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Patent Highlight

Psychoplastogens: A Novel Therapeutic Approach for Neurological Diseases and Disorders

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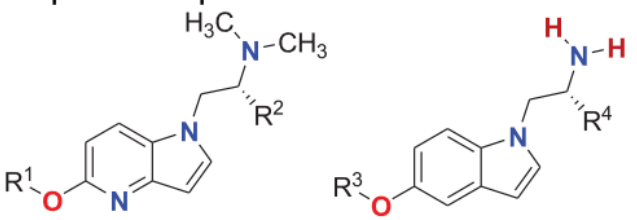
ABSTRACT: Neurological diseases often involve changes in synaptic connectivity and plasticity. Psychoplastogens, substances that stimulate neuronal growth and enhance neural structures, show promise in mitigating these changes. They activate key biological targets, including AMPA receptors, TrkB, and mTOR. Substances like ketamine, scopolamine, *N*,*N*-dimethyltryptamine, and rapastinel have psychoplastogenic properties. In clinical trials, psychedelic psychoplastogens have demonstrated antidepressant, anxiolytic, and anti-addictive effects. The research described in this Patent Highlight suggests the potential for novel therapies in neurological disorders that leverage psychoplastogens, which modulate synaptic connections and plasticity.

Important Compound Classes.



Title. Aryloxy Psychoplastogens and Uses Thereof

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Disease Area. Neurological diseases and disorders

Biological Target. AMPA receptors, TrkB, and mTOR

Summary. Neurological diseases and disorders, including neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease, are often associated with changes in synaptic connectivity and plasticity in the brain. Synaptic connectivity refers to the pattern of connections between neurons, while plasticity pertains to the ability of these connections to change over time. Emerging evidence indicates that a class of substances known as psychoplastogens may offer a promising avenue for treatment.

Unlocking Neurological Therapeutics. Psychoplastogens are molecules that stimulate the growth of neurons and enhance the architecture of neural structures. They operate by triggering the activation of several vital biological targets, specifically the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, the tropomyosin receptor kinase B (TrkB), and the mammalian target of rapamycin (mTOR). AMPA receptors and TrkB are proteins found on the surface of neurons that influence neuron function, while mTOR is a protein that regulates cell growth and survival.

Modulators of these targets, such as ketamine, scopolamine, *N*,*N*-dimethyltryptamine (DMT), and rapastinel, possess psychoplastogenic properties. These substances stimulate neuronal growth and can rectify deleterious neuronal structural changes associated with neurological diseases. For instance, ketamine, an anesthetic medication, demonstrates a remarkable ability to repair harmful structural changes in neurons, such as the loss of dendritic spines and synapses, primarily in the prefrontal cortex (PFC), or a reduction in the complexity of dendritic arbor, the branching structure of neuron extensions.

Role of Pyramidal Neurons in the Prefrontal Cortex. The PFC, a critical area of the brain that governs executive functions like decision-making and social behavior, contains pyramidal neurons. These neurons control other brain areas responsible for motivation, fear, and reward. As such, therapeutic interventions that target the PFC's pyramidal neurons could alleviate symptoms related to mood and behavior, a prospect of immense value in neuropsychiatric disorders.

Clinical Impacts of Psychedelic Psychoplastogens. Certain psychedelic psychoplastogens have demonstrated promising results in a clinical context. They have shown antidepressant effects, reducing symptoms in individuals with major depressive disorder, anxiolytic effects, mitigating anxiety symptoms, and even anti-addictive effects, aiding in the cessation of substance use disorders. The success of these clinical trials paves the way for new therapeutic approaches and underscores the importance

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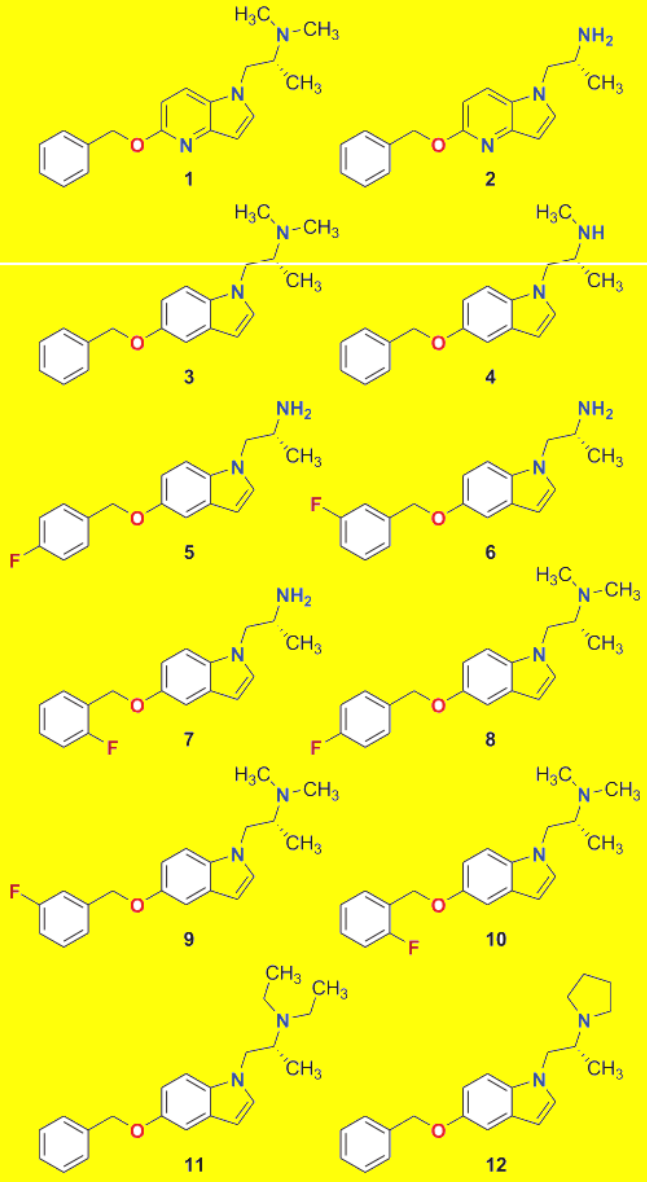
of understanding the exact mechanisms through which psychoplastogens exert their effects.

Consequently, studying psychoplastogens opens up an exciting new frontier in neurology. By leveraging these substances' ability to modulate synaptic connections and plasticity, it may be possible to develop innovative therapies for a wide range of neurological diseases and disorders, thereby enhancing the quality of life for affected individuals.

Key Structures.



Biological Assay. Forced swim test, neurite outgrowth assay, pregnant Sprague−Dawley rats dendritogenesis analysis, 5-HT2A and 5-HT2C *in vitro* cellular IPOne agonism, and radioligand binding competition assays

Biological Data. The table below shows the serotonin 5-HT2A and 5-HT2C *in vitro* radioligand binding and cellular IPOne agonism assays. The binding and agonism functional potencies of the compounds are indicated by their IC_{50} or EC_{50} values, where A means IC_{50} or EC_{50} < 0.010 μM; B means IC_{50} or EC_{50} = 0.0100−100 μM, and C means IC_{50} or EC_{50} = 0.101−1 μM.

Compound No.	Increase in Neurite Number	Increase in Neurite Length	Increase in Number of Branchpoints
1	A	A	A
3	B	A	B
4	A	A	A
5	B	B	B
6	B	A	A
7	A	B	A
8	A	A	A
9	A	A	A
10	A	A	A
11	A	A	A
12	A	A	B

Recent Review Articles. See refs 1−6.

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Notes

The author declares no competing financial interest.

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