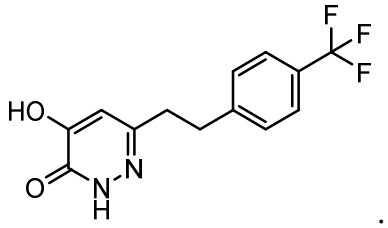
(δ)2 glutamate receptor (GluRδ2), which has been implicated in synaptic plasticity and long-term depression.

[0006] Thus, DAAO inhibitors may be useful for treating cognitive impairment, including treating cognitive symptoms associated with schizophrenia and other psychiatric disorders (e.g., psychotic disorders) and neurological disorders.

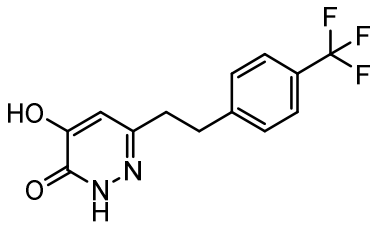
[0007] Compound (**I**) is a DAAO inhibitor of the following structure:



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See PCT Publication No. WO 2013/027000, which is incorporated herein by reference, *e.g.*, Example 36. Compound (**I**) is also referred to as luvadaxistat, TAK-831, and NBI-1065844.

[0007a] In an aspect, there is provided a use of a compound chosen from Compound (**I**):



and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating cognitive impairment in a patient in need thereof, comprising:

(i) a therapeutically effective amount of at least one compound chosen from Compound (I) and pharmaceutically acceptable salts thereof once daily for 6 to 8 days to be administered to the patient;

(ii) whether the 6 to 8 day administration improved at least one biomarker chosen from the patient's eye-blink conditioning (EBC) response, the patient's mismatch negativity (MMN) amplitude, and the patient's auditory steady state response (ASSR) gamma band power to be determined or to have been determined; and

(iii) a therapeutically effective amount of at least one compound chosen from Compound (I) and pharmaceutically acceptable salts thereof once daily if the 6 to 8 day administration improved at least one biomarker to be continued to be administered to the patient; and

wherein the patient exhibits at least one cognitive symptom prior to the administration.

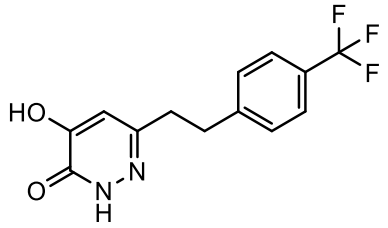
[0008] Disclosed herein is a method of treating cognitive impairment associated with schizophrenia in a patient in need thereof comprising administering to the patient 1 mg to 500 mg (*e.g.*, 1 mg to 100 mg) of at least one compound chosen from Compound (**I**) and pharmaceutically acceptable salts thereof once daily, wherein at least one cognitive symptom/domain associated with schizophrenia in the patient is treated by the administration.

[0009] Also disclosed herein is at least one compound chosen from Compound (**I**) and pharmaceutically acceptable salts thereof for use in a method of treating cognitive impairment associated with schizophrenia in a patient in need thereof, the method comprising administering to the patient 1 mg to 500 mg (*e.g.*, 1 mg to 100 mg) of the at least one compound chosen from Compound (**I**) and pharmaceutically acceptable salts thereof once daily, wherein at least one cognitive symptom associated with schizophrenia in the patient is treated by the administration.

[00010] Also disclosed herein is use of at least one compound chosen from Compound (**I**) and pharmaceutically acceptable salts thereof in the manufacture of a medicament for use in a method of treating cognitive impairment associated with schizophrenia in a patient in need thereof, the method comprising administering to the patient 1 mg to 500 mg (*e.g.*, 1 mg to 100 mg) of the at least one compound chosen from Compound (**I**) and pharmaceutically acceptable salts thereof once daily, wherein at least one cognitive symptom associated with schizophrenia in the patient is treated by the administration.

What is claimed is:

1. Use of a compound chosen from Compound (**I**):



and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating cognitive impairment in a patient in need thereof, comprising:

(i) a therapeutically effective amount of at least one compound chosen from Compound (I) and pharmaceutically acceptable salts thereof once daily for 6 to 8 days to be administered to the patient;

(ii) whether the 6 to 8 day administration improved at least one biomarker chosen from the patient's eye-blink conditioning (EBC) response, the patient's mismatch negativity (MMN) amplitude, and the patient's auditory steady state response (ASSR) gamma band power to be determined or to have been determined; and

(iii) a therapeutically effective amount of at least one compound chosen from Compound (I) and pharmaceutically acceptable salts thereof once daily if the 6 to 8 day administration improved at least one biomarker to be continued to be administered to the patient; and

wherein the patient exhibits at least one cognitive symptom prior to the administration.

2. The use according to claim 1, wherein the at least one cognitive symptom is chosen from impaired verbal memory, impaired working memory, impaired motor function, impaired attention, impaired processing speed, impaired verbal fluency, impaired executive function, impaired memory, impaired reasoning, impaired problem solving, impaired language functions, and impaired social cognition.

3. The use according to claim 1 or 2, wherein:

the cognitive impairment is cognitive impairment associated with schizophrenia (CIAS); and

the treating comprises 1 mg to 500 mg of at least one compound chosen from Compound (**I**) and pharmaceutically acceptable salts thereof once daily for 6 to 8 days to be administered to the patient.

4. The use according to claim 3, wherein:

the administration improves the patient's Brief Assessment of Cognition in Schizophrenia (BACS) Composite Score relative to a BACS Composite Score measured for the patient prior to the administration; or

the administration improves the patient's Schizophrenia Cognition Rating Scale (SCoRS) interviewer total score relative to a SCoRS interviewer total score measured for the patient prior to the administration.

5. The use according to claim 3 or 4, wherein the administration improves at least one metric chosen from:

(i) the patient's performance on the Continuous Performance Test-Identical Pairs (CPT-IP) test relative to a CPT-IP test prior to the administration;

(ii) the patient's performance on the Brief Visuospatial Memory Test-Revised (BVMT-R) test relative to the patient's performance on a BVMT-R test prior to the administration;

(iii) the patient's performance on the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) relative to the patient's performance on a MSCEIT prior to the administration;

(iv) the patient's performance on the Virtual Reality Functional Capacity Assessment Tool (VRFCAT) relative to the patient's performance on a VRFCAT prior to the administration; and

(v) the patient's Clinical Global Impression-Severity Scale (CGI-S) score relative to a CGI-S score measured for the patient prior to the administration.

6. The use according to any one of claims 3-5, wherein the patient has at least one stable negative symptom associated with schizophrenia prior to the administration.

7. The use according to claim 6, wherein:

the at least one stable negative symptom associated with schizophrenia is chosen from anhedonia, loss of motivation, and reduced interest in social interaction; and

wherein the stability of the at least one stable negative symptom associated with schizophrenia is assessed using:

(i) Positive and Negative Syndrome scale (PANSS); or

(ii) Brief Negative Symptom Scale (BNSS) instrument; and

optionally wherein the at least one stable negative symptom associated with schizophrenia is stable for at least one month prior to the administration.

8. The use according to any one of claims 3-7, wherein:

the at least one compound is to be administered in combination with at least one additional active agent that treats at least one negative symptom associated with schizophrenia in the patient; wherein:

the at least one negative symptom associated with schizophrenia is chosen from anhedonia, loss of motivation, and reduced interest in social interaction; and

the at least one additional therapeutic agent is chosen from aripiprazole, olanzapine, risperidone, and quetiapine fumarate.

9. The use according to any one of claims 3-8, wherein:

the at least one compound is to be administered to the patient for more than 14 weeks; and

optionally wherein the at least one compound is to be administered to the patient for more than 20 weeks.

10. The use according to any one of claims 3-9, wherein the patient is on a stable regimen of psychotropic medications.

11. The use according to any one of claims 3-10, wherein:

the patient was diagnosed with schizophrenia at least one year prior to the administration; and

the patient has stable symptomatology for at least 3 months prior to the administration.

12. The use according to any one of claims 3-11, wherein the patient is to be administered 1 mg to 100 mg of the at least one compound once daily.

13. The use according to any one of claims 3-5, wherein the patient has no more than moderate-severe positive symptoms associated with schizophrenia as determined by a rating of < 5 on PANSS positive symptom items P1 (delusions), P3 (hallucinatory behavior), P4 (excitement), P5 (grandiosity), and/or P6 (suspiciousness).

14. The use according to claim 1 or 2, wherein the at least one cognitive symptom is associated with a psychotic disorder chosen from psychosis, schizophreniform disorder, schizoaffective disorder, and schizophrenia unassociated with aggression.

15. The use according to claim 1 or 2, wherein the at least one cognitive symptom is associated with attention-deficit disorder, dementia, Alzheimer's disease, Parkinson’s disease, Huntington's disease, Cushing's disease, Lewy body disease, multiple sclerosis, stroke, addictive disorder, pervasive development disorder, autism, fragile X syndrome, anxiety disorder, Prader-Willi syndrome, bipolar disorder, depression, and delirium.

16. The use according to claim 14 or 15, wherein the at least one compound is to be administered in combination with at least one additional active agent that treats at least one negative symptom in the patient; wherein:

the at least one negative symptom is chosen from anhedonia, loss of motivation, and reduced interest in social interaction; and

the patient has at least one stable negative symptom chosen from anhedonia, loss of motivation, and reduced interest in social interaction prior to the administration.

17. The use according to any one of claims 1-16, wherein:

the patient is to be administered 50 mg of the at least one compound once daily; or

the patient is to be administered 20 mg of the at least one compound once daily.

18. The use according to any one of claims 1-17, wherein the at least one compound is to be administered in the form of at least one film-coated tablet.

19. The use according to any one of claims 1-18, wherein the at least one compound is to be administered with water or milk.

20. The use according to any one of claims 1-19, wherein:
the treating increases D-serine levels in the patient;
the treating increases long-term potentiation in the patient; and/or
the treating increases synaptic plasticity in the patient.