfatter (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf, til anvendelse ifølge et hvilket som helst af kravene 1 til 2, hvor den daglige dosis er 0,3 mg, 1 mg, 2 mg eller 3 mg.

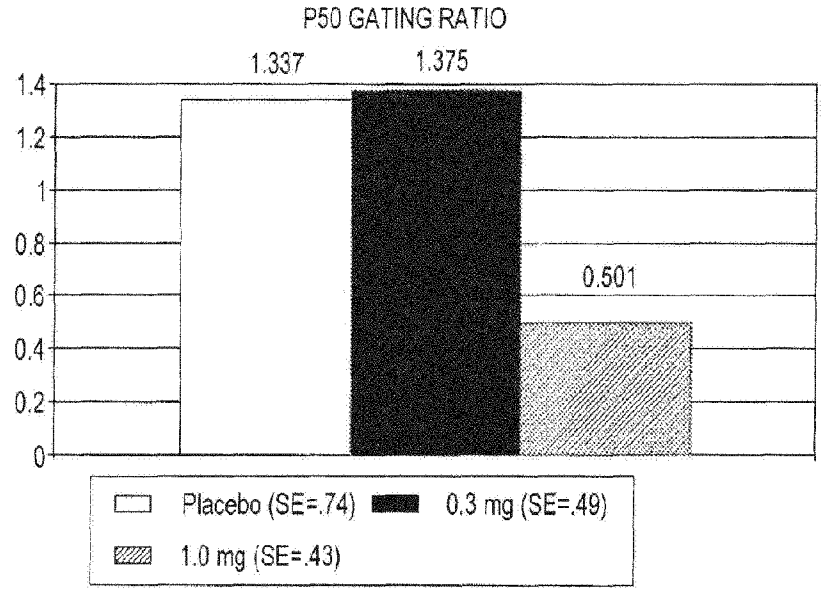
5. (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf eller en farmaceutisk sammensætning, der omfatter (R)-7-chlor-N-

(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf, til anvendelse ifølge krav 1, hvor saltet er valgt blandt (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamidhydrochlorid, (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamidhydrochloridmonohydrat eller (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamidhydrochloridsolvat.

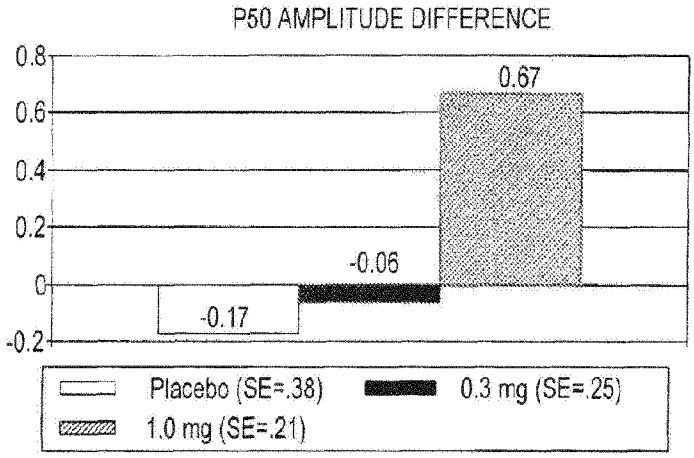
6. (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf eller en farmaceutisk sammensætning, der omfatter (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf, til anvendelse ifølge krav 1, hvor saltet er (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamidhydrochlorid.

7. (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf eller en farmaceutisk sammensætning, der omfatter (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamid eller et farmaceutisk acceptabelt salt deraf, til anvendelse ifølge krav 1, hvor saltet er (R)-7-chlor-N-(quinuclidin-3-yl)benzo[b]thiophen-2-carboxamidhydrochloridmonohydrat.

DRAWINGS

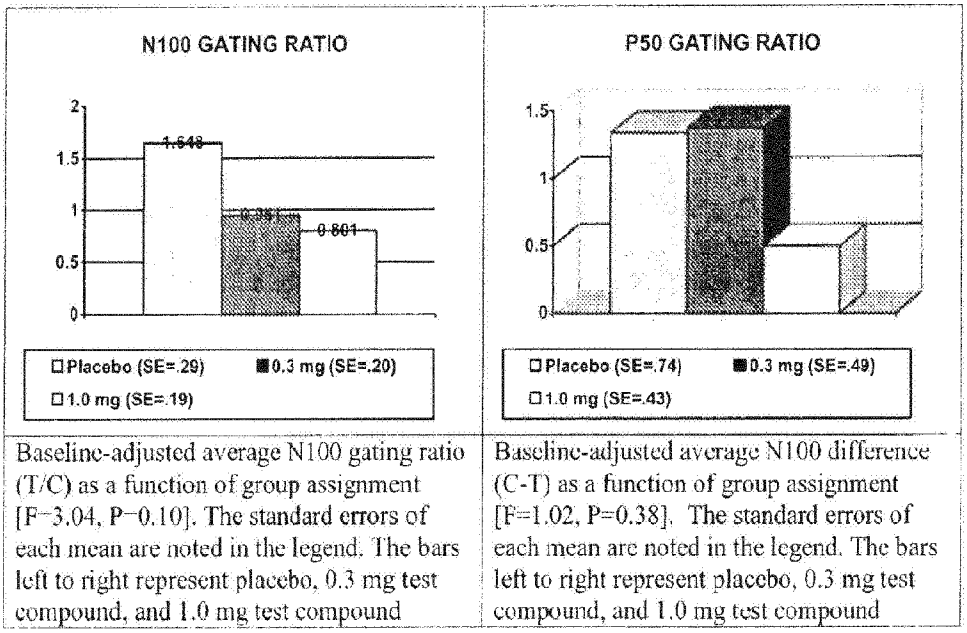


Baseline-adjusted average P50 gating ratio (T/C) as a function of group assignment [F=1.16, P=0.36]. The standard errors of each mean are noted in the legend. The bars left to right represent placebo, 0.3 mg test compound, and 1.0 mg test compound



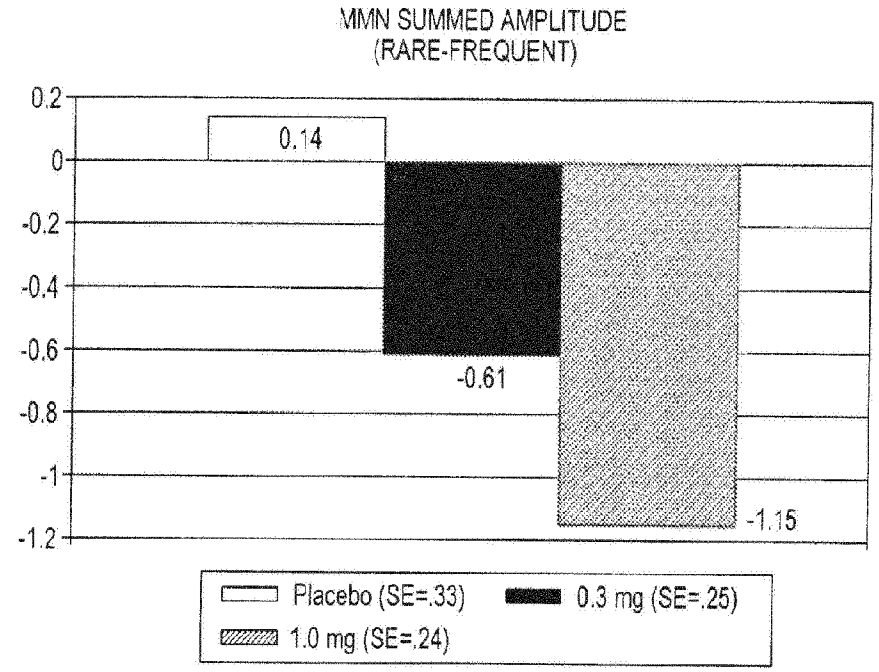
Baseline-adjusted average P50 difference (C-T) as a function of group assignment [F=3.97, P=0.07]. The standard errors of each mean are noted in the legend. The bars left to right represent placebo, 0.3 mg test compound, and 1.0 mg test compound

FIG. 1



Baseline-adjusted average N100 gating ratio (T/C) as a function of group assignment [F=3.04, P=0.10]. The standard errors of each mean are noted in the legend. The bars left to right represent placebo, 0.3 mg test compound, and 1.0 mg test compound	Baseline-adjusted average N100 difference (C-T) as a function of group assignment [F=1.02, P=0.38]. The standard errors of each mean are noted in the legend. The bars left to right represent placebo, 0.3 mg test compound, and 1.0 mg test compound

FIG. 2


MMN SUMMED AMPLITUDE
(RARE-FREQUENT)
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
0.14
-0.61
-1.15
Placebo (SE=.33)
0.3 mg (SE=.25)
1.0 mg (SE=.24)

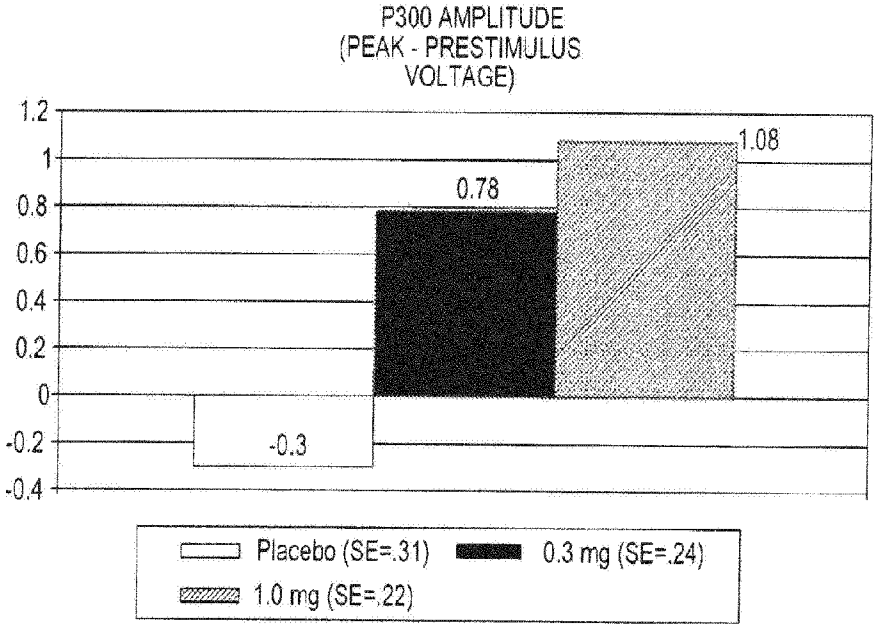

P300 AMPLITUDE
(PEAK - PRESTIMULUS
VOLTAGE)
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
1.08
0.78
-0.3
Placebo (SE=.31)
0.3 mg (SE=.24)
1.0 mg (SE=.22)

FIG. 3