SV2A is involved in vesicle trafficking and exocytosis, specifically the priming of docked vesicles to make them available for calcium-dependent fusion and, thereby, neurotransmitter release (Chang & Sudhof, J. Neurosci 2009 29 (4) 883-887. Both levetiracetam and brivaracetam are SV2A inhibitors, inhibiting synaptic function by reducing pre-synaptic vesicle fusion and neurotransmitter release. Levetiracetam and brivaracetam act as anticonvulsants. Brivaracetam binds to SV2A with a higher affinity than levetiracetam.

Kaminski et al. *Targeting SV2A for Discovery of Antiepileptic Drugs*, Jasper's Basic Mechanisms of the Epilepsies, 4th edition, 2012, describes the relationship between SV2A occupancy and seizure occurrence. In studies in audiogenic mice, it was found that levetiracetam doses providing maximum SV2A occupancy provided the best protection against clonic and tonic seizures. These studies also revealed that levetiracetam needed to occupy nearly 90% of SV2A in order to protect against clonic seizure in mice i.e. that a threshold SV2A occupancy needed to be reached to protect against seizures. Predictions for human brains based on clinically active daily dosing showed that SV2A occupancy varies from 80 to 93% at C_{min} and C_{max} for patients receiving a 1 g daily dose of levetiracetam, and from 92 to 98% for patients receiving a 3 g daily dose. Finnema et al., *A single-center, open-label positron emission tomography study to evaluate brivaracetam and levetiracetam synaptic vesicle glycoprotein 2A binding in healthy volunteers*, Epilepsia 2019; 60, 958-967, showed that after oral administration of 100 mg for 4 days an occupancy of 82-87% and 76-82% was reached at steady state at peak and trough respectively. These studies confirmed that high SV2A occupancy is needed for levetiracetam and brivaracetam to provide adequate protection against seizures.

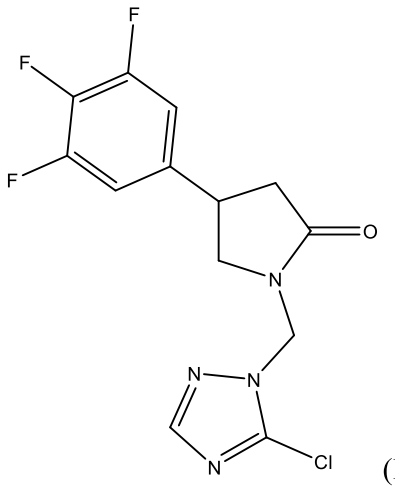
Dysfunction of SV2A may also be involved in Alzheimer's disease and other types of cognitive impairment (Löscher et al., CNS Drugs 2016, 30: pages 1055-1077). High-affinity SV2A ligands have been discovered which are devoid of anti-seizure activity, but provide pro-cognitive effects.

SUMMARY

The present disclosure provides compounds that bind with high affinity to SV2A and compositions comprising such compounds for use in treating a cognitive disorder in a

subject. These compounds increase neurotransmitter release presynaptically i.e. are positive modulators of SV2A, rather than inhibitors. In particular, the disclosure relates to treatments which involve administering these compounds and compositions in an amount which will result in levels of SV2A occupancy useful for imparting pro-cognitive effects. The inventors have surprisingly discovered that low doses of the compounds described herein, corresponding to partial SV2A occupancy, modulate brain activity in specific areas associated with a potential beneficial effect on cognitive function while being safe and well tolerated without major side effects. These findings open up the possibility of treating cognitive disorders and improving cognitive function by dosing the compounds to achieve a specific range of SV2A occupancy levels.

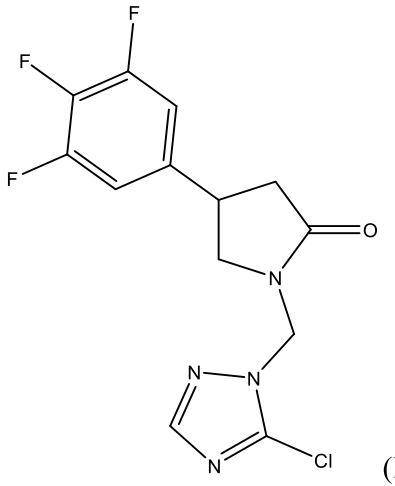
The disclosure therefore provides a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

or an isomer or a pharmaceutically acceptable salt thereof, for use in the treatment of a cognitive disorder in a subject, wherein the compound is administered to the subject in an amount of from 0.2 to 5 mg.

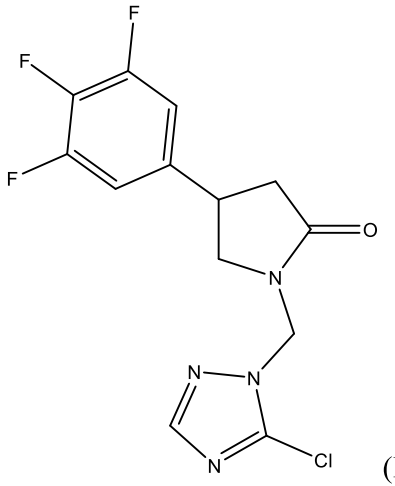
The disclosure also provides a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

or an isomer or a pharmaceutically acceptable salt thereof, for use in the treatment of a cognitive disorder in a subject, wherein the compound is administered to the subject in an amount that provides a synaptic vesicle glycoprotein 2A (SV2A) occupancy of from 10% to 80% at trough plasma concentrations after once daily dosing for at least 10 days.

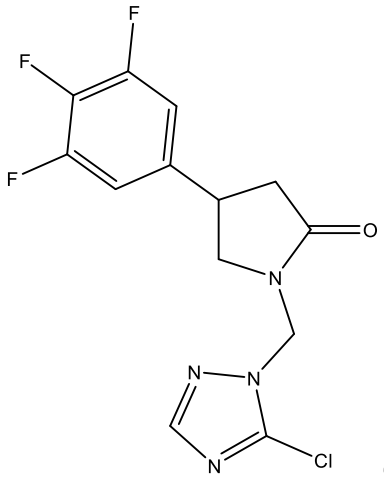
The disclosure also provides a pharmaceutical composition comprising a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

or an isomer or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, for use in the treatment of a cognitive disorder in a subject, wherein the pharmaceutical composition is administered to deliver to the subject an amount of the compound as described herein.

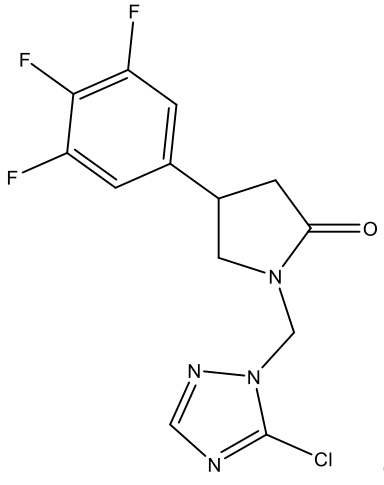
The disclosure also provides a method of treating a cognitive disorder in a subject, the method comprising administering a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

or an isomer or a pharmaceutically acceptable salt thereof to the subject in an amount of from 0.2 to 5 mg.

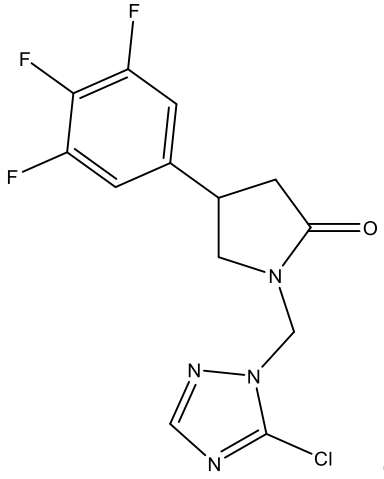
The disclosure also provides a method of treating a cognitive disorder in a subject, the method comprising administering a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

or an isomer or a pharmaceutically acceptable salt thereof to the subject in an amount that provides a synaptic vesicle glycoprotein 2A (SV2A) occupancy of from 10% to 80% at trough level after once daily dosing for at least 10 days.

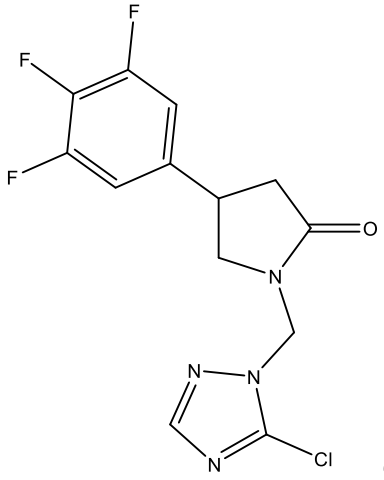
The disclosure also provides the use of a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

or an isomer or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cognitive disorder, wherein the medicament comprises from 0.2 to 5 mg of the compound.

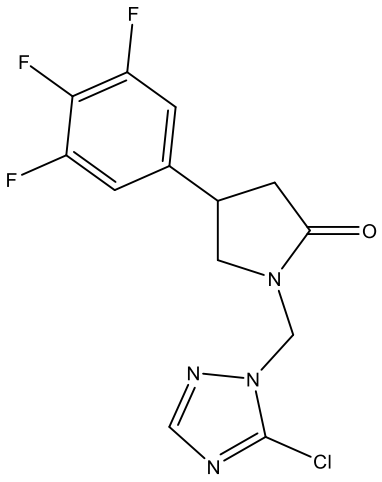
The disclosure also provides the use of a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

or an isomer or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cognitive disorder, wherein the medicament comprises an amount of the compound that provides a synaptic vesicle glycoprotein 2A (SV2A) occupancy of from 10% to 80% at trough level after once daily dosing for at least 10 days.

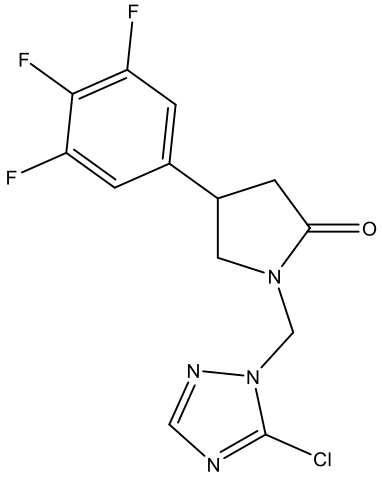
In an aspect, there is provided the use of a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

or an isomer or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cognitive disorder in a subject, wherein the compound is to be administered to the subject in an amount of from 0.2 to 5 mg.

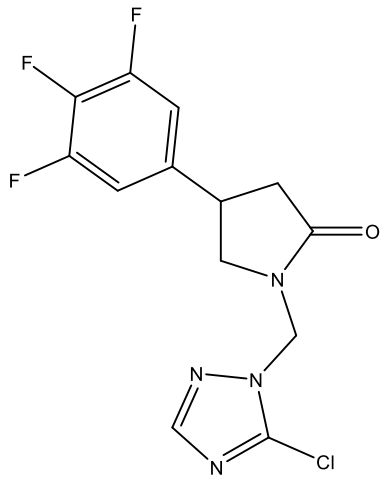
In another aspect, there is provided the use of a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

or an isomer or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cognitive disorder in a subject, wherein the compound is to be administered to the subject in an amount that provides an synaptic vesicle glycoprotein 2A (SV2A) occupancy of from 10% to 80% at trough level after once daily dosing for at least 10 days.

In another aspect, there is provided the use of a pharmaceutical composition comprising a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)

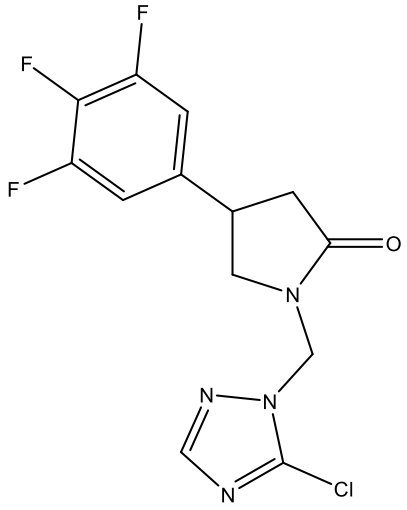


(I)

or an isomer or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, in the manufacture of a medicament for the treatment of a cognitive disorder in a subject, wherein the pharmaceutical composition is to be administered to deliver to the subject an amount of the compound as defined above.

CLAIMS

1. Use of a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

or an isomer or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cognitive disorder in a subject, wherein the compound is to be administered to the subject in an amount of from 0.2 to 5 mg.

2. The use according to claim 1, wherein the compound is to be administered to the subject in an amount of from 0.3 to 4 mg.

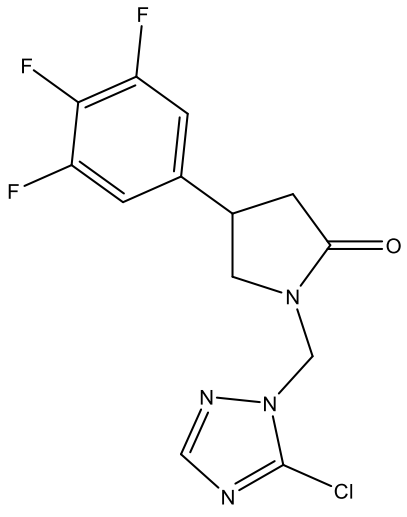
3. The use according to claim 1 or claim 2, wherein the compound is to be administered to the subject in an amount of from 1 to 3 mg.

4. The use according to any preceding claim, wherein the medicament is to be administered to the subject as a single unit dosage comprising from 0.2 to 5 mg of the compound,

preferably as a single unit dosage comprising from 0.3 to 4 mg of the compound,

more preferably as a single unit dosage comprising from 1 to 3 mg of the compound.

5. Use of a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

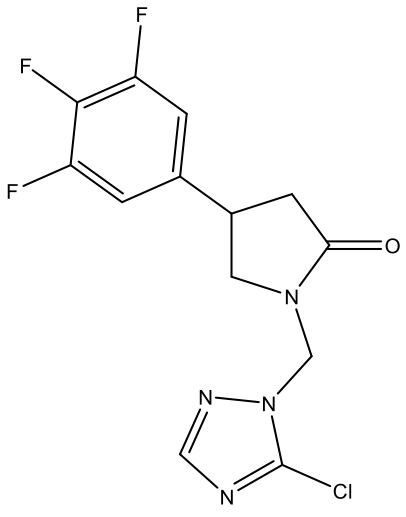
or an isomer or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cognitive disorder in a subject, wherein the compound is to be administered to the subject in an amount that provides an synaptic vesicle glycoprotein 2A (SV2A) occupancy of from 10% to 80% at trough level after once daily dosing for at least 10 days.

6. The use according to claim 5, wherein the compound is to be administered to the subject in an amount that provides an SV2A occupancy of from 10% to 70% at trough level after once daily dosing for at least 10 days.

7. The use according to claim 5 or claim 6, wherein the compound is to be administered to the subject in an amount that provides an SV2A occupancy of from 20% to 50% at trough level after once daily dosing for at least 10 days.

8. The use according to any one of claims 5 to 7, wherein the compound is to be administered to the subject in an amount as defined in any one of claims 1 to 4.

9. Use of a pharmaceutical composition comprising a compound which is a substituted 2-oxo-1-pyrrolidinyl triazole of formula (I)



(I)

or an isomer or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, in the manufacture of a medicament for the treatment of a cognitive disorder in a subject, wherein the pharmaceutical composition is to be administered to deliver to the subject an amount of the compound as defined in any one of claims 1 to 8.

10. The use according to any one of the preceding claims, wherein the compound is (4R)-1-[(5-chloro-1H-1,2,4-triazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one, or a pharmaceutically acceptable salt thereof.

11. The use according to any one of the preceding claims, wherein the compound is in the free base form.

12. The use according to any one of the preceding claims, wherein the medicament enhances or improves cognitive ability or counteracting cognitive decline.

13. The use according to any one of the preceding claims, wherein the cognitive disorder is selected from autism, dyslexia, attention deficit hyperactivity disorder, obsessive compulsive disorders, psychosis, bipolar disorders, depression (major depressive disorder), Tourette's syndrome and disorders of learning in children, adolescents and adults, Age Associated Memory Impairment, Age Associated Cognitive Decline, Parkinson's Disease, Down's Syndrome, traumatic brain injury, Huntington's Disease, Progressive Supranuclear Palsy (PSP), HIV infection, stroke, vascular diseases, Pick's or Creutzfeldt-Jacob diseases, multiple sclerosis (MS),

other white matter disorders and drug-induced cognitive worsening, Alzheimer's disease, schizophrenia, Lewy-bodies disease, front-temporal lobe degeneration, vascular narrowing or blockage in the brain (i.e. vascular dementia also known as multi-infarct dementia), head trauma, subjective cognitive decline and mild cognitive impairment,

preferably wherein the cognitive disorder is selected from subjective cognitive decline, Age Associated Memory Impairment, mild cognitive impairment, Alzheimer's disease, cognitive impairment in major depressive disorder and cognitive impairment in a subject with remitted depression following multiple episodes of major depressive disorder.

14. The use according to any one of the preceding claims, wherein the compound or pharmaceutical composition is to be administered orally.

15. The use according to any one of the preceding claims, wherein the amount of the compound as defined in any one of claims 1 to 4 is to be administered to the subject daily.