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(54) Title: NEURODEVELOPMENTAL DISORDER THERAPY

(57) Abstract: This invention addresses tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73, AV2-73, or A2-73), ANAVEX1-41 and/or Anavex19-144 in a method of treatment for neurodevelopmental disorders. Particular reference is made to the treatment of autism spectrum disorder, cerebral palsy, Rett syndrome, Angelman syndrome, Williams syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS), childhood disintegrative disorder, and Smith-Magenis syndrome. Additional reference is made to multiple sclerosis.

Neurodevelopmental Disorder Therapy

Field of the Invention

This invention addresses tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX™2-73, AV2-73, or A2-73) in a method of treatment for neurodevelopmental disorders. Particular reference is made to the treatment of autism spectrum disorder, cerebral palsy, Rett syndrome, Angelman syndrome, Williams syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS), childhood disintegrative disorder, and Smith-Magenis syndrome. Additional reference is made to multiple sclerosis therapy.

Background of the Invention

Neurodevelopmental disorders are generally categorized as disorders associated with changes in early brain development. These typically exhibit themselves as behavioral and cognitive alterations in sensory and motor systems, speech, and language. Particular reference is made to autism spectrum disorder, cerebral palsy, Rett syndrome, Angelman syndrome, Williams syndrome, and Smith-Magenis syndrome.

Rett syndrome (RTT), originally termed cerebroatrophic hyperammonemia, is a rare genetic postnatal neurological disorder of the grey matter of the brain that almost exclusively affects females but has also been found in male patients. The clinical features include small hands and feet and a deceleration of the rate of head growth (including microcephaly in some). Repetitive stereotyped hand movements, such as wringing and/or repeatedly putting hands into the mouth, are also noted. People with Rett syndrome are prone to gastrointestinal disorders and up to 80% have seizures. They typically have no verbal skills, and about 50% of affected individuals do not walk. Scoliosis, growth failure, and constipation are very common and can be problematic.

The signs of this disorder are most easily confused with those of Angelman syndrome, cerebral palsy, and autism. Rett syndrome occurs in approximately 1:10,000 live female births in all geographies, and across all races and ethnicities.

Without being bound by any particular theory it is believed that Rett syndrome is caused by mutations in the gene MECP2 located on the X chromosome (which is involved in transcriptional silencing and epigenetic regulation of methylated DNA), and can arise sporadically or from germline mutations. Reportedly, in less than 10% of RTT cases, mutations in the genes CDKL5 or FOXG1 have also been found to resemble it. Rett syndrome is initially diagnosed by clinical observation, but the diagnosis is definitive when there is a genetic defect in the MECP2 gene.

Tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73, AV2-73, or A2-73) is a compound which is believed to bind to muscarinic acetylcholine and sigma-1 receptors with affinities in the low micromolar range. It has been reported that A2-73 showed neuroprotective potential against amyloid toxicity in mice. In particular, A2-73 has been reported as attenuating oxidative stress, caspases induction, cellular loss and learning and memory deficits observed in mice one week after the i.v. injection of an oligomeric preparation of amyloid β25-35 peptide (Aβ25-35) (Villard *et al.*, J. Psychopharmacol. 2011). More recently, it has been reported that A2-73 blocked the Aβ25-35-induced P-Akt decrease and P-GSK-3β increase, indicating activation of the PI3K neuroprotective pathway (Lahmy *et al.*, Neuropsychopharmacology, 2013). In the dose-range tested, A2-73 attenuated the hyperphosphorylation of Tau on physiological epitopes (AT-8 antibody clone) and on pathological epitopes (AT-100 clone). A2-73 also has been reported decreasing the Aβ25-35-induced endogenous Aβ1-42 seeding.

It has been reported that neurodevelopmental disorders respond to N-methyl-D-aspartate receptor (NMDAR) antagonists and combination therapy. Reference is made to NMDAR antagonists selected from the group consisting of Amantadine, AZD6765, Dextrallorphan, Dextromethorphan, Dextrorphan, Diphenidine, Dizocilpine (MK-801), Ethanol, Eticyclidine, Gacyclidine, Ibogaine, Memantine, Methoxetamine, Nitrous oxide, Phencyclidine, Rolicyclidine, Tenocyclidine, Methoxydine, Tiletamine, Xenon, Neramexane, Eliprodil, Etoxadrol, Dexoxadrol, WMS-2539, NEFA, Delucemine, 8A-PDHQ, Aptiganel, HU-211, Remacemide, Rhynchophylline, Ketamine, 1-Aminocyclopropanecarboxylic acid (ACPC), 7-Chlorokynurenate' DCKA (5,7-

dichlorokynurenic acid), Kynurenic acid, Lacosamide, L-phenylalanine, Neurotransmitters, Psychedelics, Long-term potentiation, and NMDA.

Reference is made to the following publications. These publications, and all publications cited herein, are incorporated by reference in their entirety:

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5. Ricceri et al (2008). "Mouse models of Rett syndrome: From behavioural phenotyping to preclinical evaluation of new therapeutic approaches". Behavioural Pharmacology 19 (5–6): 501–17. doi:10.1097/FBP.0b013e32830c3645. PMID 18690105.
6. Lombardi, et al, "MECP2 disorders: from the clinic to mice and back," J Clin Invest. 2015 Aug 3;125(8):2914-23. doi: 10.1172/JCI78167. Epub 2015 Aug 3. Review.
7. Pohodich et al, "Rett syndrome: disruption of epigenetic control of postnatal neurological functions." Hum Mol Genet. 2015 Oct 15;24(R1): Epub 2015 Jun 9.
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13. Tan *et al.*, “Pharmacological therapies for Angelman syndrome,” Wien Med Wochenschr. 2016 Jan 12. [Epub ahead of print]
14. US Pub. No 2015/0152410 to Kreig *et al.*, . entitled “Compositions And Methods For Modulating Mecp2 Expression.”
15. US Pub. No 2015/0265554 to Roux *et al*, “Treatment of MeCP-2 Associated Disorders.”
16. US Pat. No 7,994,127 to Sur *et al.*, Treatment of Rett Syndrome And Other Disorders.

Summary of the Invention

The claimed invention concerns a method of treating a neurodevelopmental disorders such as Rett syndrome in a subject by administering to said subject a therapeutically effective amount of A2-73. In particular embodiments this includes a dosage form comprising a therapeutic amount of A2-73. Note is made of the dosages of A2-73 from about 0.5 to about 500 mg. This invention further includes a therapeutic method of treating neurodevelopmental disorders such as autism spectrum disorder, cerebral palsy, Rett syndrome, Angelman syndrome, Williams syndrome, and Smith-Magenis syndrome. Additional mention is made of multiple sclerosis therapy using A2-73.

Therapeutic doses of A2-73 are particularly noted in a range of from about 0.5 mg/day to about 100mg/day with particular reference to doses of from about 1 to about 60 mg/day and, optionally, wherein said dosage is administered daily for at least about 10 days. Adult doses of about 20mg to about 50mg/day are noted, with particular reference to about 30mg to about 40mg/day. Infant and child doses are to the lower end of the range with particular reference to from about 0.5mg/day to about 20mg/day.

Chronic administration for chronic conditions is further contemplated. Further contemplate is the therapeutic use of A2-73 analogues tetrahydro-N,N-dimethyl-5,5-diphenyl-3-furanmethanamine hydrochloride (ANAVEX™1-41), and 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*-methylmethanamine hydrochloride (ANAVEX™19-144, or A19-144). These A2-73 analogues are contemplated for use at dosages and dosage ranges similar to A2-73.

Brief Description of the Drawings

Fig. 1 is a graphic presentation of body weight of vehicle-treated and wild-type and mutant control mice.

Figs. 2A and 2B are graphic representations of rotarod stability tests of vehicle-treated 8 week old mutant mice compared to vehicle-treated WT mice.

Figs. 3A and 3B are graphic representations of rotarod stability tests of vehicle-treated 12 week old mutant mice compared to vehicle-treated WT mice.

Figs. 4A and 4B are pictures of mice showing unclasped and clasped hind leg responses.

Fig. 5 is a graphic presentation of clasping responses in mutant and wildtype mice treated with A2-73.

Figs 6A and 6B are graphic results of pre pulse inhibition (PPI) in startle response tests in mutant and wildtype 8 week old mice treated with A2-73.

Figs 7A and &B are graphic results of pre pulse inhibition (PPI) in startle response tests in mutant and wildtype 12 week old mice treated with A2-73.

Figs 8A-C show Neurocube data (8 week old mice).

Fig. 9A-D graphically display gait differences which appeared to be rescued while others enhanced the mutant gait phenotype.

Detailed Description of the Invention

As used herein, “therapeutically effective amount" of an agent or combination of agents is an amount sufficient to achieve a desired therapeutic or pharmacological effect. Particular reference is made to an amount that is capable of ameliorating biochemical and functional abnormalities associated with loss-of-function mutations of the gene encoding methyl-CpG binding protein 2 (MeCP2). It is to be understood that a therapeutically effective amount of an agent or combinatory therapy may vary according to factors such as the disease state, age, and weight of the subject, and the ability of the agent to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. A therapeutically effective amount is also one in which any toxic or detrimental effects of the active compound are outweighed by the therapeutically beneficial effects.

Studies employed wild type (WT) mice and heterozygous MECP2knockout mice (HET) All mice were provided by Jackson Laboratory, Bar Harbor, Maine. HET mice were Bird mice (Jackson Laboratories, Bar Harbor, ME, B6.129P2(C)-Mecp2$^{tm1.1Bird}$/ Stock Number: 003890) were obtained by crossing het females with wild type (WT) males (C57B/6J). 129P2(C)-Mecp2$^{tm1.1Bird}$/J is a constitutive Mecp2 knockout that exhibits Rett syndrome-like neurological defects.

Breeding of the test mice done at Jackson Laboratories (Farmington Connecticut). Mice were shipped at 4-5 weeks of age.

Mecp2 females testing at ~8 and ~12 weeks of age
20 WT – vehicle (0.25% MC/dH2O)
20 HET – vehicle (0.25% MC/dH2O)
20 HET – A2-733 (10 mg/kg)
20 HET – A2-733 (30 mg/kg)

Chronic dosing (p.o.) daily, starting at ~5.5 weeks of age and continuing through the 12-week behavioral testing time point 60 min pre-treatment during behavioral testing.

Body Weight

No differences were observed in body weight between vehicle-treated wild-type and mutant control mice. Fig. 1 There was a significant Treatment x Age effect ($p < 0.001$), where mice treated with A2-733 (30 mg/kg) weighed less than vehicle-treated mutant mice 6.5 weeks after dosing began.

Rotarod

The rotarod performance test is a performance test based on a rotating rod with forced motor activity being applied, usually by a rodent. The test measures parameters such as riding time (seconds) or endurance. Some of the functions of the test include evaluating balance, grip strength, and motor coordination of the subjects; especially in testing the effect of experimental drugs or after traumatic brain injury.

Mice are placed on the rotarod apparatus (PsychoGenics, Tarrytown New York) consisting of a rod that rotates at a constant or variable and accelerating speed of 4 rpm. Once a mouse loses its balance and falls onto an underlying platform the timer automatically stops. Mice are exposed to the apparatus for 5 min training at a constant speed and placed back on the rod after each fall. After a rest period of at least 1 hr. animals are placed back on the rotarod apparatus for testing. Once all animals in a test session are loaded on the rod, the rotarod apparatus is placed on accelerating speed (0-40 rpm) over 5 min and the time until the first fall is recorded. The test is repeated three consecutive times per animal. For each test session, the RPM score at time of fall off the rod are recorded.

Rotarod at 8 Weeks [Fig. 2A and Fig. 2B]

Vehicle-treated mutant mice fell more rapidly and at lower speeds compared to vehicle-treated WT mice. No significant treatment effects were observed for either measure.

Rotarod at 12 weeks [Fig. 3A and Fig. 3B]

Vehicle-treated mutant mice fell more rapidly and at lower speeds compared to vehicle-treated WT mice. A2-733-treated mice at both doses took more time to fall off the rod and fell at higher speeds compared to vehicle-treated mutant mice. Without outliers, the effect at the higher dose disappeared for the speed at fall measure. Mutant mice were slower and fell more quickly at both 8 and 12 weeks of age compared to wildtype controls.

Clasping [Fig. 4A and Fig. 4B]

Mice are lifted gently by the tail with front limbs remaining on surface. Clasping of hind legs is noted (normal is a spread in the hind legs).

Clasping at 8 Weeks [Fig. 5]

Vehicle-treated mutant mice clasped more than vehicle-treated wild type mice. Mice treated with A2-733 (30 mg/kg) clasped less than vehicle-treated mutant mice.

Startle/PPI

The acoustic startle measures an unconditioned reflex response to external auditory stimulation. Mice are placed in the prepulse inhibition (PPI) chambers for a 5 min session of white noise (70 dB) habituation. Then the session starts with a habituation block of 6 presentations of the startle stimulus alone, followed by 10 PPI blocks of 6 different types of trials [null (no stimuli), startle (120 dB), startle plus prepulse (4, 8 and 12 dB over background noise i.e. 74, 78 or 82 dB) and prepulse alone (82 dB)] presented at random within each block. The amount of inhibition of the normal startle is determined and expressed as a percentage of the basic startle response (from startle alone trials), excluding the startle response of the first habituation block.

Startle/PPI 8 weeks [Fig. 6A and Fig. 6B]

Vehicle-treated mutant mice startled less and but showed no differences in PPI response compared to vehicle-treated WT mice. A2-733 (30 mg/kg) treated mice showed an increased startle response compared to vehicle-treated mutant mice. No treatment differences were observed in PPI.

Startle/PPI 12 Weeks [Fig. 7 A and Fig. 7B]

Vehicle-treated mutant mice startled less but showed no differences in PPI response compared to vehicle-treated WT mice. There was a trend of a treatment effect in the startle response ($p < 0.08$). With outliers removed, this trend became significant, with A2-733 (30 mg/kg) mice showing increased startle compared to vehicle-treated mutant mice ($p < 0.01$). The PPI treatment interaction ($p < 0.05$) did not reveal any significant *post hoc* differences.

Neurological testing via a platform that employs computer vision to detect changes in gait geometry and gait dynamics in rodent models of neurological disorders, pain, and neuropathies. Complex bio-informatics algorithms similar to those used in SmartCube® are employed to detect a disease phenotype and screen compounds. (NeuroCube, PsychoGenics, Tarrytown NY)

A platform that employs computer vision to detect changes in gait geometry and gait dynamics in rodent models of neurological disorders, pain, and neuropathies. Mice are allowed to walk in the chamber for 5 min. When the paw touches the screen, LED light reflects creating bright spots. Images are captured and processed using proprietary computer vision and bio-informatics data mining algorithms.

Figs. 8A-C graphically display Neurocube 8 week data. Significant separation between WT and HET vehicle mice ($p = 0$). There was no separation between A2-733 versus Het vehicle. There was 9-17% recovery of the overall signature due to mild beneficial effects of the drug on gait and imaging features.

Figs. 9A-D graphically display gait differences which appeared to be rescued while others enhanced the mutant gait phenotype.

NeuroCube 8 week gait analysis is presented in Table 1 (below):

	WT vehicle v. Het vehicle	Het vehicle v. Het AV2-73, 10 mg/kg	Het vehicle v. Het AV2-73, 30 mg/kg
Overall			
	90, $p = 0$	53, $p > 0.69$	62, $p > 0.24$
GAIT			
	78, $p < 0.01$	63, $p > 0.09$	69, $p < 0.05$
Paw Features			
	91, $p < 0.001$	52, $p > 0.78$	55, $p > 0.56$
Correlation			
	53, $p > 0.66$	56, $p > 0.40$	76, $p < 0.005$
Body Motion			
	71, $p < 0.02$	60, $p > 0.20$	81, $p < 0.003$
Paw Positioning			
	84, $p < 0.0001$	53, $p > 0.57$	57, $p > 0.36$

NeuroCube 12 week gait analysis is presented in Table 2 (below):

	WT vehicle v. Het vehicle	Het vehicle v. Het AV2-73, 10 mg/kg	Het vehicle v. Het AV2-73, 30 mg/kg
Overall			
	95, $p = 0$	53, $p > 0.70$	61, $p > 0.21$
GAIT			
	77, $p < 0.0001$	57, $p > 0.29$	57, $p > 0.37$
Paw Features			
	86, $p = 0$	56, $p > 0.35$	53, $p > 0.65$
Correlation			
	76, $p < 0.005$	53, $p > 0.70$	69, $p < 0.03$
Body Motion			
	83, $p = 0$	52, $p > 0.71$	68, $p < 0.04$
Paw Positioning			
	80, $p < 0.001$	53, $p > 0.57$	53, $p > 0.62$

It is believed that therapeutic doses of A-2-73 increases lifespan and improves locomotor, respiratory, and cardiac function in children with Rett Syndrome.

Example 1
Breathing variability reduction

A 6 year old female presenting with Rett syndrome is administered oral doses of A2-73 at 4mg daily for 10 days. On presentation, her breathing is abnormal. Her mean breaths per minute is calculated to assess breathing variability. After 10 days of A2-73, administration the Δ (breaths/minute) was significantly reduced (implying less variability).

Example 2
Cardiac pulse rate

A 10 year old female presents with Rett syndrome. Her real time cardiac pulse rate is monitored. Prior to commencing therapy, her heart rate is 49 beats per minute with substantial variability. Following treatment with oral doses of A2-73 at 20mg daily for 5 days, the variability is reduced while the average rate is increased to 75 beats per minutes.

Example 3
Seizure reduction

An 18 month old female presents with Rett syndrome. She experiences 6 to 10 seizures per day prior to commencing therapy. She begins treatment with oral doses of A2-73 at 2 mg daily. After 5 days of treatment, the number of daily seizures is reduced to 3 or fewer.

Example 4
Eating and choking

A 20 year-old female presents with Rett syndrome. She experiences feeding difficulties exhibiting as choking and poor food intake prior to commencing therapy. She begins treatment with oral doses of A2-73 at 40 mg every other day. After 60 days of treatment, the instances of choking are reduced and she exhibits a 10% weight gain.

Example 5
Angelman – sleep and seizures

A 25 year-old male presents with Angelman syndrome. He experiences disturbed sleep and frequent seizures prior to commencing therapy. He begins treatment with oral doses of A2-73 at 30 mg/day. After 15 days of treatment, his sleep is markedly less disturbed and his instances of seizure are reduced by 50%.

Example 6
Williams Syndrome – weight gain

A 2 year-old male presents with Williams syndrome. He exhibits a failure to thrive with low weight gain. He begins treatment with *i.v.* doses of A2-73 at 5 mg every other day. After 60 days of treatment, he exhibits a 10% weight gain.

Example 7
Smith–Magenis syndrome – sleep

A 5 year-old male presents with Smith–Magenis syndrome. He experiences disturbed sleep. He begins treatment with oral doses of A2-73 at 10 mg/day. After 15 days of treatment, his sleep is markedly less disturbed.

Example 8
Multiple Sclerosis

A 17 year-old male presents with multiple sclerosis. He begins treatment with oral doses of A2-73 at 40 mg every fifth day. The total number of gadolinium-enhanced lesions on MRI at weeks 12, 16, 20 and 24 is substantially reduced as compared to his 12 week pretreatment MRI.

Example 9
Multiple Sclerosis

A 27 year-old female presents with relapsing-remitting multiple sclerosis. She begins treatment with oral doses of A2-73 at 30 mg every other day for 3 months. She exhibits a significantly lower number of total gadolinium-enhancing lesions on monthly brain MRI up to month 6.

The pharmaceutical compositions provided herein can be administered chronically ("chronic administration"). Chronic administration refers to administration of a compound or pharmaceutical composition thereof over an extended period of time, e.g., for example, over 3 months, 6 months, 1 year, 2 years, 3 years, 5 years, etc., or may be continued indefinitely, for example, for the rest of the subject's life. In certain embodiments, the chronic administration is intended to provide a constant level of the compound in the blood, e.g., within the therapeutic window over the extended period of time.

The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such

as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as a ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or Formulation. All such known transdermal formulations and ingredients are included within the scope provided herein.

The compounds provided herein can also, in some embodiments, be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

The noted components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Remington: The Science and Practice of Pharmacy, 22nd Edition (2012), Pharmaceutical Press, which is incorporated herein by reference.

The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington's Pharmaceutical Sciences.

Claims

1. A method of treating neurodevelopmental autism spectrum disorder in a subject by administering to said subject a therapeutically effective amount of a therapeutic agent selected from the group consisting of A2-73, ANAVEX1-41, Anavex19-144 or combinations thereof.

2. The method of Claim1 wherein the neurodevelopmental autism spectrum disorder is Rett syndrome.

3. The method of Claim1 wherein the therapeutic agent is A2-73.

4. The method of Claim 3 wherein the therapeutically effective amount of A2-73 is a dosage of from about 0.5 mg/day to about 100 mg/day.

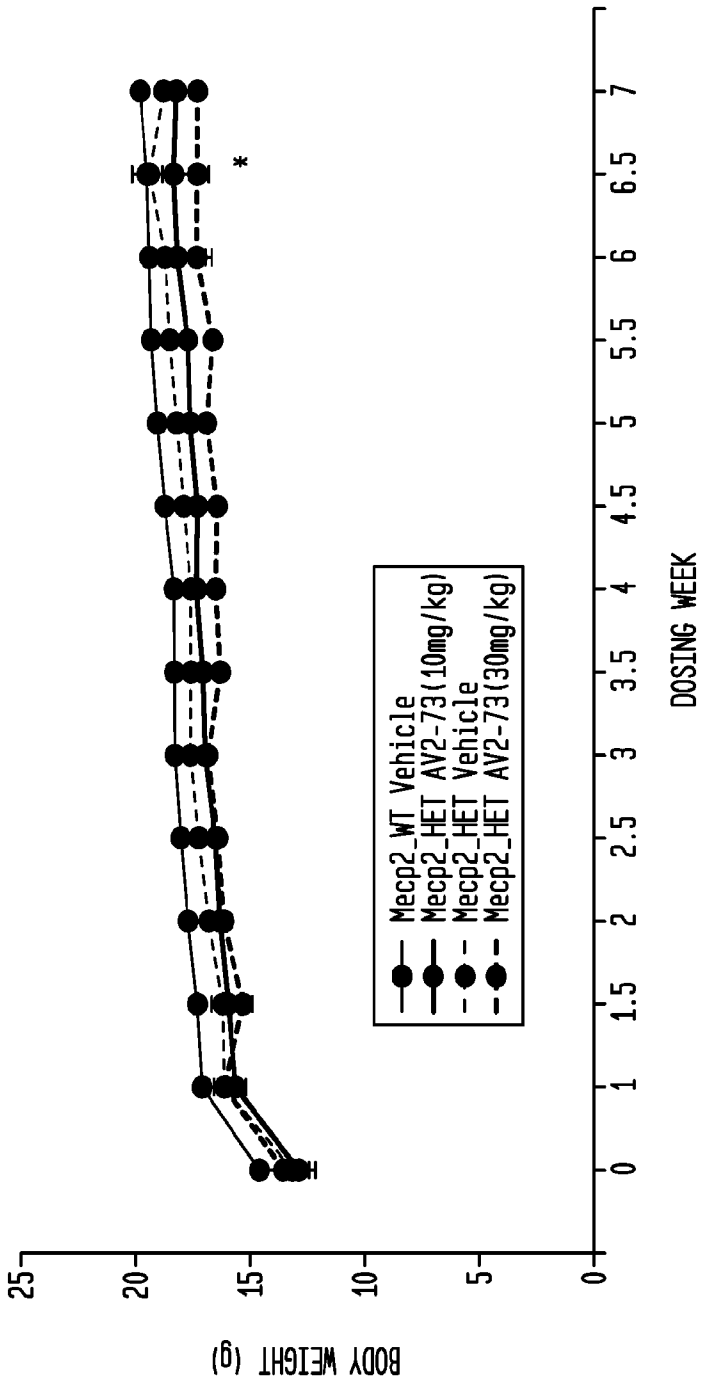
5. The method of Claims 3 through 4 wherein said dosage is from about 1 to about 60 mg/day

6. The method of Claims 3 through 5 wherein said dosage is from about 20 to about 50 mg/day.

7. The method of Claims 1 through 6 wherein said dosage is administered daily for at least about 10 days.

8. The method Claim 1 wherein the neurodevelopmental autism spectrum disorder is selected from the group consisting of cerebral palsy, Angelman syndrome, Williams syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS), childhood disintegrative disorder, Smith-Magenis syndrome or multiple sclerosis..

FIG. 1


BODY WEIGHT (g)
25
20
15
10
5
0
0
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
DOSING WEEK
*
Mecp2_WT Vehicle
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Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)

FIG. 2A

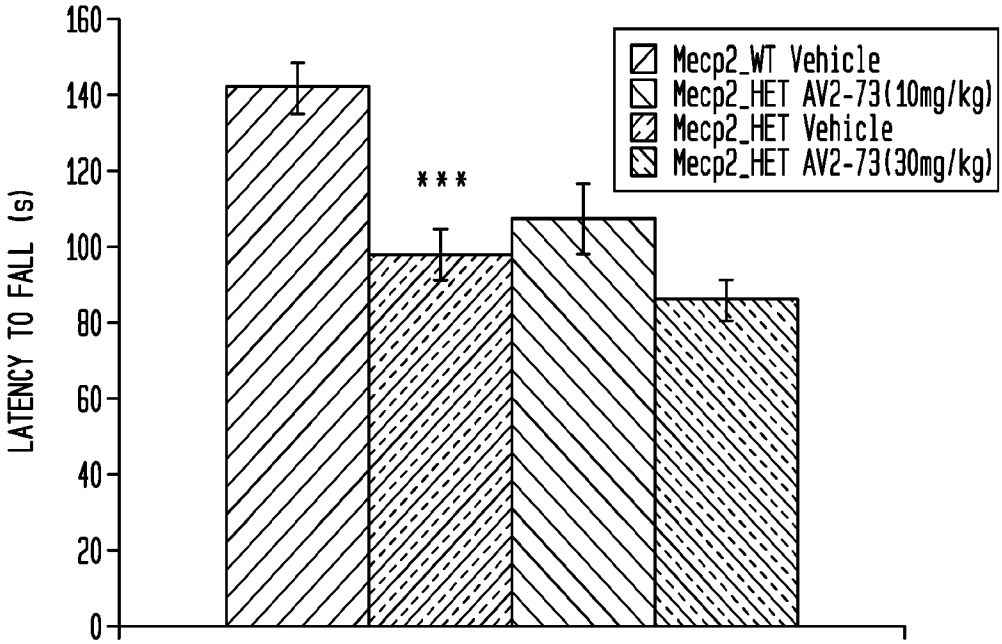

LATENCY TO FALL (s)
160
140
120
100
80
60
40
20
0
***
Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)

FIG. 2B

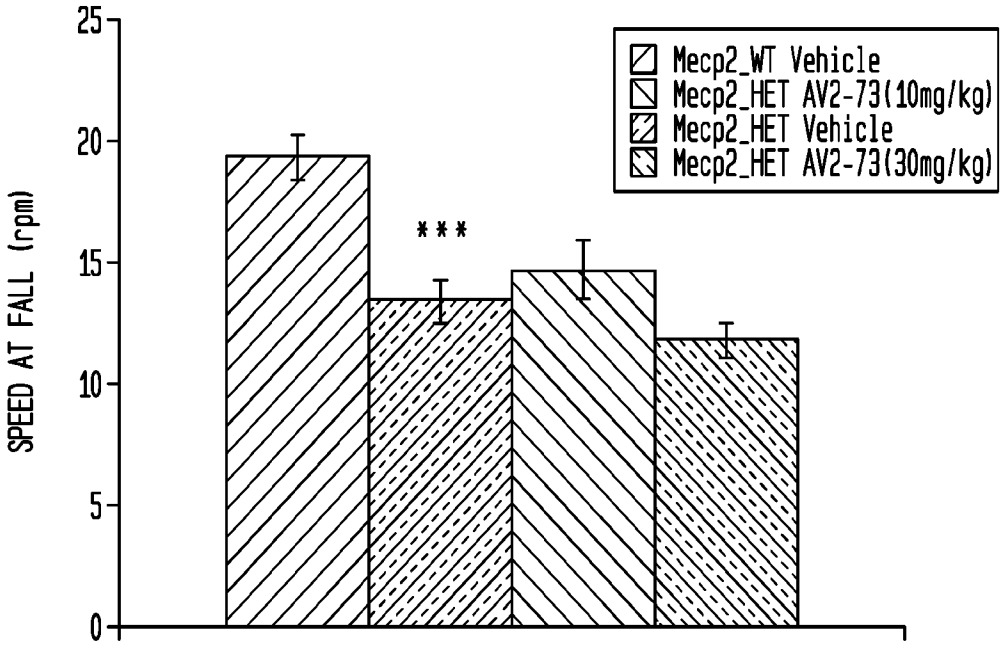

SPEED AT FALL (rpm)
25
20
15
10
5
0
***
Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)

FIG. 3A

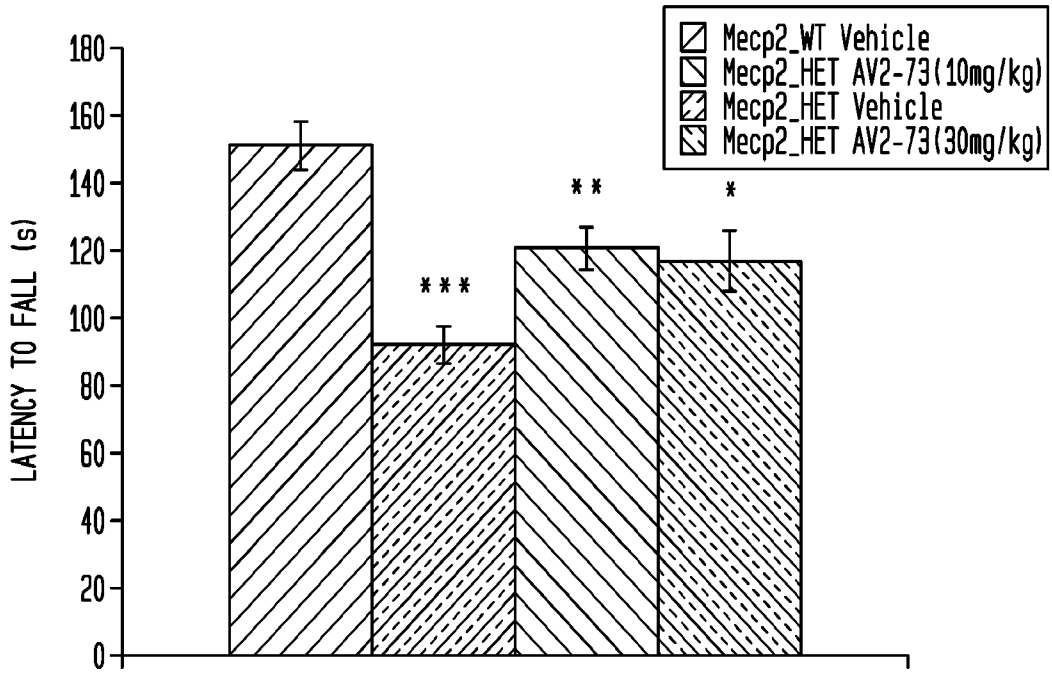

Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)
LATENCY TO FALL (s)
180
160
140
120
100
80
60
40
20
0
***
**
*

FIG. 3B

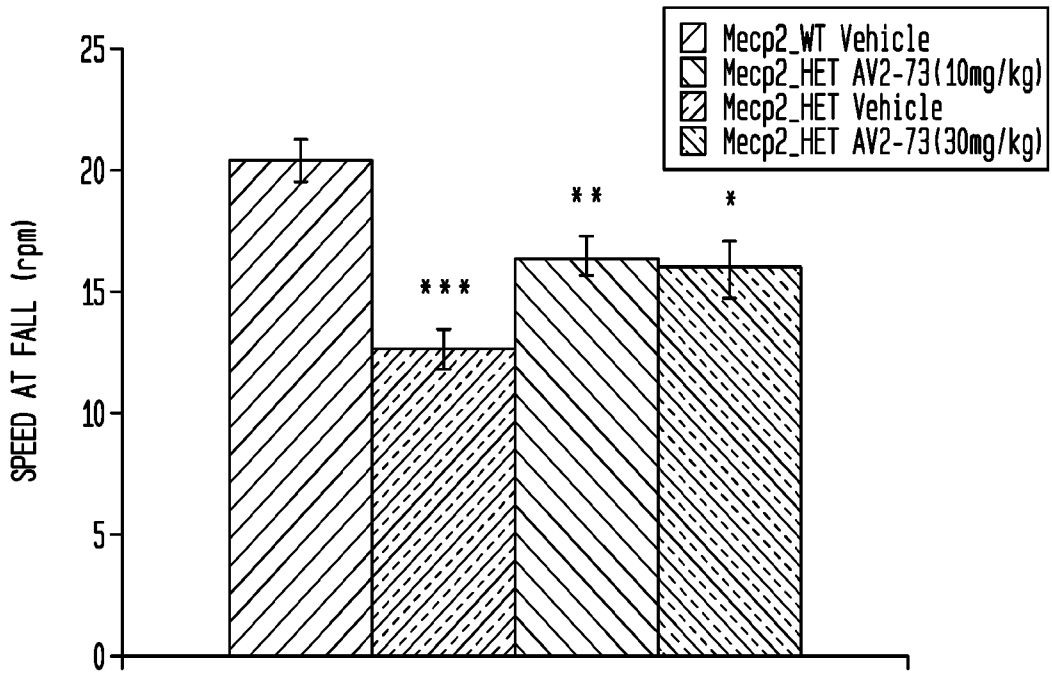

Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)
SPEED AT FALL (rpm)
25
20
15
10
5
0
***
**
*

FIG. 4A

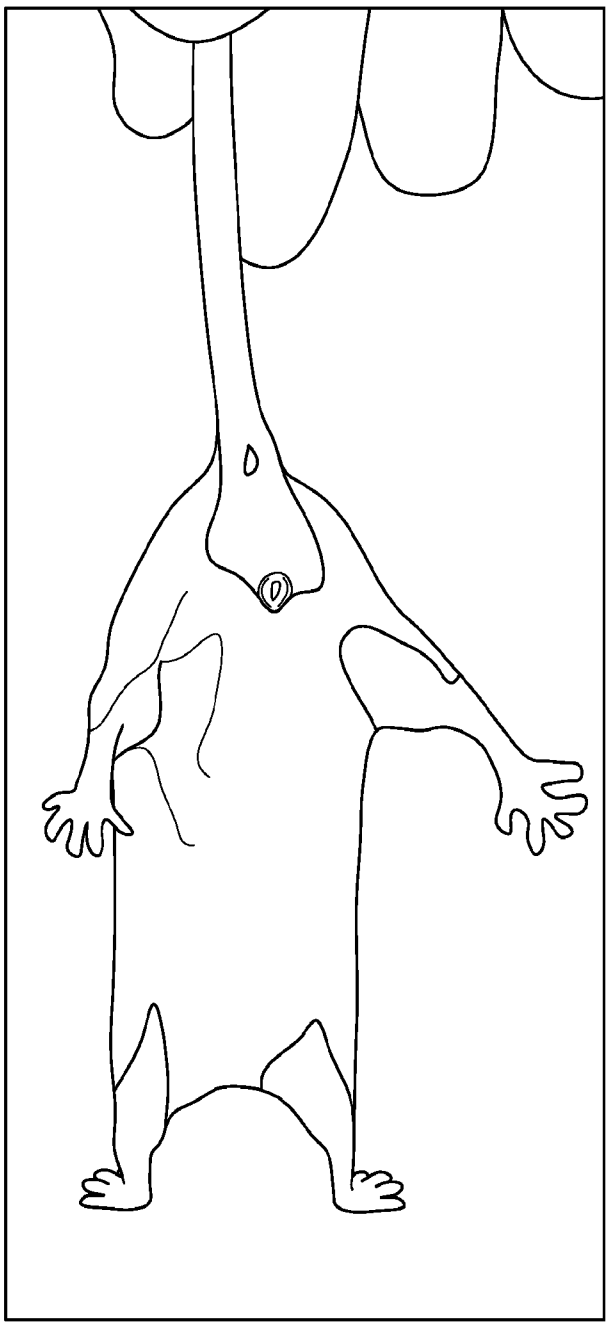


FIG. 4B

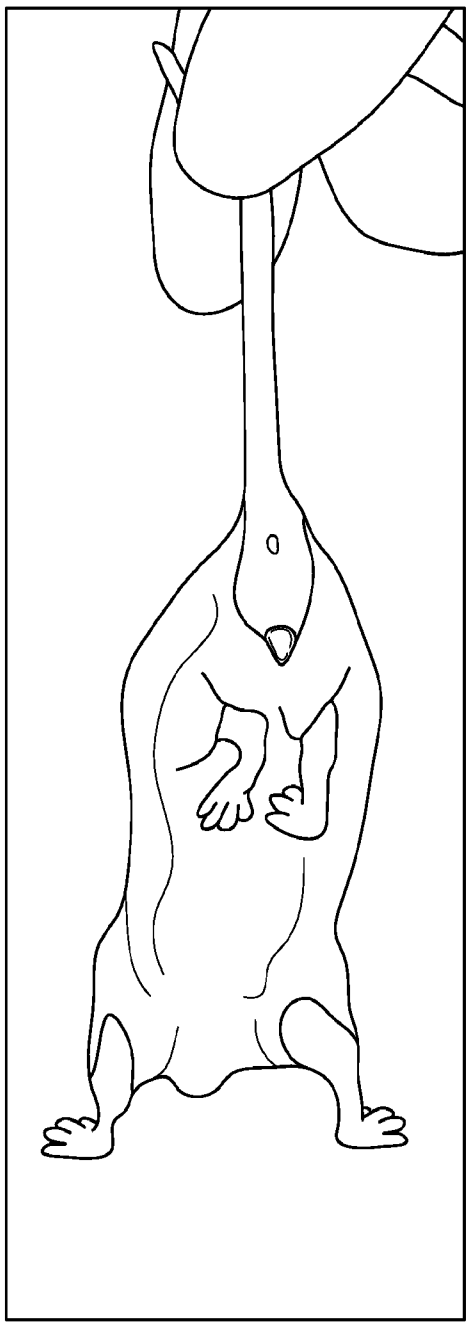


FIG. 5

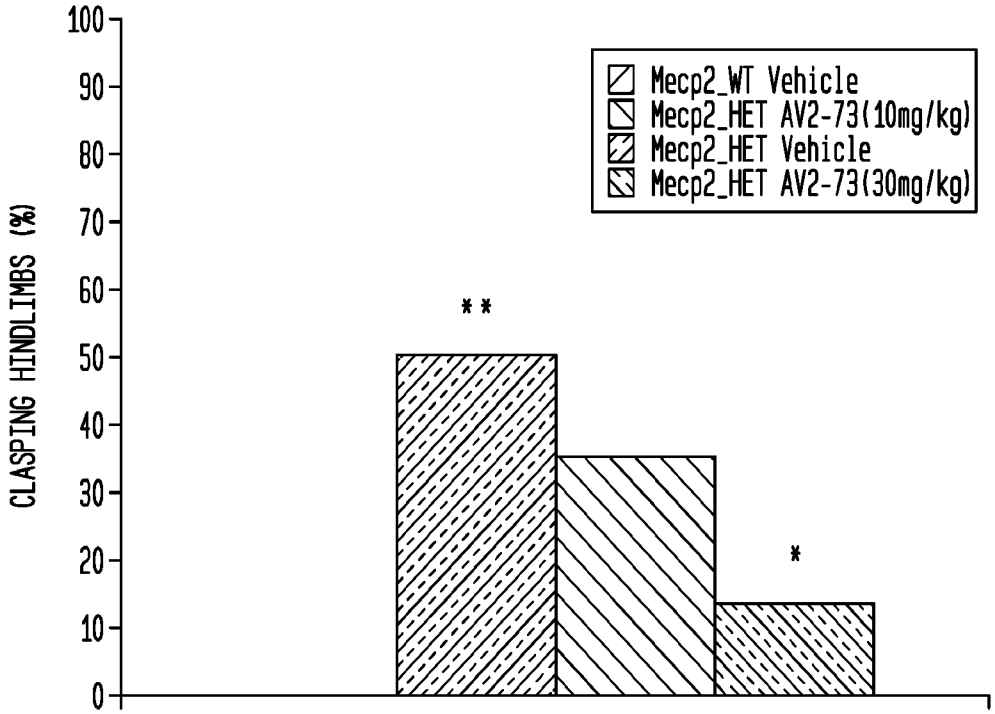

CLASPING HINDLIMBS (%)
100
90
80
70
60
50
40
30
20
10
0
**
*
Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)

FIG. 6A

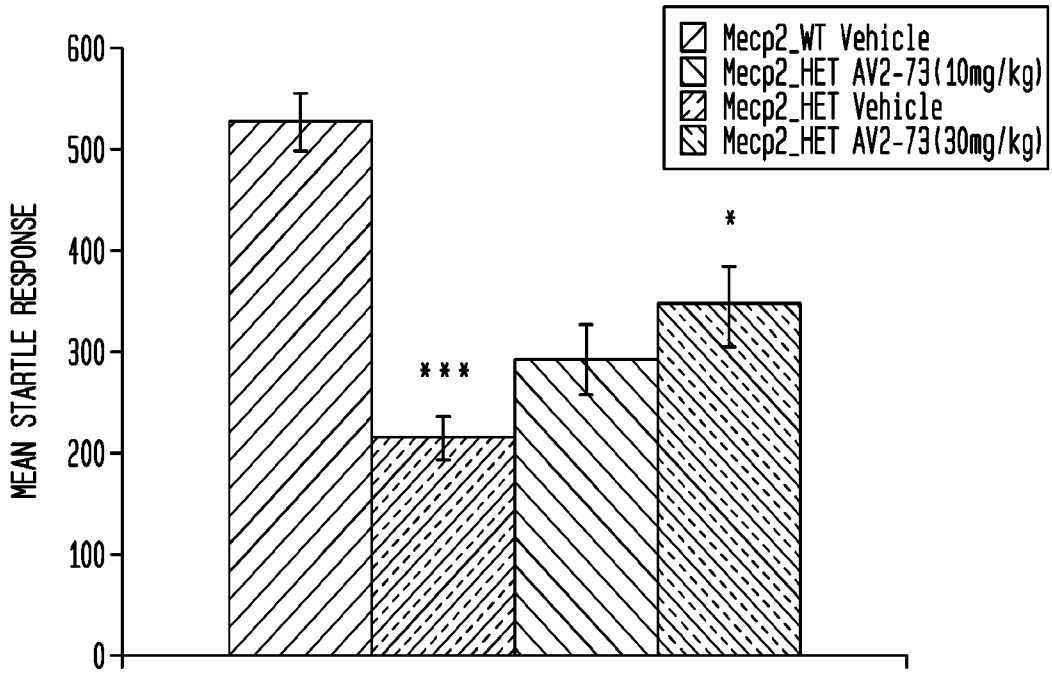

Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)
MEAN STARTLE RESPONSE
600
500
400
300
200
100
0
***
*

FIG. 6B

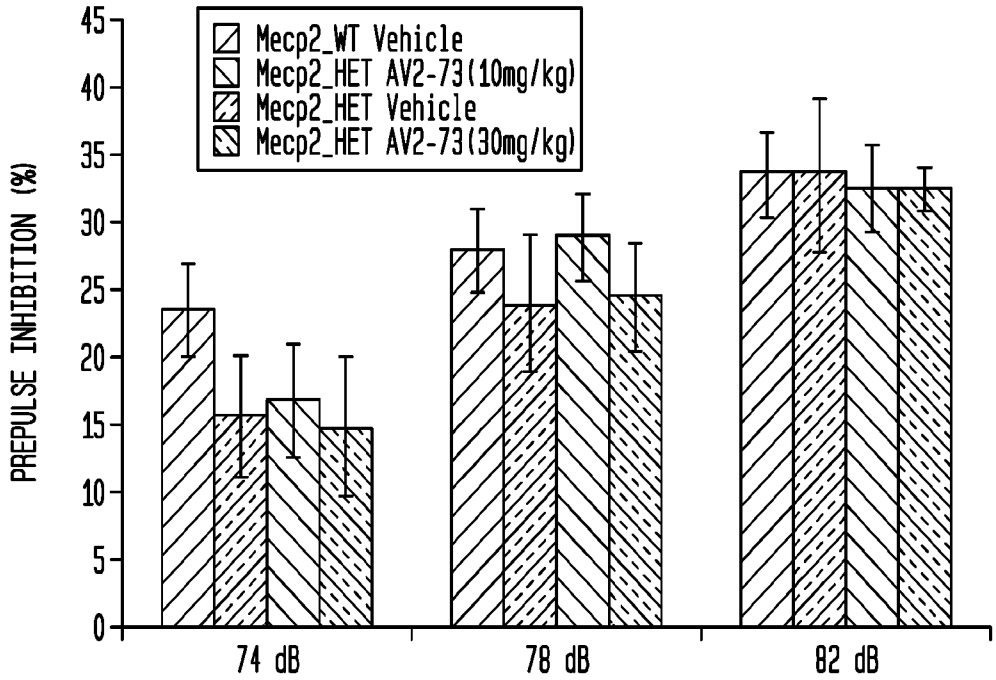

Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)
PREPULSE INHIBITION (%)
45
40
35
30
25
20
15
10
5
0
74 dB
78 dB
82 dB

FIG. 7A

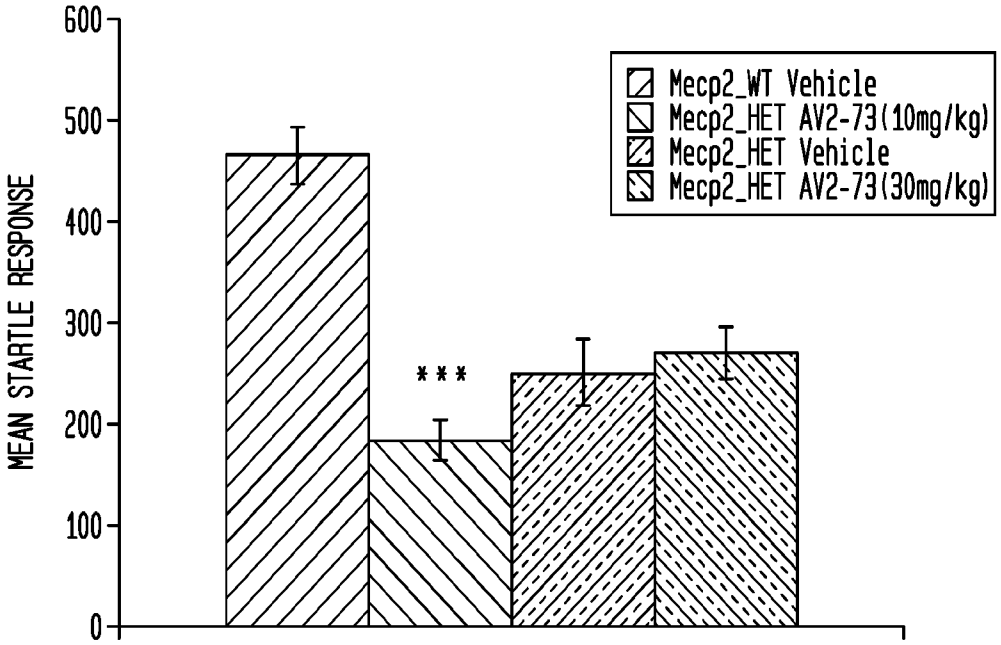

MEAN STARTLE RESPONSE
600
500
400
300
200
100
0
***
Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)

FIG. 7B

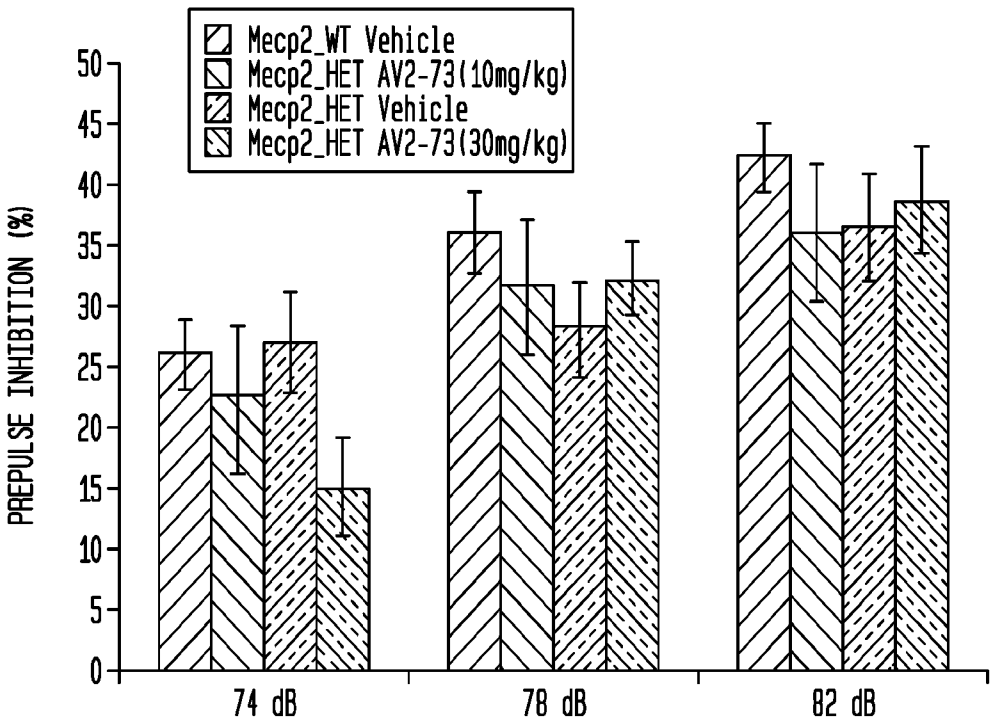

PREPULSE INHIBITION (%)
50
45
40
35
30
25
20
15
10
5
0
74 dB
78 dB
82 dB
Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)

FIG. 8A

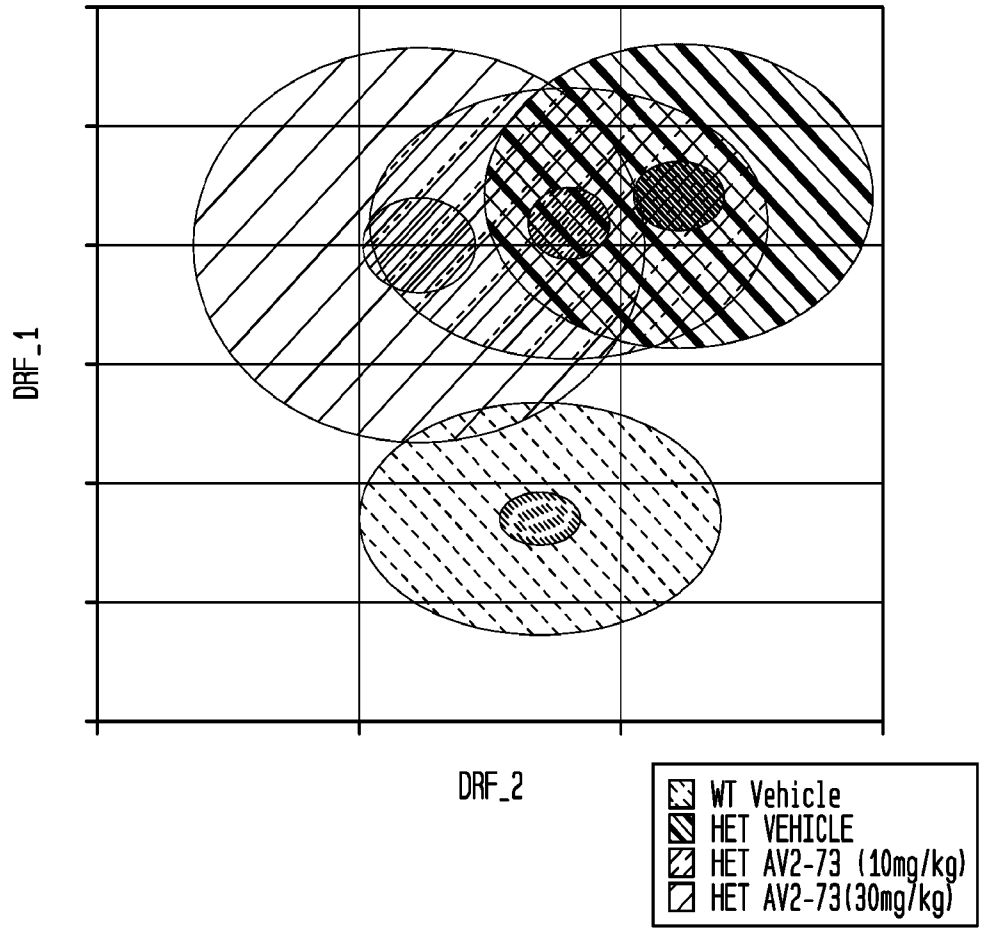

DRF_1
DRF_2
WT Vehicle
HET VEHICLE
HET AV2-73 (10mg/kg)
HET AV2-73(30mg/kg)

FIG. 8B

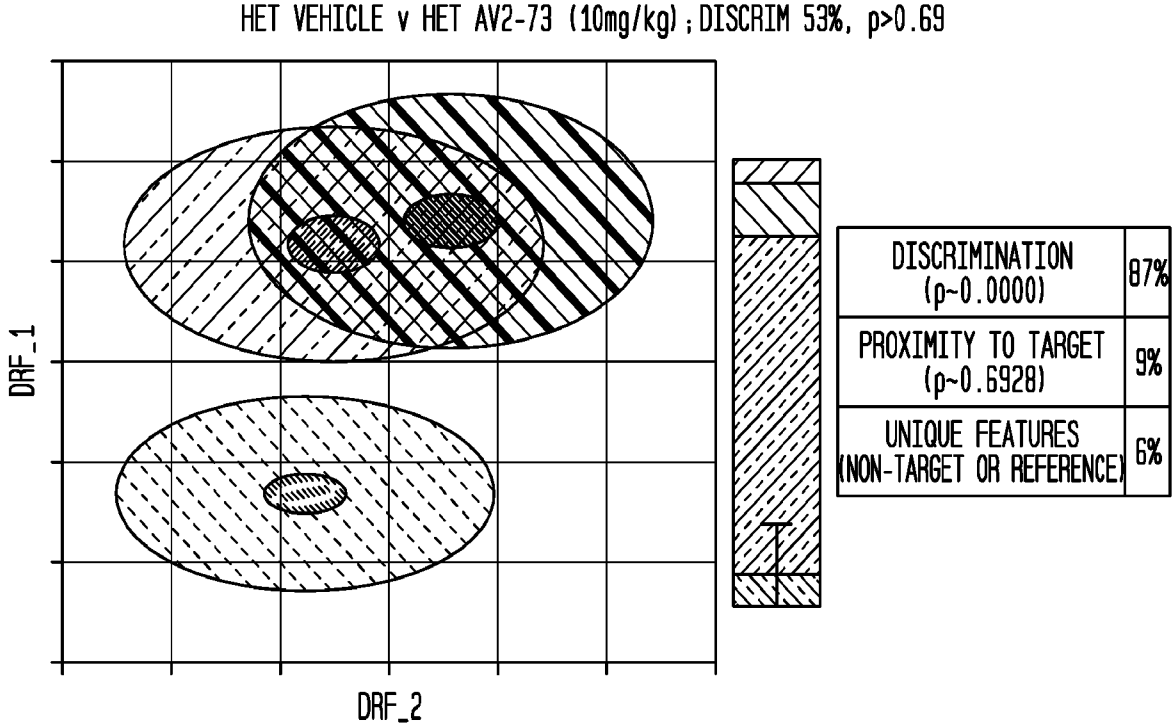

HET VEHICLE v HET AV2-73 (10mg/kg); DISCRIM 53%, p>0.69
DRF_1
DRF_2
DISCRIMINATION (p~0.0000) 87%
PROXIMITY TO TARGET (p~0.6928) 9%
UNIQUE FEATURES (NON-TARGET OR REFERENCE) 6%

FIG. 8C

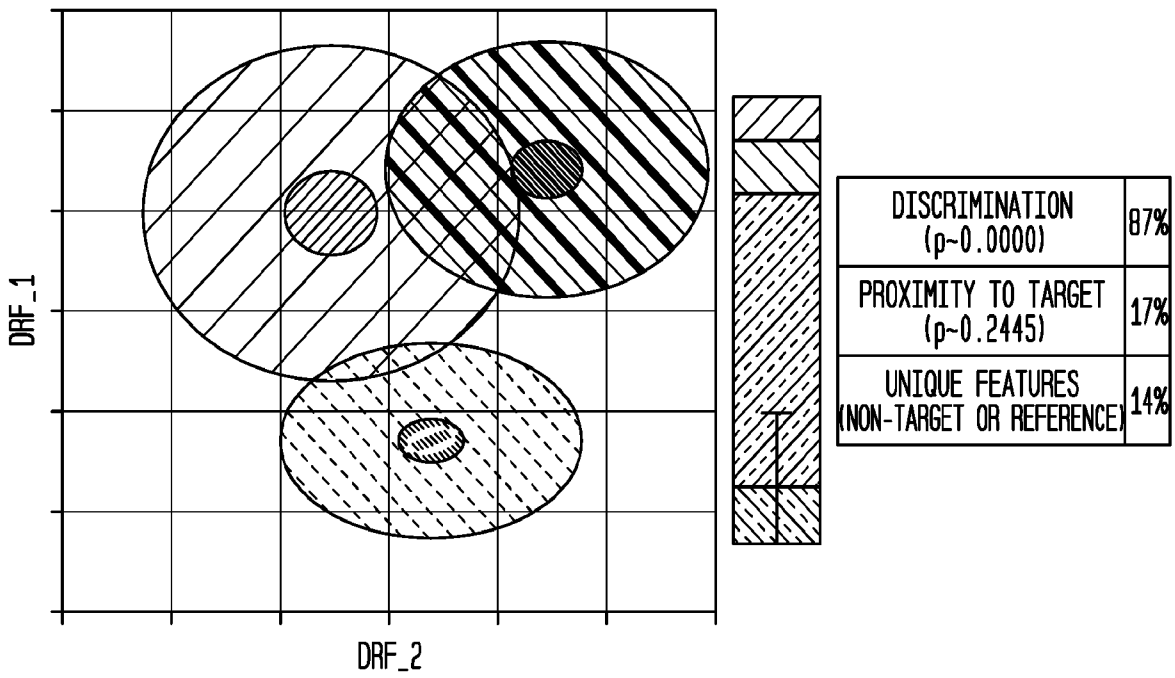

HET VEHICLE v HET AV2-73 (30mg/kg); DISCRIM 62%, p>0.24
DRF_1
DRF_2
DISCRIMINATION (p~0.0000) 87%
PROXIMITY TO TARGET (p~0.2445) 17%
UNIQUE FEATURES (NON-TARGET OR REFERENCE) 14%

FIG. 9A

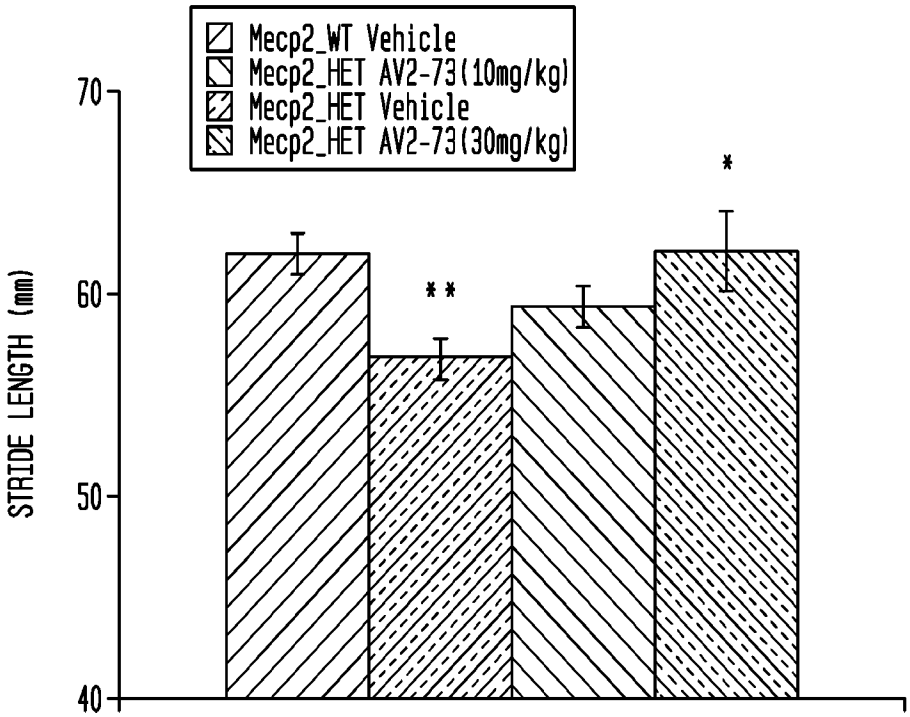

Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)
STRIDE LENGTH (mm)
70
60
50
40
**
*

FIG. 9B

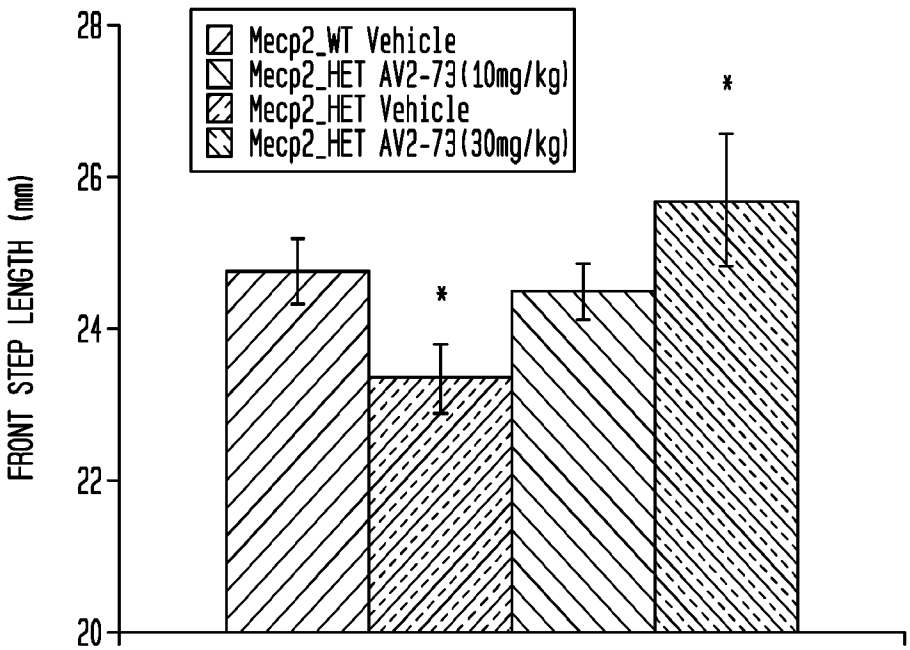

Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)
FRONT STEP LENGTH (mm)
28
26
24
22
20
*
*

FIG. 9C

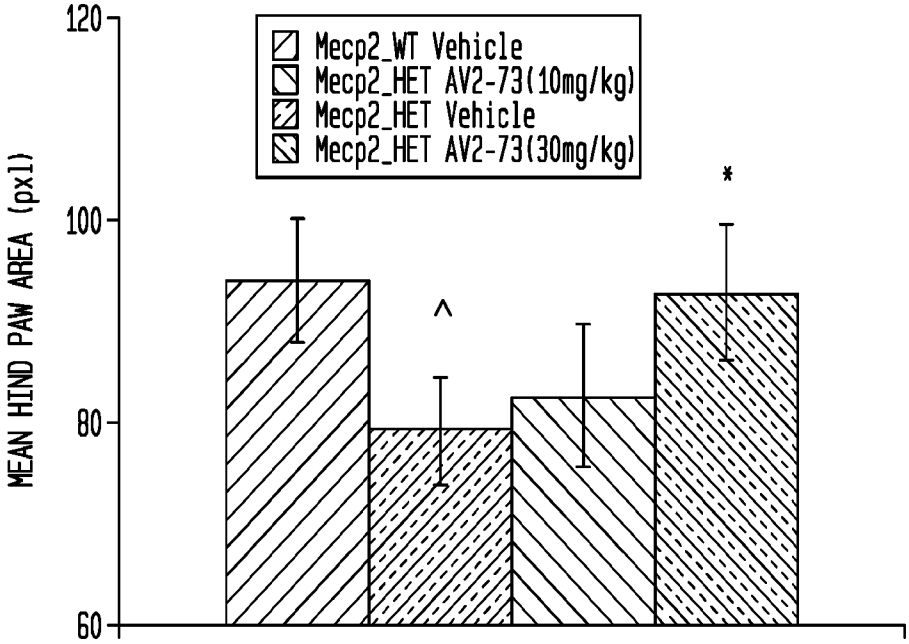
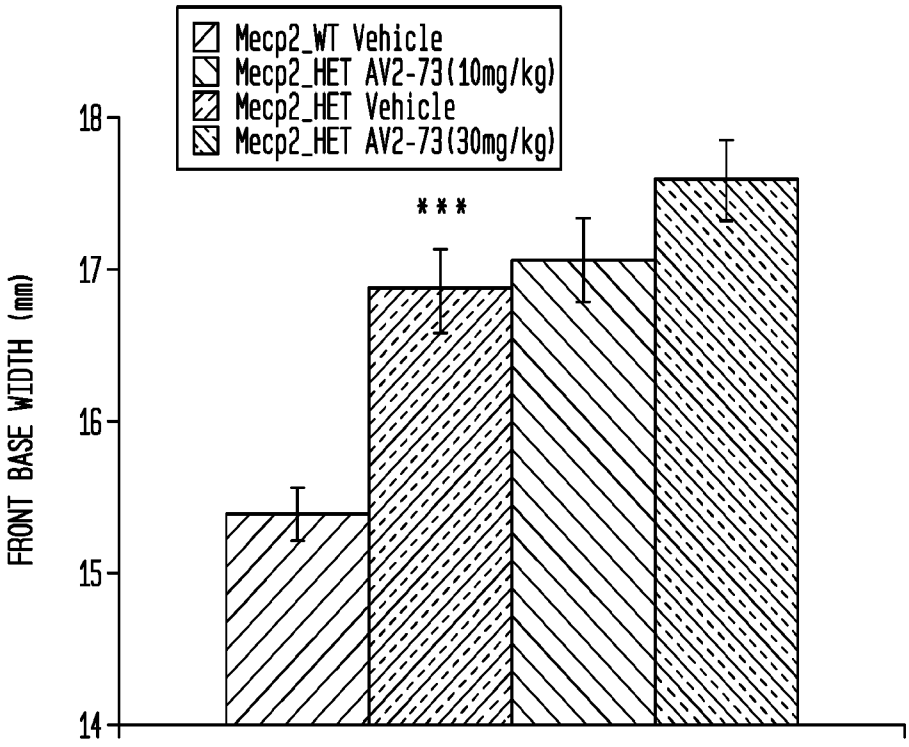

Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)
MEAN HIND PAW AREA (px1)
120
100
80
60
^
*

FIG. 9D


Mecp2_WT Vehicle
Mecp2_HET AV2-73(10mg/kg)
Mecp2_HET Vehicle
Mecp2_HET AV2-73(30mg/kg)
FRONT BASE WIDTH (mm)
18
17
16
15
14
***

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/014702

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/341 A61P25/00 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, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GR 1 004 208 B (VAMVAKIDIS ALEXANDROS) 4 April 2003 (2003-04-04) abstract claims 1-3 page 5, line 25 - page 7, line 5; compounds AE-37 -----	1,3-5,7, 8
A	WO 97/30983 A1 (VAMVAKIDES ALEXANDRE [GR]; COLOCOURIS NIKOLAOS [GR]; FOSCOLOS GEORGE [) 28 August 1997 (1997-08-28) page 3, line 20 - page 5, line 5 the whole document abstract ----- -/--	1-8

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 March 2017	04/04/2017

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	Langer, Oliver

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MATTHEW J. LYST ET AL: "Rett syndrome: a complex disorder with simple roots", NATURE REVIEWS GENETICS, vol. 16, no. 5, 3 March 2015 (2015-03-03), pages 261-275, XP055358535, GB ISSN: 1471-0056, DOI: 10.1038/nrg3897 the whole document	1-7
A	Eveline Hagebeuk: "UvA-DARE (Digital Academic Repository)", Rett Syndrome: Neurologic and metabolic aspects - PhD thesis, 7 November 2013 (2013-11-07), pages 12-33, XP055358580, Retrieved from the Internet: URL:https://pure.uva.nl/ws/files/2312678/129068_05.pdf [retrieved on 2017-03-24] the whole document	1-6
X,P	N Rebowe: "ANAVEX 2-73 as a Potential Treatment for Rett Syndrome and Other Pediatric or Infantile Disorders with Seizure Pathology", , 23 June 2016 (2016-06-23), XP055358591, Retrieved from the Internet: URL:https://s3.amazonaws.com/foxg1-sbfq/Rett%20and%20infantile%20Spasms%20AV2-73%20Presentation.pdf [retrieved on 2017-03-24] the whole document	1-7
X,P	Anavex Life Sciences: "Assessment of ANAVEX 2---73 in a MECP2 Re5 Syndrome Mouse Model 2016 Epilepsy Pipeline Conference February 26 th 2016", , 26 February 2016 (2016-02-26), XP055358593, Retrieved from the Internet: URL:http://www.anavex.com/my_uploads/Assessment-of-Anavex-2-73-in-a-MECP2-Rett-Syndrome-Mouse-Model.pdf [retrieved on 2017-03-24] the whole document	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/014702

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GR 1004208 B	04-04-2003		
WO 9730983 A1	28-08-1997	AU 1614097 A	10-09-1997
		GR 1002616 B	20-02-1997
		WO 9730983 A1	28-08-1997