

METHODS OF USE FOR KV7 CHANNEL ACTIVATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/901,621 filed September 17, 2019 and U.S. Provisional Application No. 62/945,300 filed December 9, 2019, which are incorporated herein by reference in their entirety.

GOVERNMENT INTERESTS

[0002] This invention was made with United States Government support under Grant No. U44NS093160 awarded by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health. The United States Government has certain rights in the invention.

SUMMARY OF INVENTION

[0003] ~~Embodiments~~ Examples described herein are directed to methods of treating a neurodevelopmental disease or disorder comprising administering a therapeutically effective amount of a Compound A, or pharmaceutically acceptable salt thereof, to a pediatric subject in need thereof. In some embodiments, the subject is a fetus, a neonate from birth to about 1 month, an infant from about 1 month to about 24 months, a child of about 2 years to about 11 years old, or an adolescent of about 12 years to 18 years old.

[0003a] In an aspect, there is provided the use of a Compound A, or a pharmaceutically acceptable salt thereof, to a pediatric subject in need thereof,

wherein Compound A, or a pharmaceutically acceptable salt thereof, is selected from the group consisting of N-(1-cyclobutyl-4-fluoro-6-(1-hydroxycyclobutyl)-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3,3-dimethylbutanamide; N-(1-(tert-butyl)-6-(difluoromethoxy)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(6-cyano-1-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-cyclobutyl-4-fluoro-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-(1-methylcyclopropyl)acetamide; N-(6-cyano-1-cyclobutyl-4-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-cyclobutyl-6-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-(tert-butyl)-6-cyano-4-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(7-cyano-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3-cyclopropyl-3-methylbutanamide; N-(6-chloro-7-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-cyclobutyl-5-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-(tert-butyl)-6-cyano-4,7-difluoro-1H-benzo[d]imidazol-2-yl)-3,3-

dimethylbutanamide; N-(6-cyano-1-cyclobutyl-7-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(6-cyano-4,7-difluoro-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-(tert-butyl)-5,7-difluoro-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3,3-dimethylbutanamide; and N-(1-(tert-butyl)-5,6-difluoro-1H-benzo[d]imidazol-2-yl)-2-(2,2,3,3-tetrafluorocyclobutyl)acetamide,

in the manufacture of a medicament for the treatment of a neurodevelopmental disease or disorder.

[0004] EmbodimentsExamples described herein are directed to methods of treating a neurodevelopmental disease or disorder comprising administering a therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of N-(1-cyclobutyl-4-fluoro-6-(1-hydroxycyclobutyl)-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3,3-dimethylbutanamide; N-(1-(tert-butyl)-6-(difluoromethoxy)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(6-cyano-1-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-cyclobutyl-4-fluoro-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-(1-methylcyclopropyl)acetamide; N-(6-cyano-1-cyclobutyl-4-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-cyclobutyl-6-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-(tert-butyl)-6-cyano-4-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(7-cyano-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3-cyclopropyl-3-methylbutanamide; N-(6-chloro-7-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-cyclobutyl-5-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-(tert-butyl)-6-cyano-4,7-difluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(6-cyano-1-cyclobutyl-7-(trifluoromethyl)-1H-benzo[d]imidazol-2-

yl)-3,3-dimethylbutanamide; N-(6-cyano-4,7-difluoro-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-(tert-butyl)-5,7-difluoro-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3,3-dimethylbutanamide; and N-(1-(tert-butyl)-5,6-difluoro-1H-benzo[d]imidazol-2-yl)-2-(2,2,3,3-tetrafluorocyclobutyl)acetamide.

[0005] ~~Embodiments~~—Examples described herein are directed to methods of treating a neurodevelopmental disease or disorder (NDD) comprising administering a therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, wherein the neurodevelopmental disease or disorder (NDD) is selected from the group consisting of Angelman syndrome, neonatal abstinence syndrome, early myoclonic encephalopathy, Landau Kleffner syndrome, electrical status epilepticus during sleep, Ohtahara syndrome, autism spectrum disorders, Dravet syndrome, Lennox–Gastaut syndrome, Rett syndrome, West syndrome, SCN8A-related epilepsy with encephalopathy (EIEE13), epilepsy of infancy with migrating focal seizures (EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), Doose syndrome, adrenoleukodystrophy (ALD), ATP6V1A encephalopathy, atypical childhood epilepsy with centrotemporal spikes (ACECTS), autosomal dominant rolandic epilepsy with speech dyspraxia (ADRES), CDKL5 encephalopathy, childhood epilepsy with centrotemporal spikes (CECTS), epileptic encephalopathy with continuous spike-and-wave during sleep syndrome (ECSWS), GRIN1 encephalopathy, GRIN2A epilepsy-aphasia syndrome, GRIN2B encephalopathy, intermediate epilepsy-aphasia disorder (IEAD), KCNT1 epilepsy of infancy with migrating focal seizures, neuronal ceroid lipofuscinoses (NCL), non-syndromic developmental and epileptic encephalopathy, PTPN23 encephalopathy, Rasmussen syndrome, SCN2A-related neonatal epilepsies, STXBP1 encephalopathy, tuberous sclerosis (TS)/tuberous sclerosis complex (TSC), and combinations thereof.

[0006] ~~Embodiments~~—Examples described herein are directed to methods of treating a neurodevelopmental disease or disorder (NDD) comprising administering a therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, wherein the neurodevelopmental disease or disorder (NDD) is selected from the group consisting of Angelman syndrome, neonatal abstinence syndrome, early myoclonic encephalopathy, Landau Kleffner syndrome, electrical status epilepticus during sleep, Ohtahara syndrome, autism spectrum disorders, Dravet syndrome, Lennox–Gastaut syndrome, Rett syndrome, West syndrome, SCN8A-related epilepsy with encephalopathy (EIEE13), epilepsy of infancy with migrating focal seizures (EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), and combinations thereof.

[0007] ~~Embodiments—Examples~~ described herein are directed to methods of treating a neurodevelopmental disease or disorder (NDD) comprising administering a therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, wherein the neurodevelopmental disease or disorder (NDD) is Doose syndrome.

[0008] ~~Embodiments—Examples~~ described herein are directed to methods of treating a neurodevelopmental disease or disorder (NDD) comprising administering a therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, wherein the neurodevelopmental disease or disorder (NDD) is selected from the group consisting of adrenoleukodystrophy (ALD), ATP6V1A encephalopathy, atypical childhood epilepsy with centrotemporal spikes (ACECTS), autosomal dominant rolandic epilepsy with speech dyspraxia (ADRES), CDKL5 encephalopathy, childhood epilepsy with centrotemporal spikes (CECTS), epileptic encephalopathy with continuous spike-and-wave during sleep syndrome (ECSWS), GRIN1 encephalopathy, GRIN2A epilepsy-aphasia syndrome, GRIN2B encephalopathy, intermediate epilepsy-aphasia disorder (IEAD), KCNT1 epilepsy of infancy with migrating focal seizures, neuronal ceroid lipofuscinoses (NCL), non-syndromic developmental and epileptic encephalopathy, PTPN23 encephalopathy, Rasmussen syndrome, SCN2A-related neonatal epilepsies, STXBP1 encephalopathy, tuberous sclerosis (TS)/tuberous sclerosis complex (TSC), and combinations thereof.

[0009] ~~Embodiments—Examples~~ described herein are directed to methods of treating a developmental and epileptic encephalopathy (DEE) comprising administering a therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, wherein the developmental and epileptic encephalopathy (DEE) is selected from the group consisting of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), Dravet syndrome, early myoclonic encephalopathy, electrical status epilepticus during sleep (ESES), epilepsy of infancy with migrating focal seizures (EIMFS), Landau Kleffner syndrome, Lennox–Gastaut syndrome, Ohtahara syndrome, SCN8A-related epilepsy with encephalopathy (EIEE13), West syndrome, Doose syndrome, ATP6V1A encephalopathy, autosomal dominant rolandic epilepsy with speech dyspraxia (ADRES), CDKL5 encephalopathy, epileptic encephalopathy with continuous spike-and-wave during sleep syndrome (ECSWS), GRIN1 encephalopathy, GRIN2A epilepsy-aphasia syndrome, GRIN2B encephalopathy, intermediate epilepsy-aphasia disorder (IEAD), KCNT1 epilepsy of infancy with migrating focal seizures, non-syndromic developmental and epileptic encephalopathy, PTPN23 encephalopathy, Rasmussen syndrome, SCN2A-related neonatal epilepsies, STXBP1 encephalopathy, and combinations thereof.

[0010] ~~Embodiments—Examples~~ described herein are directed to methods of treating a developmental and epileptic encephalopathy (DEE) comprising administering a therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, wherein the developmental and epileptic encephalopathy (DEE) is selected from the group consisting of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), Dravet syndrome, early myoclonic encephalopathy, electrical status epilepticus during sleep (ESES), epilepsy of infancy with migrating focal seizures (EIMFS), Landau Kleffner syndrome, Lennox–Gastaut syndrome, Ohtahara syndrome, SCN8A-related epilepsy with encephalopathy (EIEE13), West syndrome, and combinations thereof.

[0011] ~~Embodiments—Examples~~ described herein are directed to methods of treating a developmental and epileptic encephalopathy (DEE) comprising administering a therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, wherein the developmental and epileptic encephalopathy (DEE) is Doose syndrome.

[0012] ~~Embodiments—Examples~~ described herein are directed to methods of treating a developmental and epileptic encephalopathy (DEE) comprising administering a therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, wherein the developmental and epileptic encephalopathy (DEE) is selected from the group consisting of ATP6V1A encephalopathy, autosomal dominant rolandic epilepsy with speech dyspraxia (ADRES), CDKL5 encephalopathy, Epileptic encephalopathy with continuous spike-and-wave during sleep syndrome (ECSWS), GRIN1 encephalopathy, GRIN2A epilepsy-aphasia syndrome, GRIN2B encephalopathy, intermediate epilepsy-aphasia disorder (IEAD), KCNT1 epilepsy of infancy with migrating focal seizures, non-syndromic developmental and epileptic encephalopathy, PTPN23 encephalopathy, Rasmussen syndrome, SCN2A-related neonatal epilepsies, STXBP1 encephalopathy, and combinations thereof.

DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 demonstrates that Compound A negatively shifts activation voltage dependence more strongly for KCNQ2 homomers than for KCNQ2/Q3 heteromers and KCNQ3 homomers.

[0014] FIG. 2 demonstrates Compound A activation of KCNQ2 homomers.

[0015] FIG. 3 depicts the KCNQ2 subunit membrane folding pattern showing locations of some recurrent pathogenic KCNQ2 EE variants.

[0016] FIG. 4 demonstrates that Compound A (0.3 μ M and 1.0 μ M) increases homomeric channel density at -40 mV in wild type KCNQ2.

CLAIMS

What is claimed is:

1. ~~A method of treating a neurodevelopmental disease or disorder comprising administering a therapeutically effective amount~~Use of a Compound A, or a pharmaceutically acceptable salt thereof, to a pediatric subject in need thereof,

wherein Compound A, or a pharmaceutically acceptable salt thereof, is selected from the group consisting of N-(1-cyclobutyl-4-fluoro-6-(1-hydroxycyclobutyl)-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3,3-dimethylbutanamide; N-(1-(tert-butyl)-6-(difluoromethoxy)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(6-cyano-1-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-cyclobutyl-4-fluoro-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-(1-methylcyclopropyl)acetamide; N-(6-cyano-1-cyclobutyl-4-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-cyclobutyl-6-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-(tert-butyl)-6-cyano-4-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(7-cyano-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3-cyclopropyl-3-methylbutanamide; N-(6-chloro-7-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-cyclobutyl-5-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-(tert-butyl)-6-cyano-4,7-difluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(6-cyano-1-cyclobutyl-7-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(6-cyano-4,7-difluoro-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide; N-(1-(tert-butyl)-5,7-difluoro-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3,3-dimethylbutanamide; and N-(1-(tert-butyl)-5,6-difluoro-1H-benzo[d]imidazol-2-yl)-2-(2,2,3,3-tetrafluorocyclobutyl)acetamide₂.

in the manufacture of a medicament for the treatment of a neurodevelopmental disease or disorder.

2. The ~~method~~use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(1-cyclobutyl-4-fluoro-6-(1-hydroxycyclobutyl)-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3,3-dimethylbutanamide
3. The ~~method~~use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(1-(tert-butyl)-6-(difluoromethoxy)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide
4. The ~~method~~use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(6-cyano-1-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide
5. The ~~method~~use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(1-cyclobutyl-4-fluoro-6-(2-hydroxypropan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-(1-methylcyclopropyl)acetamide
6. The ~~method~~use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(6-cyano-1-cyclobutyl-4-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide
7. The ~~method~~use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(1-cyclobutyl-6-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide
8. The ~~method~~use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(1-(tert-butyl)-6-cyano-4-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide
9. The ~~method~~use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(7-cyano-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3-cyclopropyl-3-methylbutanamide
10. The ~~method~~use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(6-chloro-7-cyano-1-cyclobutyl-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide

11. The ~~method~~-use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(1-cyclobutyl-5-fluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide
12. The ~~method~~-use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(1-(tert-butyl)-6-cyano-4,7-difluoro-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide
13. The ~~method~~-use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(6-cyano-1-cyclobutyl-7-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide
14. The ~~method~~-use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(6-cyano-4,7-difluoro-1-(1-methylcyclobutyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethylbutanamide
15. The ~~method~~-use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(1-(tert-butyl)-5,7-difluoro-1H-benzo[d]imidazol-2-yl)-4,4,4-trifluoro-3,3-dimethylbutanamide
16. The ~~method~~-use of claim 1, wherein Compound A, or a pharmaceutically acceptable salt thereof, is N-(1-(tert-butyl)-5,6-difluoro-1H-benzo[d]imidazol-2-yl)-2-(2,2,3,3-tetrafluorocyclobutyl)acetamide.
17. The ~~method~~-use of Claim 1, wherein the neurodevelopmental disease or disorder are selected from the group consisting of Angelman syndrome, neonatal abstinence syndrome, early myoclonic encephalopathy, Landau Kleffner syndrome, electrical status epilepticus during sleep, Ohtahara syndrome, autism spectrum disorders, Dravet syndrome, Lennox–Gastaut syndrome, Rett syndrome, West syndrome, SCN8A-related epilepsy with encephalopathy (EIEE13), epilepsy of infancy with migrating focal seizures (EIMFS), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), Doose syndrome, adrenoleukodystrophy (ALD), ATP6V1A encephalopathy, atypical childhood epilepsy with centrotemporal spikes (ACECTS), autosomal dominant rolandic epilepsy with speech dyspraxia (ADRES), CDKL5 encephalopathy, childhood epilepsy with centrotemporal spikes (CECTS), Epileptic encephalopathy with continuous spike-and-wave during sleep syndrome (ECSWS), GRIN1 encephalopathy, GRIN2A epilepsy-aphasia syndrome, GRIN2B

encephalopathy, intermediate epilepsy-aphasia disorder (IEAD), KCNT1 epilepsy of infancy with migrating focal seizures, neuronal ceroid lipofuscinoses (NCL), non-syndromic developmental and epileptic encephalopathy, PTPN23 encephalopathy, Rasmussen syndrome, SCN2A-related neonatal epilepsies, STXBP1 encephalopathy, tuberous sclerosis (TS)/tuberous sclerosis complex (TSC), and combinations thereof.