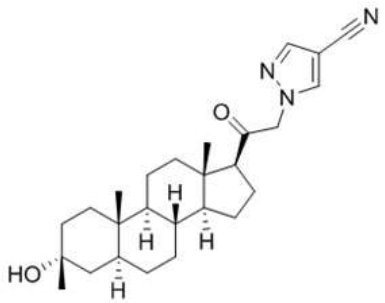
neurological conditions due to the limited arsenal of neuroactive steroids currently at our disposal.

Summary

The ~~invention~~disclosure provides compositions that contain isomerically pure forms of selected neurosteroids. The ~~invention~~disclosure recognizes that interactions between neurosteroids and $GABA_A$ receptors are highly sensitive to the stereochemical structure of the neurosteroids and that certain neurosteroids display strong $GABA_A$ receptor subtype specificity when provided in compositions that are substantially free of isomeric contaminants. Because the compositions of the ~~invention~~disclosure selectively target particular $GABA_A$ receptor subtypes, they have greatly improved pharmacological efficacy over prior compositions, including those that contain biologically active compounds contaminated with isomers that are less active.

In a particular ~~embodiment~~example, the ~~invention~~disclosure provides compositions that contain an isomerically pure form of a compound of Formula (I):

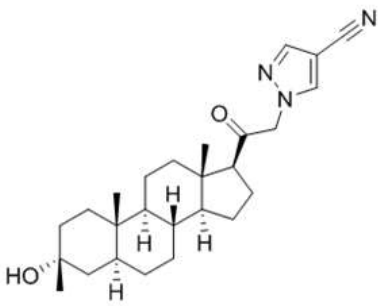


(I).

The present ~~invention~~disclosure includes the finding that isomerically pure compositions of Formula (I) are considerably more active on α4β3δ $GABA_A$ receptors than on α1β2γ2 $GABA_A$ receptors. As described herein, such compositions modulate the activity of α4β3δ receptors with an EC_{50} at least 5-fold lower than for α1β2γ2 receptors. Without wishing to be bound by a particular theory, it is believed that the stereochemical configurations at all of the chiral centers of the molecule and the atomic bonding patterns within the molecule are important in conferring $GABA_A$ receptor subtype selectivity. Thus, mixtures that contain the compound of Formula (I) together with isomers thereof, such as regioisomers of Formula (I) or stereoisomers that differ structurally from Formula (I) at only a single chiral center, lack such selectivity. Because

compositions that contain an isomerically pure form of the compound of Formula (I) preferentially target α4β3δ $GABA_A$ receptors, they are useful for therapeutic applications in which altering the activity of this receptor is beneficial.

In an aspect, the ~~invention~~disclosure provides pharmaceutical compositions containing an isomerically pure form of a compound of Formula (I):

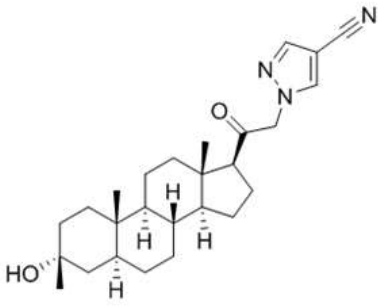


(I),

wherein the compound of Formula (I) is present in a therapeutically effective amount to preferentially potentiate an α4β3δ $GABA_A$ receptor as compared to an α1β2γ2 $GABA_A$ receptor.

In another aspect, the present disclosure provides the composition as described herein for use in therapy. In yet another aspect, the present disclosure provides a use of the composition as described herein in the manufacture of a medicament for treating a $GABA_A$ disorder.

In another ~~aspect~~example, the ~~invention~~disclosure provides methods for treating a $GABA_A$ disorder by providing to a subject a pharmaceutical composition comprising an isomerically pure form of a compound of Formula (I):



(I),

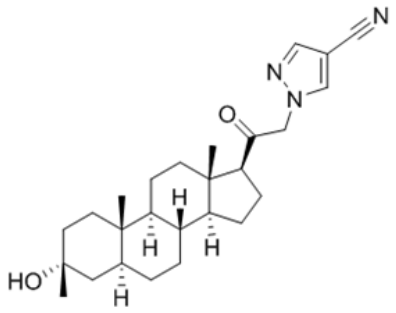
wherein the compound of Formula (I) is present in a therapeutically effective amount to preferentially potentiate an α4β3δ $GABA_A$ receptor as compared to an α1β2γ2 $GABA_A$ receptor.

The composition may be chemically pure, i.e., free from other molecules or chemical species. For example, the other molecule or chemical species may have a distinct chemical

Claims

What is claimed is:

1. A pharmaceutical composition comprising an isomerically pure form of a compound of Formula (I):



(I),

wherein the compound of Formula (I) is present in a therapeutically effective amount to preferentially potentiate an α4β3δ $GABA_A$ receptor as compared to an α1β2γ2 $GABA_A$ receptor.

2. The composition of claim 1, wherein the compound of Formula (I) preferentially positively modulates an α4β3δ $GABA_A$ receptor as compared to an α1β2γ2 $GABA_A$ receptor.

3. The composition of claim 2, wherein an EC_{50} of the compound of Formula (I) for an α4β3δ $GABA_A$ receptor is less than 50% of an EC_{50} of the compound of Formula (I) for an α1β2γ2 $GABA_A$ receptor.

4. The composition of claim 3, wherein an EC_{50} of the compound of Formula (I) for an α4β3δ $GABA_A$ receptor is less than 20% of an EC_{50} of the compound of Formula (I) for an α1β2γ2 $GABA_A$ receptor.

5. The composition of claim 1, wherein an EC_{50} of the compound of Formula (I) for an α4β3δ $GABA_A$ receptor is less than 500 nM.

6. The composition of claim 1, wherein the composition is effective for treatment of a $GABA_A$ disorder.

7. The composition of 6, wherein the $GABA_A$ disorder is selected from the group consisting of acute pain, an addictive disorder, Alzheimer's disease, Angelman's syndrome, anti-social personality disorder, an anxiety disorder, attention deficit hyperactivity disorder (ADHD), an attention disorder, an auditory disorder, autism, an autism spectrum disorder, bipolar disorder, chronic pain, a cognitive disorder, a compulsive disorder, a convulsive disorder, dementia, depression, dysthymia, an epileptic disorder, essential tremor, epileptogenesis, fragile X syndrome, generalized anxiety disorder (GAD), Huntington's disease, injury related pain syndrome, insomnia, ischemia, Lewis body type dementia, a memory disorder, migraines, a mood disorder, movement disorder, a neurodegenerative disease, neuropathic pain, an obsessive compulsive disorder, pain, a panic disorder, Parkinson's disease, a personality disorder, posttraumatic stress disorder (PTSD), psychosis, Rett syndrome, a schizoaffective disorder, schizophrenia, a schizophrenia spectrum disorder, a seizure disorder, a sleep disorder, social anxiety disorder, status epilepticus, stress, stroke, tinnitus, traumatic brain injury (TBI), vascular disease, vascular malformation, vascular type dementia movement disorder, Wilson's disease, and withdrawal syndrome.

8. The composition of 7, wherein the $GABA_A$ disorder is an epileptic disorder, epileptogenesis, or a seizure disorder.

9. The composition of claim 1, wherein the composition is formulated for oral administration.

10. The composition of claim 1, the composition is formulated as a single daily dosage.

11. The composition of any one of claims 1 to 10 for use in therapy.

12. Use of the composition of any one of claims 1 to 10 in the manufacture of a medicament for treating a $GABA_A$ disorder.