

**(S)-TIANEPTINE AND USE IN TREATING DISORDERS AND CONDITIONS
ASSOCIATED WITH PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR**

5 **CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to and benefit from United States Provisional Application No. 63/454,958, filed March 27, 2023, United States Provisional Application No. 63/463,299, filed May 1, 2023, United States Provisional Application No. 63/466,999, filed May 16, 2023, United States Provisional Application No. 63/468,221, filed May 22, 2023, and United States Provisional Application No. 63/528,631, filed July 24, 2023. The contents of each of the foregoing applications are hereby incorporated by reference in their entireties.

TECHNICAL FIELD

[0002] The present disclosure relates to the (S)-enantiomer of 7-(3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-ylamino)heptanoic acid ((S)-tianeptine) and the (S)-enantiomer of deuterated tianeptine (11-D-(S)-tianeptine), both being characterized as comprising no more than about 2%, or no more than about 0.1%, of the corresponding (R)-enantiomer. The present disclosure further provides salts, amides, esters, co-crystals, crystals, analogs and pharmaceutical compositions thereof and methods of using the (S)-enantiomers and those compounds and compositions for treating diseases, disorders or conditions of the CNS as well as diseases, conditions and disorders associated with altered activity of, exacerbated by or modulated by the peroxisome proliferator-activated receptors (PPAR)- β/δ and/or PPAR- γ , while minimizing or eliminating the potential for opioid abuse. Among these diseases, disorders and conditions are CNS disorders (*e.g.*, major depressive disorder, age-related cognitive impairments and neurodegenerative conditions), asthma, and primary biliary cholangitis. The present disclosure also provides methods of producing the (S)-enantiomer and 11-D-(S)-enantiomer and related compounds of this disclosure.

BACKGROUND

30 [0003] Tianeptine, a racemate of 7-[(3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][2,1]benzothiazepine-11-yl)amino]heptanoic acid, is an antidepressant with neuroprotective and cognitive restorative effects. Investigators have reported that tianeptine can be used to treat post-traumatic stress disorder (PTSD) (Onder E et al., *Eur Psychiatry*. 2005), attention-deficit/hyperactivity disorder (ADHD) (Niederhofer H.,

Neuropsychobiology. 2004), Alzheimer's disease (García-Alberca JM et al., *J Alzheimers Dis*. 2022), asthma (Lechin F et al., *Methods Find Exp Clin Pharmacol*. 2004), and fibromyalgia (ISRCTN16400909). Although tianeptine shares structural similarities to classic tricyclic antidepressants, its pharmacological behavior is unique. No tianeptine-containing drug is approved by the U.S. Food and Drug Administration (FDA) for any indication. Tianeptine is, however, currently available, as the active ingredient of products approved and sold under the commercial names, *inter alia*, Stablon®, Coaxil®, Tatinol, Tianeurax®, and Salymbra, throughout Europe, Asia, and Latin America for the treatment of depression. For example, France first authorized the marketing of tianeptine (e.g., Stablon®) in 1989 as an antidepressant at a dose of 12.5 mg, three times daily. Tianeptine-containing products are also available in certain areas of the U.S. as over-the-counter food supplements or research chemicals.

[0004] Racemic tianeptine has been reported to affect serotonin reuptake, modulate glutamatergic activity, and has more recently been reported to weakly activate μ -opioid receptors. In animal studies involving severe stress exposure, tianeptine was reported to restore brain neuroplasticity through synaptogenesis by exerting biological effects on neurons and glial cells that increase arborization of dendrites in critical hippocampal circuits, to restore hippocampal neurogenesis, and to reverse stress-induced impairments in synaptic glutamate neurotransmission (McEwen BS et al., *Mol Psychiatry*. 2010). Further, tianeptine was shown to increase brain-derived neurotrophic factor (BDNF) in the rat amygdala (Reagan LP et al., *Eur J Pharmacol*. 2007; Della FP, et al., *Behav Brain Res*. 2012). However, these mechanistic studies are difficult to interpret as many are based on assays with a 50:50 mixture of the (R)- and (S)-enantiomers of tianeptine (the racemate).

[0005] Moreover, the Center for Disease Control and Prevention (CDC) published a Morbidity and Mortality Weekly Report (MMWR) in August 2018 that described incidences of tianeptine overdose from over-the-counter products, associated with the abuse potential of tianeptine due to its opioid-like effects, and issued a warning of public health risk. Indeed, marketing authorization in the country of Georgia was withdrawn in June 2010, and tianeptine was included on the list of psychotropic agents in Russia, Ukraine and Armenia because of its misappropriation by "drug addicts" by intravenous injection. As a result of these actions and reports of abuse, in September 2012, tianeptine was added to List I in France, for medicines in which there is special status for prescribing and dispensing conditions. Other common adverse events associated with tianeptine include anorexia,

nightmares, insomnia, somnolence, dizziness, headache, tachycardia, dyspnea, gastrointestinal distress, myalgia, and asthenia.

[0006] Peroxisome proliferator-activated receptors (PPARs) are a group of ligand-activated transcription factors that belong to the nuclear receptor superfamily involved in the regulation of inflammatory reactions and lipid metabolism both peripherally and in the central nervous system (CNS). The PPAR subfamily comprises three isotypes: PPAR- α , PPAR- γ and PPAR- β/δ . Studies have implicated PPAR- α and PPAR- γ activation in the modulation of neuroinflammation, mitochondrial alterations and memory impairment. PPAR- γ has also been shown to play roles in depression, neurogenesis and the expression of brain-derived neurotrophic factor (BDNF) (Nicolakakis N et al., *J Neurosci.* 2008; Heneka MT et al., *Brain.* 2005; Gold PW. *Int J Mol Sci.* 2021). PPAR- γ modulation is also used to treat diabetes, for example by agonists of the “Thiazolidinedione” (“TZD”) class, which are often called, “glitazones”, including rosiglitazone (Avandia®) and pioglitazone (Actos®). Alzheimer’s Disease has been called “Type 3 diabetes” to capture the concept that it may be a metabolic derangement of the CNS glucose metabolism, similar to how Type 1 and Type 2 Diabetes are metabolic derangements of peripheral glucose metabolism (de la Monte SM, Wands JR. *J Diabetes Sci Technol.* 2008). PPAR- β/δ downregulation has also been associated with depressive behaviors, while PPAR- β/δ activation has been shown to ameliorate clinical symptoms of CNS pathologies by modulating oxidative stress and inflammatory responses (Chen F et al., *Int J Neuropsychopharmacol.* 2019; Strosznajder AK, *Neuromolecular Med.* 2021; Espinosa-Jiménez T et al. *Front Pharmacol.* 2022). PPAR- β/δ activation is also now under investigation for the treatment of primary biliary cholangitis by MBX-8025 (Seladelpar®) from CymaBay Therapeutics, currently in Phase 3 trials.

[0007] Major depressive disorder (MDD) is a mood disorder that persists for 2 or more weeks and is a leading cause of disability worldwide. MDD affects how a person feels, thinks, and handles daily activities and can significantly impair all aspects of life as patients present with persistent sadness or anxiousness, irritability, anhedonia, significant weight change, appetite disturbances, sleep disturbances, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, diminished ability to think or concentrate, indecisiveness, aches or pains without a clear physical cause, or recurrent thoughts of death or suicide. In 2020, an estimated 21 million adults in the U.S., a number representing about 8.4% of all adults (age 18 or older), experienced at least one major depressive episode. The annual prevalence of a major depressive episode is higher among adult females (e.g., about 10.5%) compared to males (e.g., about 6.2%). In addition, the annual prevalence of a major

depressive episode is highest among individuals aged 18-25 (e.g., about 17.0%). Human and animal studies have shown that depression is associated with reduced size of brain regions which are believed to regulate mood and cognition, including the prefrontal cortex and the hippocampus. In addition, these areas of the brain have decreased neuronal synapses in depression (MacQueen G, Frodl T. *Mol Psychiatry*. 2011; Price JL, Drevets WC. *Neuropsychopharmacology*. 2010).

[0008] The current mainstays of pharmacological treatments for MDD include the use of selective serotonin reuptake inhibitors (SSRIs) (Fava *et al.*, *Int J Neuropsychopharmacol*. 2007), serotonin-norepinephrine reuptake inhibitors (SNRIs) (Stahl *et al.*, *CNS Spectr*. 2005) and tricyclic antidepressants (TCAs). However, these therapies are not effective in all patients, and are often associated with undesirable side effects, such as weight gain and sexual dysfunction. And, even with multiple consecutive treatments, only a small proportion of patients achieve an asymptomatic state, *i.e.*, remission (Rush, *Am J Psychiatry*. 2007). Many patients, who do not respond adequately to therapy with SSRIs, SNRIs and TCAs, receive augmentation therapy with mood stabilizers or antipsychotics (Strawbridge R *et al.*, *Br J Psychiatry*. 2019) and other such patients, without a sound basis of experimental evidence, sometimes receive off-label opioids and narcotic painkillers (e.g., oxycodone, hydrocodone, fentanyl, and tramadol). The use of opioids to treat MDD is associated with an increased risk with long-term use, abuse (e.g., parenteral, transmucosal, intranasal or oral drug abuse), and addiction.

[0009] Depression is also associated with impaired neuroplasticity and cellular resilience. Traditional antidepressant medications act in part by normalizing this impairment and restoring neuronal connections. For example, ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist, was found to produce rapid (within hours) antidepressant responses in patients with treatment-resistant depression, and in animal models to rapidly induce BDNF dependent-synaptogenesis and to reverse the synaptic deficits caused by chronic stress by activating the mammalian target of rapamycin (mTOR) signaling pathway (Duman RS, Aghajanian GK. *Science*. 2012). Intranasal S-ketamine (Spravato®) is approved by the U.S. FDA for the acute treatment of depression. Dextromethorphan, another NMDA receptor antagonist, in combination with bupropion as a fixed dose oral product (Auvelity®), is also FDA approved for the treatment of depression. However, ketamine, S-ketamine, dextromethorphan and other ligands of the NMDA receptor have dissociative effects which limit their use. Another proposed approach to inducing synaptogenesis is the 5-HT_{2A}

receptor agonist psilocybin, but that approach is limited by hallucinations, which are a pseudo-psychotic side effect.

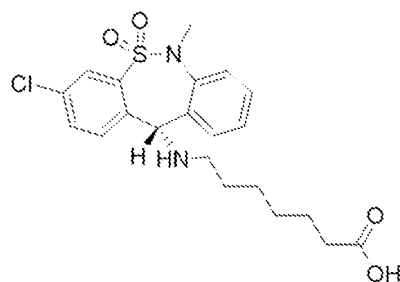
[0010] There is, therefore, a long-felt and unmet need to safely treat MDD and various other CNS disorders and conditions, and various disorders and conditions associated with altered activity of or modulated by PPAR- β/δ and/or PPAR- γ . These disorders and conditions include stress (psychological, environmental, chemical, radiation, oxidative, hormonal, vascular and traumatic), depression, aging and chronic illness, each of which is associated with decreased neuronal connections.

[0011] The (S)-enantiomer of tianeptine, its zwitterion, its co-crystals, its esters, amides and deuterated analogs of any of them or pharmaceutically acceptable salts and crystalline forms thereof of the (S)-enantiomers and compositions thereof, as well as various analogs of the two tianeptine enantiomers and compositions of them, as described in various embodiments of this disclosure, and methods of using those compositions meet this unmet need and improve the treatment of various CNS disorders and conditions, including MDD, and disorders and conditions associated with altered activity of or modulated by PPAR- β/δ and/or PPAR- γ , while at the same time minimizing or eliminating the potential for opioid abuse.

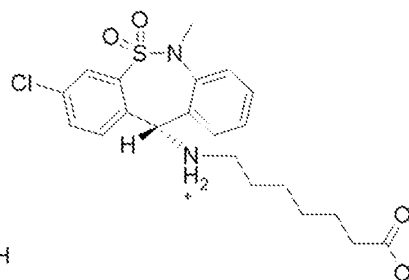
SUMMARY OF THE DISCLOSURE

[0012] Some embodiments of this disclosure are:

1. The (S)-enantiomer of 7-(3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-ylamino)heptanoic acid ((S)-enantiomer of tianeptine) of the general Formula (Ia), the zwitterion thereof of Formula (Ib) or a pharmaceutically acceptable salt of the (S)-enantiomer, or a mixture of two or more of these species, wherein the (S)-enantiomer, zwitterion or pharmaceutically acceptable salt are characterized by comprising $\leq$ about 2% of the (R)-enantiomer of tianeptine, the zwitterion thereof or a pharmaceutically acceptable salt of the (R)-enantiomer:



Formula (Ia)

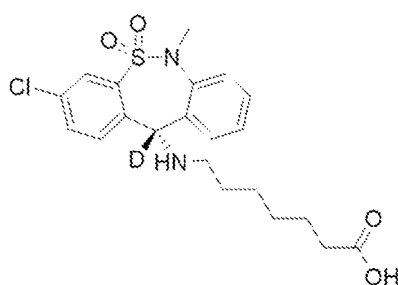


Formula (Ib).

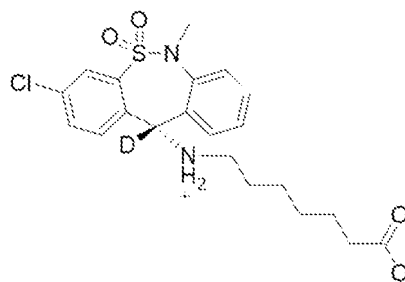
2. The (S)-enantiomer according to embodiment 1, wherein the (S)-enantiomer, the
5 zwitterion or pharmaceutically acceptable salt of the (S)-enantiomer are characterized by comprising $\leq$ about 0.1% of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer.
3. A pharmaceutically acceptable salt of the (S)-enantiomer according to embodiment 1
10 or 2, wherein the pharmaceutically acceptable salt is (S)-tianeptine benzenesulfonate (1:1), (S)-tianeptine fumarate (1:1), (S)-tianeptine fumarate (2:1), (S)-tianeptine hippurate (1:1), (S)-tianeptine maleate (1:1), (S)-tianeptine maleate (2:1), (S)-tianeptine p-toluenesulfonate (1:1), (S)-tianeptine orotate (1:1), (S)-tianeptine camphorsulfonate (1:1), (S)-tianeptine N-acetyl-L-tyrosinate (1:1), (S)-tianeptine
15 polisterix, (S)-tianeptine: L-DBTA (2:1), (S)-tianeptine sodium, (S)-tianeptine oxalate or (S)-tianeptine hemi-oxalate (2:1).
4. The pharmaceutically acceptable salt of the (S)-enantiomer according to embodiment
20 3, wherein the pharmaceutically acceptable salt is (S)-tianeptine benzenesulfonate (1:1), (S)-tianeptine fumarate (1:1), (S)-tianeptine fumarate (2:1), (S)-tianeptine hippurate (1:1), (S)-tianeptine maleate (1:1), (S)-tianeptine maleate (2:1), (S)-tianeptine p-toluenesulfonate (1:1) or (S)-tianeptine orotate (1:1).
5. The pharmaceutically acceptable salt of the (S)-enantiomer according to embodiment
25 3, wherein the pharmaceutically acceptable salt is (S)-tianeptine camphorsulfonate (1:1), (S)-tianeptine N-acetyl-L-tyrosinate (1:1) or (S)-tianeptine polisterix.

6. The pharmaceutically acceptable salt of the (S)-enantiomer according to embodiment 3, wherein the pharmaceutically acceptable salt is (S)-tianeptine hemi-oxalate (2:1).
7. A zwitterion comprising the zwitterion of the (S)-enantiomer according to embodiment 1 or 2.
8. A co-crystal of the (S)-enantiomer according to embodiment 1 or 2, wherein the (S)-enantiomer or the zwitterion thereof forms a complex with L-tyrosine, L-tryptophan, L-phenylalanine, or another L-amino acid.
9. The co-crystal according to embodiment 8, wherein the complex comprises a 1:1, 1:2, or 2:1 ratio of the (S)-enantiomer or the zwitterion thereof and L-tyrosine, L-tryptophan, L-phenylalanine, or another L-amino acid.
10. The co-crystal according to embodiment 8 or 9, wherein the co-crystal comprises an inorganic monoacid salt of the (S)-enantiomer and a zwitterion of the L-amino acid.
11. The co-crystal according to embodiment 8 or 9, wherein the co-crystal comprises an inorganic monoacid salt of the L-amino acid and the zwitterion of the (S)-enantiomer.
12. The co-crystal according to embodiment 10 or 11, wherein the inorganic monoacid is hydrochloric acid (HCl).
13. An ester of the (S)-enantiomer according to embodiment 1 or 2, wherein the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof.
14. The ester of the (S)-enantiomer according to embodiment 13, wherein the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof.

15. The ester of the (S)-enantiomer according to embodiment 13 or 14, wherein the ester of the (S)-enantiomer is the methyl ester of the (S)-enantiomer, the ethyl ester of the (S)-enantiomer, or another C₁-C₆ alkyl ester of the (S)-enantiomer or a pharmaceutically acceptable salt of any of them.
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16. An amide of the (S)-enantiomer according to embodiment 1 or 2, wherein the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof.
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17. The amide of the (S)-enantiomer according to embodiment 16, wherein the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof.
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18. The amide of the (S)-enantiomer according to embodiment 13 or 14, wherein the amide of the (S)-enantiomer is a simple amide or a C₁-C₆ alkyl amide optionally substituted with at least one hydroxyl or a pharmaceutically acceptable salt of either.
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19. The (S)-enantiomer of deuterated 7-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl-11-d)amino)heptanoic acid (11-D-(S)-enantiomer of tianeptine) of the general Formula (IIa) or the zwitterion thereof of Formula (IIb) or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, or a mixture of two or more of these species, wherein deuterium replaces hydrogen at the 11- position, and wherein the 11-D-(S)-enantiomer or zwitterion or pharmaceutically acceptable salt thereof are characterized by comprising $\leq$ about 2% of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of the 11-D-(R)-enantiomer.
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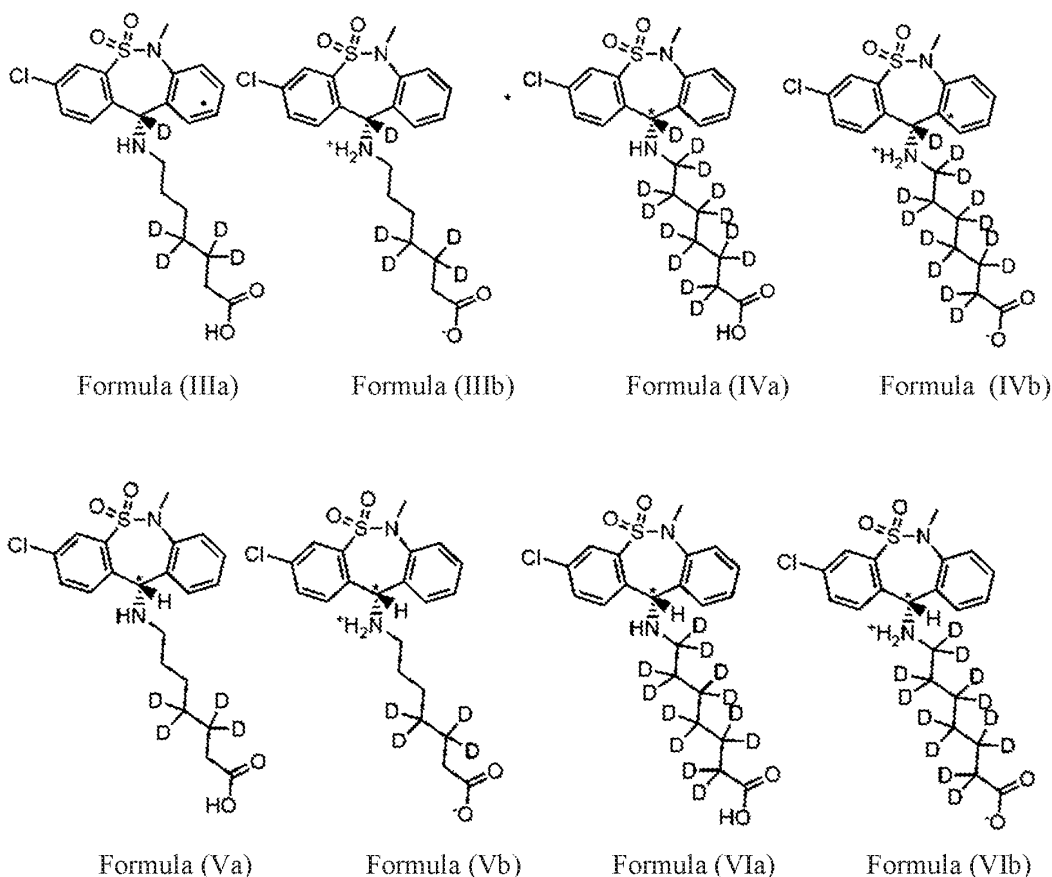


Formula (IIIa)



Formula (IIIb).

20. The (S)-enantiomer according to embodiment 19, wherein the 11-D-(S)-enantiomer, the zwitterion or pharmaceutically acceptable salt of the 11-D-(S)-enantiomer are characterized by comprising $\leq$ about 0.1% of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer.
21. The (S)-enantiomer according to embodiment 19 or 20, wherein the 11-D-(S)-enantiomer or the zwitterion or pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is characterized by reduced racemization at position 11 as compared to the (S)-enantiomer of tianeptine or the zwitterion or a pharmaceutically acceptable salt of that enantiomer.
22. The (S)-enantiomer according to any one of embodiments 19-21, wherein the 11-D-(S)-enantiomer, the zwitterion thereof or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is further deuterated at least one of the 3' positions, and optionally deuterated at other positions on the aminoheptanoic side chain.
23. The (S)-enantiomer according to embodiment 22, wherein the 11-D-(S)-enantiomer is the (S)-enantiomer of 3', 3', 4', 4', 11- pentadeuterotianeptine of Formula (IIIa) or the zwitterion thereof of Formula (IIIb); the (S)-enantiomer of 2', 2', 3', 3', 4', 4', 5', 5', 6', 6', 7', 7', 11-tridecadeuterotianeptine of the general Formula (IVa) or the zwitterion thereof of Formula (IVb); the (S)-enantiomer of 3', 3', 4', 4', tetradeuterotianeptine of Formula (Va) or the zwitterion thereof of Formula (Vb); or the (S)-enantiomer of 2', 2', 3', 3', 4', 4', 5', 5', 6', 6', 7', 7', dodecadeuterotianeptine of the general formula (VIa) or the zwitterion thereof of Formula (VIb).



24. A pharmaceutically acceptable salt of the 11-D-(S)-enantiomer according to any one of embodiments 19-23, wherein the pharmaceutically acceptable salt is 11-D-(S)-tianeptine benzenesulfonate (1:1), 11-D-(S)-tianeptine fumarate (1:1), 11-D-(S)-tianeptine fumarate (2:1), 11-D-(S)-tianeptine hippurate (1:1), 11-D-(S)-tianeptine maleate (1:1), 11-D-(S)-tianeptine maleate (2:1), 11-D-(S)-tianeptine p-toluenesulfonate (1:1), 11-D-(S)-tianeptine orotate (1:1), 11-D-(S)-tianeptine camphorsulfonate (1:1), 11-D-(S)-tianeptine N-acetyl-L-tyrosinate (1:1), 11-D-(S)-tianeptine polisterix, 11-D-(S)-tianeptine: L-DBTA (2:1), 11-D-(S)-tianeptine sodium, 11-D-(S)-tianeptine oxalate or 11-D-(S)-tianeptine hemi-oxalate (2:1).
25. The pharmaceutically acceptable salt of the 11-D-(S)-enantiomer according to embodiment 24, wherein the pharmaceutically acceptable salt is 11-D-(S)-tianeptine benzenesulfonate (1:1), 11-D-(S)-tianeptine fumarate (1:1), 11-D-(S)-tianeptine fumarate (2:1), 11-D-(S)-tianeptine hippurate (1:1), 11-D-(S)-tianeptine maleate (1:1),

11-D-(S)-tianeptine maleate (2:1), 11-D-(S)-tianeptine p-toluenesulfonate (1:1) or 11-D-(S)-tianeptine orotate (1:1).

- 5 26. The pharmaceutically acceptable salt of the 11-D-(S)-enantiomer according to embodiment 24, wherein the pharmaceutically acceptable salt is 11-D-(S)-tianeptine camphorsulfonate (1:1), 11-D-(S)-tianeptine N-acetyl-L-tyrosinate (1:1) or 11-D-(S)-tianeptine polisterix.
- 10 27. The pharmaceutically acceptable salt of the 11-D-(S)-enantiomer according to embodiment 24, wherein the pharmaceutically acceptable salt is 11-D-(S)-tianeptine hemi-oxalate (2:1).
- 15 28. A zwitterion comprising the zwitterion of the 11-D-(S)-enantiomer according to any one of embodiments 19-23.
29. A co-crystal of the 11-D-(S)-enantiomer according to any one of embodiments 19-23 or 26, wherein the 11-D-(S)-enantiomer or the zwitterion thereof forms a complex with L- tyrosine, L-tryptophan, L-phenylalanine, or another L-amino acid.
- 20 30. The co-crystal according to embodiment 29, wherein the complex comprises a 1:1, 1:2, or 2:1 ratio of the 11-D-(S)-enantiomer or the zwitterion thereof and L- tyrosine, L-tryptophan, L-phenylalanine, or another L-amino acid.
- 25 31. The co-crystal according to embodiment 29 or 30, wherein the co-crystal comprises an inorganic monoacid salt of the 11-D-(S)-enantiomer and a zwitterion of the L-amino acid.
- 30 32. The co-crystal according to embodiment or 29 or 30, wherein the co-crystal comprises an inorganic monoacid salt of the L-amino acid and the zwitterion of the 11-D-(S)-enantiomer.
33. The co-crystal according to embodiment 31 or 32, wherein the inorganic monoacid is hydrochloric acid (HCl).

34. An ester of the (S)-enantiomer according to any one of embodiments 19-23, wherein the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.
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35. The ester of the (S)-enantiomer according to embodiment 34, wherein the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.
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36. The ester of the (S)-enantiomer according to embodiment 34 or 35, wherein the ester of the 11-D-(S)-enantiomer is the methyl ester of the 11-D-(S)-enantiomer, the ethyl ester of the 11-D-(S)-enantiomer, or another C₁-C₆ alkyl ester of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt of any of them.
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37. An amide of the (S)-enantiomer according to any one of embodiments 19-23, wherein the amide of the 11-D-(S)-enantiomer or the pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the amide of the 11-D-(R)-enantiomer or the pharmaceutically acceptable salt thereof.
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38. The amide of the (S)-enantiomer according to embodiment 37, wherein the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.
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39. The amide of the (S)-enantiomer according to embodiment 37 or 38, wherein the amide of the (S)-enantiomer is a simple amide or a C₁-C₆ alkyl amide optionally substituted with at least one hydroxyl or a pharmaceutically acceptable salt of either.
- 30
40. A pharmaceutically acceptable acid salt of the (S)-enantiomer or the 11-D-(S)-enantiomer according to any one of embodiments 1, 2 or 19-23, wherein the nitrogen atom in the sidechain attached to Carbon-11 (C-11) is 100% protonated, the 100% protonated salt being less sensitive to air oxidation in solid or solution forms when

compared to the (S)-enantiomer, 11-D-(S)-enantiomer, the zwitterion of either or the sodium salts of either.

41. A pharmaceutical composition comprising the (S)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or zwitterion thereof according to any one of embodiments 1-12, or an ester of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of embodiments 13-15, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of embodiments 16-18 and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises $\leq$ about 2% of the (R)-enantiomer of tianeptine, the zwitterion thereof or a pharmaceutically acceptable salt of the (R)-enantiomer, or a co-crystal of the (R)-enantiomer or zwitterion thereof, or the ester of the (R)-enantiomer or a pharmaceutically acceptable salt thereof, or the amide of the (R)-enantiomer or a pharmaceutically acceptable salt thereof.
42. The pharmaceutical composition of claim 41, wherein the pharmaceutical composition comprises $\leq$ about 0.1% of the (R)-enantiomer of tianeptine, the zwitterion thereof or a pharmaceutically acceptable salt of the (R)-enantiomer, or a co-crystal of the (R)-enantiomer or zwitterion thereof, or the ester of the (R)-enantiomer or a pharmaceutically acceptable salt thereof, or the amide of the (R)-enantiomer or a pharmaceutically acceptable salt thereof.
43. A pharmaceutical composition comprising the 11-D-(S)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, or a co-crystal of the 11-D-(S)-enantiomer or zwitterion thereof according to any one of embodiments 19-33, or an ester of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of embodiments 34-36, or an amide of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of embodiments 37-39 and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises $\leq$ about 2% of the 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(R)-enantiomer, or a co-crystal of the 11-D-(R)-enantiomer or zwitterion thereof, or

an ester of the 11-D-(R)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the 11-D-(R)-enantiomer or a pharmaceutically acceptable salt thereof.

- 5 44. The pharmaceutical composition according to embodiment 43, wherein the pharmaceutical composition comprises $\leq$ about 0.1% of the 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(R)-enantiomer, or a co-crystal of the 11-D-(R)-enantiomer or zwitterion thereof, or the ester of the (R)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the 11-D-(R)-enantiomer or a pharmaceutically acceptable salt thereof.
- 10 45. The pharmaceutical composition according to any one of embodiments 41-44, wherein the composition is in the form of a tablet, a thin film, a powder, a caplet, a capsule, a soft gel, a suppository, a nasal spray, an oral spray or a lung spray.
- 15 46. The pharmaceutical composition according to any one of embodiments 41-45, wherein the composition is formulated for immediate release, controlled release, sustained release, extended release, or slow release of the (S)-enantiomer or the 11-D-(S)-enantiomer, or the zwitterion or an ester or an amide of either, or a pharmaceutically acceptable salt of either, or a co-crystal of the (S)-enantiomer or the 11-D-(S)-enantiomer or the zwitterion of either.
- 20 47. The pharmaceutical composition according to embodiment 46, wherein the composition is formulated for controlled release of the (S)-enantiomer or the 11-D-(S)-enantiomer, or the zwitterion or an ester or an amide of either, or a pharmaceutically acceptable salt of either, or a co-crystal of the (S)-enantiomer or the 11-D-(S)-enantiomer or the zwitterion of either.
- 25 48. A pharmaceutical composition comprising a mixture of two or more pharmaceutically acceptable salts or co-crystals of the (S)-enantiomer or the 11-D-(S)-enantiomer according to any one of embodiments 41-47, wherein the mixture is characterized by an enhanced extended release when administered orally as compared to administering a composition comprising a single pharmaceutically acceptable salt or co-crystal of the (S)-enantiomer or the 11-D-(S)-enantiomer according to any one of embodiments 41-47.
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49. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of embodiments 1-18, or a pharmaceutical composition according to any one of embodiments 41, 42 or 45-48.
50. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of embodiments 19-39, or a pharmaceutical composition according to any one of embodiments 43-48.
51. The method according to embodiment 49 or 50, wherein the disease, disorder or condition is selected from the group consisting of a central nervous system (CNS) disorder, inflammatory disease, autoimmune disease, infectious illness, a hearing loss condition, ocular disease, musculoskeletal disease, metabolic disease, mitochondrial disease, hypertriglyceridemia, cancer, menopause and chronic overlapping pain conditions (COPCs), and psychological, physical, metabolic or hormonal stress and COPCs.
52. The method according to embodiment 51, wherein the disease, disorder or condition is a CNS disorder.

53. The method according to embodiment 52, wherein the CNS disorder is selected from the group consisting of a mood disorder, a trauma and stress-related disorder, an anxiety disorder, obsessive-compulsive disorder, a neurodegenerative or neuroinflammatory disorder, a neurodevelopmental disorder, a leukodystrophy and CNS oxidative stress.
54. The method according to embodiment 53, wherein the mood disorder is a depressive disorder, a bipolar disorder, or a substance-induced disorder.
55. The method according to embodiment 54, wherein the depressive disorder is major depressive disorder (MDD).
56. The method according to embodiment 53, wherein the trauma and stress-related disorder is post-traumatic stress disorder (PTSD), acute stress disorder (ASD), adjustment disorder, or reactive attachment disorder.
57. The method according to embodiment 53, wherein the anxiety disorder is panic disorder, generalized anxiety disorder (GAD), a specific phobia, agoraphobia or social phobia.
58. The method according to embodiment 53, wherein the neurodegenerative or neuroinflammatory disorder is Mild Cognitive Impairment, Alzheimer's Disease, dementia, Parkinson's disease, Huntington's disease, multiple sclerosis (MS) amyotrophic lateral sclerosis (ALS), traumatic brain injury, neuromyelitis optica, myasthenia gravis, autoimmune encephalitis, prion disease, transverse myelitis, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), vanishing white matter disease, childhood ataxia with CNS hypo myelination, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease, kuru or dementia.
59. The method according to embodiment 53, wherein the neurodevelopmental disorder is attention-deficit/ hyperactivity disorder (ADHD), schizophrenia, Prader-Will Syndrome (including hyperphagia and other symptoms (*e.g.*, depression and anxiety) or autism.

60. The method according to embodiment 53, wherein the leukodystrophy is leukoencephalopathy, a hypomyelinating or demyelinating disease, an intellectual disability syndrome, a cognitive impairment, a glial cell dysfunction or a brain injury.
- 5 61. The method according to embodiment 60, wherein the cognitive impairment is age-related cognitive impairment, age-related cognitive decline (ARCD), age-associated memory impairment (AAMI), cognitive impairment associated with Mild Cognitive Impairment, prodromal Alzheimer's Disease or Alzheimer's Disease, prodromal fronto-temporal dementia (FTD) or FTD, prodromal posterior cortical atrophy (PCA) or PCA, cognitive impairment associated with schizophrenia, a drug-induced cognitive disorder, radiotherapy-induced cognitive dysfunction, space travel-related cognitive decline, or cognitive deficit and neuropathic pain associated with diabetes mellitus.
- 10 62. The method of embodiment 60, wherein the drug-induced cognitive disorder is corticosteroid-induced cognitive dysfunction, doxorubicin-induced cognitive dysfunction, chemotherapy-induced cognitive dysfunction, alcohol-induced cognitive dysfunction, or substance-induced cognitive dysfunction.
- 15 63. The method according to embodiment 60, wherein the brain injury is a traumatic brain injury, hypoxia-induced brain injury, toxin-induced brain injury, stroke or reperfusion injury following ischemic stroke.
- 20 64. The method according to embodiment 51, wherein the inflammatory disease is asthma, postoperative cognitive dysfunction, arthritis, systemic lupus erythematosus (SLE), myasthenia gravis, diabetes, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, ankylosing spondylitis, psoriasis, Sjogren's syndrome, vasculitis, glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, ichthyosis, Graves' ophthalmopathy, inflammatory bowel disease, Addison's disease, vitiligo, acne vulgaris, celiac disease, chronic prostatitis, pelvic inflammatory disease, reperfusion injury, sarcoidosis, transplant rejection, interstitial cystitis, atherosclerosis or atopic dermatitis.
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65. The method according to embodiment 51, wherein the autoimmune disease is Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune orchitis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Balo disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammaglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neonatal Lupus, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry

- Romberg syndrome, Pars planitis (peripheral uveitis), Parsonnage -Turner syndrome, Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndrome type I, Polyglandular syndrome type II, Polyglandular syndrome type III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, Vogt-Koyanagi-Harada Disease, or Wegener's granulomatosis (or Granulomatosis with Polyangiitis (GPA)).
66. The method according to embodiment 51, wherein the infectious illness is a viral infection or post-viral condition.
67. The method according to embodiment 51, wherein the hearing loss condition is mitochondrial nonsyndromic hearing loss and deafness, hair cell death, age-related hearing loss, noise-induced hearing loss, genetic or inherited hearing loss, hearing loss experienced as a result of ototoxic exposure, hearing loss resulting from disease, or hearing loss resulting from trauma.
68. The method according to embodiment 51, wherein the ocular disease is cataracts, glaucoma, endoplasmic reticulum (ER) stress, autophagy deficiency, age-related macular degeneration (AMD), or diabetic retinopathy.
69. The method according to embodiment 51, wherein the musculoskeletal disease is muscular dystrophy, multiple sclerosis, amyotrophic lateral sclerosis (ALS), primary

- lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, spinal muscular atrophy, progressive spinobulbar muscular atrophy, spinal cord spasticity, spinal muscle atrophy, myasthenia gravis, neuralgia, fibromyalgia, Machado-Joseph disease, cramp fasciculation syndrome, Freidrich's ataxia, a muscle wasting disorder, an inclusion body myopathy, motor neuron disease, or paralysis.
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70. The method according to embodiment 51, wherein the metabolic disease is non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver
- 10 fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes, phenylketonuria, proliferative retinopathy, and Keams-Sayre disease.
71. The method according to embodiment 51, wherein the mitochondrial disease is Barth syndrome, chronic progressive external ophthalmoplegia (cPEO), Keams-Sayre
- 15 syndrome (KSS), Leigh syndrome, mitochondrial DNA depletion syndromes (MDDS), mitochondrial encephalomyopathy, mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), myoclonus epilepsy with ragged red fibers (MERRF), neuropathy, ataxia, retinitis pigmentosa (NARP), Leber's hereditary optic neuropathy (LHON), and Pearson syndrome.
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72. The method according to embodiment 51, wherein the cancer is glioblastoma or glioma.
73. A method of treating a disease, disorder or condition modulated by, exacerbated by,
- 25 or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, in a subject who has experienced high stress, comprising administering to the subject a therapeutically effective amount of the (S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or a co-crystal of the (S)-
- 30 enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of embodiments 1-18, or a pharmaceutical composition according to any one of embodiments 41, 42 or 45-48.

74. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, in a subject who has experienced high stress, comprising administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of embodiments 19-39, or a pharmaceutical composition according to any one of embodiments 43-48.
75. The method according to embodiment 73 or 74, wherein the stress is caused by adversity early in life or by childhood trauma.
76. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, while reducing μ -opioid receptor agonism associated with treatment with racemic tianeptine, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 1-18, or a pharmaceutical composition according to any one of embodiments 41, 42 or 45-48.
77. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, while reducing μ -opioid receptor agonism associated with treatment with racemic tianeptine, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the 11-D-(S)-enantiomer or a co-crystal of the 11-

D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of embodiments 19-39, or a pharmaceutical composition according to any one of embodiments 43-48.

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78. The method according to any one of embodiments 49-77 or 104-124, wherein the (S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or a pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof or the 11-D-(S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, the co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or the ester of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt thereof, or the amide of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt thereof or the pharmaceutical composition is administered one or more times daily.

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79. The method according to embodiment 78, wherein the (S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof or the 11-D-(S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, the co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof or the pharmaceutical composition is administered once daily.

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80. The method according to any one of embodiments 49-77 or 104-124, wherein the (S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof or the 11-D-(S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, the co-crystal of the 11-D-(S)-enantiomer or the zwitterion

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thereof, or the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition is administered parenterally, orally, sublingually, buccally, inhalationally, palatally, transdermally, rectally, or vaginally.

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81. The method according to embodiment 80, wherein the (S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof or the 11-D-(S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, the co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition is administered orally.

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82. The method according to embodiment 80, wherein the (S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof or the 11-D-(S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, the co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition is administered inhalationally.

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83. The method according to any one of embodiments 49-82 or 104-124, wherein the (S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof or the 11-D-(S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, the co-crystal of the 11-D-(S)-enantiomer or the zwitterion

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thereof, or the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof or the pharmaceutical composition is administered sequentially or concurrently with one or more additional therapeutic agents selected from the group consisting of an antidepressant, an anticonvulsant, an anti-anxiety agent, an antipsychotic agent, a cholinesterase inhibitor, an N-methyl-D-aspartate (NMDA) receptor antagonist, a 5HT2 modulator, a corticosteroid, an anti-amyloid agent, an anti-tau agent and a chemotherapeutic agent.

84. The method according to any one of embodiments 49-82 or 104-124, wherein the (S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof or the 11-D-(S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, the co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof or the pharmaceutical composition is administered as part of a treatment regime also including psychotherapeutic intervention.

85. A method of reducing the potential racemization of the (S)-enantiomer, the zwitterion thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 1-19, comprising the step of deuterating the (S)-enantiomer, the zwitterion thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof at position C-11.

86. A method of producing the (S)-enantiomer of tianeptine according to embodiment 1 or 2, said method comprising the steps of:

- (i) resolving a racemic or other mixture of the (S)- and (R)-enantiomers of a chiral amine tianeptine intermediate, which mixtures are characterized by $\geq 0.1\%$ of the (R)-enantiomer of the chiral amine tianeptine intermediate by enantioselective crystallization using a conformer selective for the (S)-enantiomer in a solvent mixture to produce an (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer, the (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer being crystallized from the solvent mixture, and being characterized in that it comprises $\leq 2\%$ of the (R)-amine tianeptine intermediate: (R)-enantiomer-selective-conformer;
- (ii) reacting the (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer with a 7-bromoheptanoate alkyl ester to produce an (S)-tianeptine alkyl ester intermediate:(S)-enantiomer-selective-conformer;
- (iii) reacting the (S)-tianeptine alkyl ester intermediate:(S)-enantiomer-selective-conformer with a base to produce the (S)-tianeptine alkyl ester intermediate and
- (iv) saponifying the (S)-tianeptine alkyl ester intermediate to produce the (S)-enantiomer of tianeptine, which tianeptine comprises $\leq 2\%$ of the (R) enantiomer of tianeptine.
87. The method according to embodiment 86, wherein the (S)-enantiomer of tianeptine is characterized by $\leq 0.1\%$ of the (R)-enantiomer of tianeptine.
88. The method according to embodiment 86, wherein the chiral amine tianeptine intermediate is 3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-amine, the (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer is (11S)- 3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-amine:(S)-enantiomer-selective-conformer and the (S)-tianeptine ester intermediate:(S)-enantiomer-selective-conformer is ethyl 7-[[[(11S)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate:(S)-enantiomer-selective-conformer.
89. A method of producing the 11-D-(S)-tianeptine according to embodiment 19 or 20, said method comprising the steps of:

- (i) resolving a racemic or other mixture of the (S)- and (R)-enantiomers of a chiral amine 11-D-tianeptine intermediate, which mixtures are characterized by $\geq 0.1\%$ of the (R)-enantiomer of the chiral amine 11-D-tianeptine intermediate by enantioselective crystallization using a conformer selective for the (S)-enantiomer in a solvent mixture to produce an (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer, the (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer being crystallized from the solvent mixture, and being characterized in that it comprises $\leq 2\%$ of the (R)-amine 11-D-tianeptine intermediate:(R)-enantiomer-selective-conformer -conformer;
- (ii) reacting the (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer with a 7-bromoheptanoate alkyl ester to produce an 11-D-(S)-tianeptine alkyl ester intermediate:(S)-enantiomer-selective-conformer;
- (iii) reacting the 11-D-(S)-tianeptine alkyl ester intermediate:(S)-enantiomer-selective-conformer with a base to produce the 11-D-(S)-tianeptine alkyl ester intermediate and
- (iv) saponifying the 11-D-(S)-tianeptine alkyl ester intermediate to produce the 11-D-(S)-enantiomer of tianeptine, which 11-D-(S)-tianeptine comprises $\leq 2\%$ of the (R) enantiomer of 11-D-tianeptine.
90. The method according to embodiment 89, wherein the (S)-enantiomer of 11-D-tianeptine is characterized by $\leq 0.1\%$ of the (R)-enantiomer of 11-D-tianeptine.
91. The method according to embodiment 89, wherein the chiral amine 11-D-tianeptine intermediate is 11-amino-3-chloro-6-methyl-6,11-dihydrodibenzo[*c,f*][1,2]thiazepine 5,5-dioxide-11-*d*, the (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer is (S)-11-amino-3-chloro-6-methyl-6,11-dihydrodibenzo[*c,f*][1,2]thiazepine 5,5-dioxide-11-*d*:(S)-enantiomer-selective-conformer and the 11-D-(S)-tianeptine alkyl ester intermediate:(S)-enantiomer-selective-conformer is ethyl (S)-7-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[*c,f*][1,2]thiazepine-11-yl-11-*d*)amino)heptanoate:(S)-enantiomer-selective-conformer.

92. A method of producing the (S)-enantiomer of tianeptine or zwitterion thereof according to embodiment 1 or 2, said method comprising the steps of:
- (i) resolving a racemic or other mixture of the (S)- and (R)-enantiomers of a tianeptine alkyl ester, which mixtures are characterized by $\geq 0.1\%$ of the (R)-enantiomer of a tianeptine alkyl ester by enantioselective crystallization using conformer selective for the (R)-enantiomer in a solvent mixture to produce an (R)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer and an (S)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer, crystallizing and separating the (R)-tianeptine alkyl ester from the solvent mixture, the (S)-tianeptine alkyl ester remaining in the solvent mixture and being characterized in that it comprises $\leq 2\%$ of the (R)-tianeptine alkyl ester;
 - (ii) hydrolyzing the (S)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer with a strong acid to produce the (S)-tianeptine acid salt, which tianeptine acid salt comprises $\leq 2\%$ of the (R)-tianeptine acid salt; and
 - (iii) neutralizing the (S)-tianeptine acid salt with a base to produce the zwitterion of the (S)-enantiomer of tianeptine.
93. A method of producing the 11-D-(S)-enantiomer or zwitterion thereof according to embodiment 19 or 20, said method comprising the steps of:
- (i) resolving a racemic or other mixture of the (S)- and (R)-enantiomers of an 11-D-tianeptine alkyl ester, which mixtures are characterized by $\geq 0.1\%$ of the (R)-enantiomer of an 11-D-tianeptine alkyl ester by enantioselective crystallization using a conformer selective for the (R)-enantiomer in a solvent mixture to produce an 11-D-(R)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer and an 11-D-(S)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer, crystallizing and separating the 11-D-(R)-tianeptine alkyl ester from the solvent mixture, the 11-D-(S)-tianeptine alkyl ester remaining in the solvent mixture and being characterized in that it comprises $\leq 2\%$ of the 11-D-(R)-tianeptine alkyl ester;
 - (ii) hydrolyzing the 11-D-(S)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer with a strong acid to produce the 11-D-(S)-tianeptine acid salt, which 11-D-tianeptine acid salt comprises $\leq 2\%$ of the 11-D-(R)-tianeptine acid salt; and

- (iii) neutralizing the 11-D-(S)-tianeptine acid salt with a base to produce the zwitterion of the 11-D-(S)-enantiomer of tianeptine.
94. The method according to any one of embodiments 86, 89, 92 or 93, wherein the tianeptine alkyl ester is a methyl ester, an ethyl ester or any other C₁-C₆ alkyl ester.
95. The method according to any one of embodiments 86, 89, 92 or 93, wherein the enantioselective crystallization comprises using a conformer selected from the group consisting of L-dibenzoyl tartaric acid (DBTA), D-DBTA, Di-o-toluoyl-L-tartaric acid (L-D(2-Me)BTA), D-D(2-Me)BTA, other DBTA derivatives, (S)-1,1'-Bi-2-naphthol-2,2'-diyl hydrogen phosphate, (R)-1,1'-Bi-2-naphthol-2,2'-diyl hydrogen phosphate, (S)-(R)-mandelic acid, (R)-(S)-mandelic acid, (S)-(S)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid, (R)-(S)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid, (1S)-(R)-10-camphorsulfonic acid and (1R)-(R)-10-camphorsulfonic acid.
96. The method according to any one of embodiments 86, 89, 92 or 93, wherein the solvent comprises a mixture of benzene, acetone and trichloromethane.
97. The method according to embodiment 96, wherein the solvent comprises benzene, acetone and trichloromethane in a ratio of 2:1:1.
98. The method according to any one of embodiments 86, 89, 92 or 93, wherein the enantioselective crystallization of the (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer, the (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer, (R)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer or the 11-D-(R)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer comprises the step of slow evaporation of the solvent mixture.
99. The method according to any one of embodiments 86, 89, 92 or 93, wherein the enantioselective crystallization is repeated to increase the enantiomeric purity or chiral purity of the resolved (S)-amine tianeptine intermediate, the (S)-amine 11-D-tianeptine intermediate, the (S)-tianeptine methyl ester or 11-D-(S)-tianeptine methyl ester.

100. The method according to embodiment 92 or 93, wherein the wherein the strong acid is selected from the group consisting of hydrochloric acid, sulfuric acid and phosphoric acid.
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101. The method according to any one of embodiments 86, 89, 92 or 93, wherein the base is sodium bicarbonate, sodium carbonate, potassium bicarbonate or sodium hydroxide.
- 10
102. The method according to any one of embodiments 86, 89, 92 or 93, wherein resolving the racemic or other mixture is performed using high performance liquid chromatography (HPLC).
- 15
103. The method according to any one of embodiments 86, 89, 92 or 93, wherein resolving the racemic or other mixture is performed using supercritical fluid chromatography with a chiral column.
- 20
104. A method of treating a disease, disorder or condition selected from the group consisting of a central nervous system (CNS) disorder, inflammatory disease, autoimmune disease, infectious illness, a hearing loss condition, ocular disease, musculoskeletal disease, metabolic disease, mitochondrial disease, hypertriglyceridemia, cancer, menopause and chronic overlapping pain conditions (COPCs), and psychological, physical, metabolic or hormonal stress and COPCs, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 1-18, or a pharmaceutical composition according to any one of embodiments 41, 42 or 45-48 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or
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pharmaceutically acceptable salt thereof according to any one of embodiments 19-39, or a pharmaceutical composition according to any one of embodiments 43-48.

- 5 105. The method according to embodiment 104, wherein the CNS disorder is selected from the group consisting of a mood disorder, a trauma and stress-related disorder, an anxiety disorder, obsessive-compulsive disorder, a neurodegenerative or neuroinflammatory disorder, a neurodevelopmental disorder, a leukodystrophy and CNS oxidative stress.
- 10 106. The method according to embodiment 105, wherein the mood disorder is a depressive disorder, a bipolar disorder, or a substance-induced disorder.
- 15 107. The method according to embodiment 106, wherein the depressive disorder is major depressive disorder (MDD).
108. The method according to embodiment 105, wherein the trauma and stress-related disorder is post-traumatic stress disorder (PTSD), acute stress disorder (ASD), adjustment disorder, or reactive attachment disorder.
- 20 109. The method according to embodiment 105, wherein the anxiety disorder is panic disorder, generalized anxiety disorder (GAD), a specific phobia, agoraphobia or social phobia.
- 25 110. The method according to embodiment 105, wherein the neurodegenerative or neuroinflammatory disorder is Mild Cognitive Impairment, Alzheimer's Disease, dementia, Parkinson's disease, Huntington's disease, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), traumatic brain injury, neuromyelitis optica, myasthenia gravis, autoimmune encephalitis, prion disease, transverse myelitis, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), vanishing white matter disease, childhood ataxia with CNS hypo myelination, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease, kuru or dementia.
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111. The method according to embodiment 105, wherein the neurodevelopmental disorder is attention-deficit/ hyperactivity disorder (ADHD), schizophrenia, Prader-Will Syndrome (including hyperphagia and other symptoms (*e.g.*, depression and anxiety) or autism.
- 5 112. The method according to embodiment 105, wherein the leukodystrophy is leukoencephalopathy, a hypomyelinating or demyelinating disease, an intellectual disability syndrome, a cognitive impairment, a glial cell dysfunction or a brain injury.
- 10 113. The method according to embodiment 112, wherein the cognitive impairment is age-related cognitive impairment, age-related cognitive decline (ARCD), age-associated memory impairment (AAMI), cognitive impairment associated with Mild Cognitive Impairment, prodromal Alzheimer's Disease or Alzheimer's Disease, prodromal fronto-temporal dementia (FTD) or FTD, prodromal posterior cortical atrophy (PCA) or PCA, cognitive impairment associated with schizophrenia, a drug-induced cognitive disorder, radiotherapy-induced cognitive dysfunction, space travel-related cognitive decline, or cognitive deficit and neuropathic pain associated with diabetes mellitus.
- 15 114. The method of embodiment 113, wherein the drug-induced cognitive disorder is corticosteroid-induced cognitive dysfunction, doxorubicin-induced cognitive dysfunction, chemotherapy-induced cognitive dysfunction, alcohol-induced cognitive dysfunction, or substance-induced cognitive dysfunction.
- 20 115. The method according to embodiment 112, wherein the brain injury is a traumatic brain injury, hypoxia-induced brain injury, toxin-induced brain injury, stroke or reperfusion injury following ischemic stroke.
- 25 116. The method according to embodiment 104, wherein the inflammatory disease is asthma, postoperative cognitive dysfunction, arthritis, systemic lupus erythematosus (SLE), myasthenia gravis, diabetes, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, ankylosing spondylitis, psoriasis, Sjogren's syndrome, vasculitis, glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, ichthyosis,
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Graves' ophthalmopathy, inflammatory bowel disease, Addison's disease, vitiligo, acne vulgaris, celiac disease, chronic prostatitis, pelvic inflammatory disease, reperfusion injury, sarcoidosis, transplant rejection, interstitial cystitis, atherosclerosis or atopic dermatitis.

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117. The method according to embodiment 104, wherein the autoimmune disease is Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune orchitis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Balo disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammaglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor

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- Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neonatal Lupus, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry
- 5 Romberg syndrome, Pars planitis (peripheral uveitis), Parsonnage -Turner syndrome, Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndrome type I, Polyglandular syndrome type II, Polyglandular syndrome type III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy
- 10 syndrome, primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome,
- 15 Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated
- 20 connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, Vogt-Koyanagi-Harada Disease, or Wegener's granulomatosis (or Granulomatosis with Polyangiitis (GPA)).
118. The method according to embodiment 104, wherein the infectious illness is a viral
- 25 infection or a post-viral condition.
119. The method according to embodiment 104, wherein the hearing loss condition is mitochondrial nonsyndromic hearing loss and deafness, hair cell death, age-related hearing loss, noise-induced hearing loss, genetic or inherited hearing loss, hearing loss
- 30 experienced as a result of ototoxic exposure, hearing loss resulting from disease, or hearing loss resulting from trauma.

120. The method according to embodiment 104, wherein the ocular disease is cataracts, glaucoma, endoplasmic reticulum (ER) stress, autophagy deficiency, age-related macular degeneration (AMD), or diabetic retinopathy.
- 5 121. The method according to embodiment 104, wherein the musculoskeletal disease is muscular dystrophy, multiple sclerosis, amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, spinal muscular atrophy, progressive spinobulbar muscular atrophy, spinal cord spasticity, spinal muscle atrophy, myasthenia gravis, neuralgia, 10 fibromyalgia, Machado-Joseph disease, cramp fasciculation syndrome, Freidrich's ataxia, a muscle wasting disorder, an inclusion body myopathy, motor neuron disease, or paralysis.
122. The method according to embodiment 104, wherein the metabolic disease is non- 15 alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes, phenylketonuria, proliferative retinopathy, and Keams-Sayre disease.
123. The method according to embodiment 104, wherein the mitochondrial disease is Barth 20 syndrome, chronic progressive external ophthalmoplegia (cPEO), Keams-Sayre syndrome (KSS), Leigh syndrome, mitochondrial DNA depletion syndromes (MDDS), mitochondrial encephalomyopathy, mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), myoclonus epilepsy with ragged red fibers (MERRF), neuropathy, ataxia, retinitis pigmentosa (NARP), Leber's hereditary optic neuropathy 25 (LHON), and Pearson syndrome.
124. The method according to embodiment 104, wherein the cancer is glioblastoma or glioma.
- 30 125. A method of enhancing neurite outgrowth comprising administering to a subject in need thereof the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 1-18, or a pharmaceutical composition

according to any one of embodiments 41, 42 or 45-48 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 19-39, or a pharmaceutical composition according to any one of embodiments 43-48.

126. The method according to embodiment 125, wherein the neurite outgrowth is observed in a glutamatergic neuron.

127. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with excessive levels of metal ions in circulation, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 1-18, or a pharmaceutical composition according to any one of embodiments 41, 42 or 45-48 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 19-39, or a pharmaceutical composition according to any one of embodiments 43-48.

128. The method according to claim 127, wherein the metal ion is iron or copper.

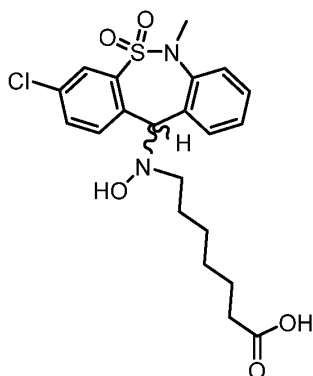
129. The method according to embodiment 127 or 128, wherein the disease, disorder or condition is selected from the group consisting of a central nervous system (CNS) disorder, inflammatory disease, autoimmune disease, infectious illness, a hearing loss condition, ocular disease, musculoskeletal disease, metabolic disease, mitochondrial disease, hypertriglyceridemia, cancer, menopause and chronic overlapping pain

conditions (COPCs), and psychological, physical, metabolic or hormonal stress and COPCs.

- 5 130. The method according to embodiment 129, wherein the CNS disorder is selected from the group consisting of a mood disorder, a trauma and stress-related disorder, an anxiety disorder, obsessive-compulsive disorder, a neurodegenerative or neuroinflammatory disorder, a neurodevelopmental disorder, a leukodystrophy and CNS oxidative stress.
- 10 131. A method of reducing violent or aggressive behavior associated with a CNS disorder, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 1-18, or a pharmaceutical composition according to any one of embodiments 41, 42 or 45-48 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 19-39, or a pharmaceutical composition according to any one of embodiments 43-48.
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- 25 132. A method of reducing the potential of being committed to a psychiatric hospital or being incarcerated due to behavior or actions associated with a CNS disorder, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 1-18, or a pharmaceutical composition according to any one of embodiments 41, 42 or 45-48 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer
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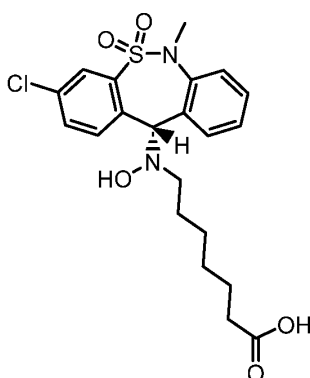
or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 19-39, or a pharmaceutical composition according to any one of embodiments 43-48.

- 5 133. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with high levels of S-nitrosylation of PPAR- β/δ and/or PPAR- γ , comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable
10 salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 1-18, or a pharmaceutical composition according to any one of embodiments 41, 42 or 45-48 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the
15 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of embodiments 19-39, or a pharmaceutical composition according to any one of embodiments 43-48.
- 20 134. The method according to embodiment 133, wherein the disease, disorder or condition is selected from the group consisting of a central nervous system (CNS) disorder, inflammatory disease, autoimmune disease, infectious illness, a hearing loss condition, ocular disease, musculoskeletal disease, metabolic disease, mitochondrial disease, hypertriglyceridemia, cancer, menopause and chronic overlapping pain
25 conditions (COPCs), and psychological, physical, metabolic or hormonal stress and COPCs.
135. The method according to embodiment 134, wherein the CNS disorder is selected from a group consisting of a mood disorder, a trauma and stress-related disorder, an anxiety
30 disorder, obsessive-compulsive disorder, a neurodegenerative or neuroinflammatory disorder, a neurodevelopmental disorder, a leukodystrophy and CNS oxidative stress.
136. N-hydroxy-tianeptine of the Formula (XV) or a pharmaceutically acceptable salt thereof:



Formula (XV).

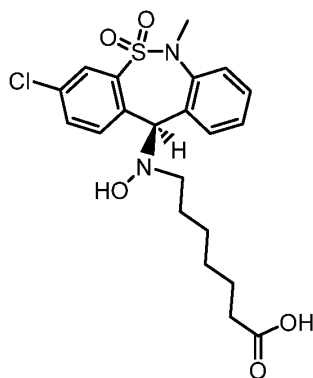
137. The (S)-enantiomer of N-hydroxy-tianeptine (N-hydroxy-(S)-tianeptine) of the
 5 Formula (XVI) or a pharmaceutically acceptable salt thereof, wherein the (S)-
 enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are
 characterized by comprising $\leq$ about 2% of the (R)-enantiomer of N-hydroxy-
 tianeptine or a pharmaceutically acceptable salt of the (R)-enantiomer of N-hydroxy-
 tianeptine:



Formula (XVI).

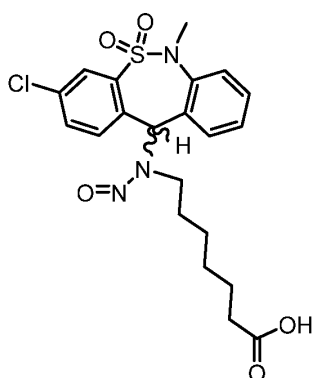
138. The (S)-enantiomer of N-hydroxy-tianeptine according to embodiment 137, wherein
 the (S)-enantiomer or pharmaceutically acceptable salt of the (S)-enantiomer N-
 15 hydroxy-tianeptine are characterized by comprising $\leq$ about 0.1% of the (R)-
 enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that
 enantiomer.

139. The (R)-enantiomer of N-hydroxy-tianeptine (N-hydroxy-(R)-tianeptine) of the Formula (XVII) or a pharmaceutically acceptable salt thereof, wherein the (R)-enantiomer, of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising $\leq$ about 2% of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of the (S)-enantiomer of N-hydroxy-tianeptine:



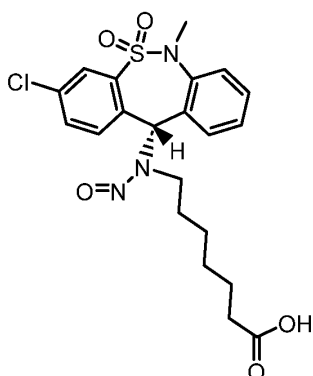
Formula (XVII).

140. The (R)-enantiomer of N-hydroxy-tianeptine according to embodiment 139, wherein the (R)-enantiomer or pharmaceutically acceptable salt of the (R)-enantiomer N-hydroxy-tianeptine are characterized by comprising $\leq$ about 0.1% of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer.
141. N-nitroso-tianeptine of the Formula (XVIII) or a pharmaceutically acceptable salt thereof:



Formula (XVIII).

142. The (S)-enantiomer of N-nitroso-tianeptine (N-nitroso-(S)-tianeptine) of the Formula (XIX) or a pharmaceutically acceptable salt thereof, wherein the (S)-enantiomer, of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising $\leq$ about 2% of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of the (R)-enantiomer of N-nitroso-tianeptine:

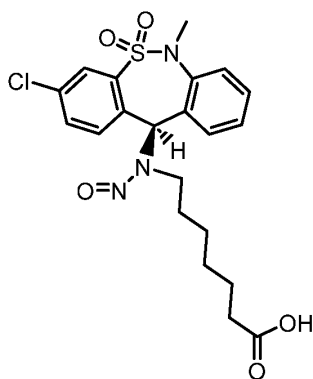


Formula (XIX).

143. The (S)-enantiomer of N-nitroso-tianeptine according to embodiment 142, wherein the (S)-enantiomer or pharmaceutically acceptable salt of the (S)-enantiomer N-nitroso-tianeptine are characterized by comprising $\leq$ about 0.1% of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

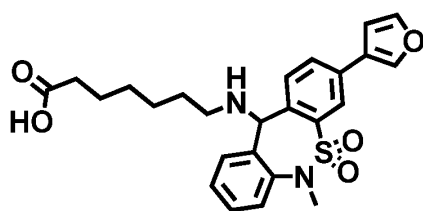
144. The (R)-enantiomer of N-nitroso-tianeptine (N-nitroso-(R)-tianeptine) of the Formula (XX) or a pharmaceutically acceptable salt thereof, wherein the (R)-enantiomer, of N-

nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising $\leq$ about 2% of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of the (S)-enantiomer of N-nitroso-tianeptine:

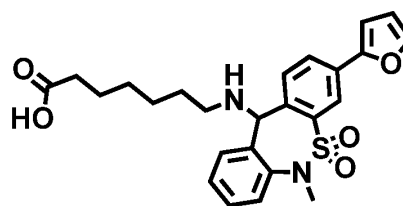


Formula (XX).

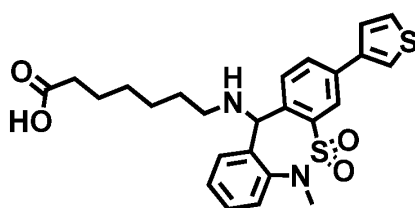
145. The (R)-enantiomer of N-nitroso-tianeptine according to embodiment 144, wherein the (R)-enantiomer or pharmaceutically acceptable salt of the (R)-enantiomer N-nitroso-tianeptine are characterized by comprising $\leq$ about 0.1% of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer.
146. An aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof.
147. The aryl substituted tianeptine analog according to embodiment 146, wherein the aryl substituted tianeptine derivative is 7-((3-(furan-2-yl)-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid of Formula (XXI), 7-((3-(furan-3-yl)-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid of Formula (XXII), 7-((6-methyl-5,5-dioxido-3-(thiophen-3-yl)-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid of Formula (XXIII) or 2-(4-(((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)methyl)-2-methylphenoxy)acetic acid of Formula (XXIV).



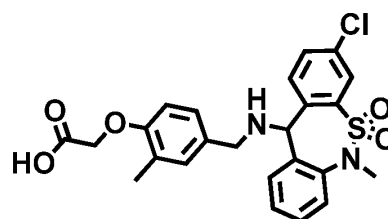
Formula (XXI)



Formula (XXII)



Formula (XXIII)



Formula (XXIV)

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148. A pharmaceutical composition comprising the N-hydroxy-tianeptine or a pharmaceutically acceptable salt thereof according to embodiment 136, or the N-nitroso-tianeptine or a pharmaceutically acceptable salt thereof according to embodiment 141, or an aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof according to embodiment 146 or 147 and a pharmaceutically acceptable carrier, diluent, or excipient.

149. A pharmaceutical composition comprising the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt thereof according to embodiment 137 or 138, or the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt thereof according to embodiment 142 or 143 and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises $\leq$ about 2%, or $\leq$ about 0.1%, of the (R)-enantiomer of N-hydroxy-tianeptine or N-nitroso-tianeptine or pharmaceutically acceptable salt of the (R)-enantiomer of N-hydroxy-tianeptine or N-nitroso-tianeptine or pharmaceutically acceptable salt thereof.

150. A pharmaceutical composition comprising the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt thereof according to embodiment 139 or 140, or the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically

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- acceptable salt thereof according to embodiment 144 or 145 and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises $\leq$ about 2%, or $\leq$ about 0.1%, of the (S)-enantiomer of N-hydroxy-tianeptine or N-nitroso-tianeptine or pharmaceutically acceptable salt of the (S)-enantiomer of N-hydroxy-tianeptine or N-nitroso-tianeptine or pharmaceutically acceptable salt thereof.
151. The pharmaceutical composition according to any one of embodiments 148-150, wherein the composition is in the form of a tablet, a thin film, a powder, a caplet, a capsule, a soft gel, a suppository, a nasal spray, an oral spray or a lung spray.
152. The pharmaceutical composition according to any one of embodiments 148-150, wherein the composition is formulated for immediate release, controlled release, sustained release, extended release, or slow release of the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, the N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, the (R)-enantiomer of N-nitroso-tianeptine, or an aryl substituted tianeptine analog or a pharmaceutically acceptable salt of any of them.
153. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of embodiments 136-140, or the N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, or the (R)-enantiomer of N-nitroso-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of embodiments 141-145, or an aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof according to embodiment 146 or 147 or the pharmaceutical composition according to any one of embodiments 148-152.
154. The method according to embodiment 153, wherein the disease, disorder or condition is selected from the group consisting of a central nervous system (CNS) disorder,

inflammatory disease, autoimmune disease, infectious illness, a hearing loss condition, ocular disease, musculoskeletal disease, metabolic disease, mitochondrial disease, hypertriglyceridemia, cancer, menopause and chronic overlapping pain conditions (COPCs), and psychological, physical, metabolic or hormonal stress and COPCs.

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155. The method according to embodiment 154, wherein the CNS disorder is selected from the group consisting of a mood disorder, a trauma and stress-related disorder, an anxiety disorder, obsessive-compulsive disorder, a neurodegenerative or neuroinflammatory disorder, a neurodevelopmental disorder, a leukodystrophy and CNS oxidative stress.

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156. The method according to embodiment 155, wherein the mood disorder is a depressive disorder, a bipolar disorder, or a substance-induced disorder.

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157. The method according to embodiment 156, wherein the depressive disorder is major depressive disorder (MDD).

158. The method according to embodiment 155, wherein the trauma and stress-related disorder is post-traumatic stress disorder (PTSD), acute stress disorder (ASD), adjustment disorder, or reactive attachment disorder.

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159. The method according to embodiment 155, wherein the anxiety disorder is panic disorder, generalized anxiety disorder (GAD), a specific phobia, agoraphobia or social phobia.

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160. The method according to embodiment 155, wherein the neurodegenerative or neuroinflammatory disorder is Mild Cognitive Impairment, Alzheimer's Disease, dementia, Parkinson's disease, Huntington's disease, multiple sclerosis (MS) amyotrophic lateral sclerosis (ALS), traumatic brain injury, neuromyelitis optica, myasthenia gravis, autoimmune encephalitis, prion disease, transverse myelitis, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), vanishing white matter disease, childhood ataxia with CNS

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hypo myelination, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease, kuru or dementia.

- 5 161. The method according to embodiment 155, wherein the neurodevelopmental disorder is attention-deficit/ hyperactivity disorder (ADHD), schizophrenia, Prader-Will Syndrome (including hyperphagia and other symptoms (*e.g.*, depression and anxiety) or autism.
- 10 162. The method according to embodiment 155, wherein the leukodystrophy is leukoencephalopathy, a hypomyelinating or demyelinating disease, an intellectual disability syndrome, a cognitive impairment, a glial cell dysfunction or a brain injury.
- 15 163. The method according to embodiment 162, wherein the cognitive impairment is age-related cognitive impairment, age-related cognitive decline (ARCD), age-associated memory impairment (AAMI), cognitive impairment associated with Mild Cognitive Impairment, prodromal Alzheimer's Disease or Alzheimer's Disease, prodromal fronto-temporal dementia (FTD) or FTD, prodromal posterior cortical atrophy (PCA) or PCA, cognitive impairment associated with schizophrenia, a drug-induced cognitive disorder, radiotherapy-induced cognitive dysfunction, space travel-related cognitive decline, or cognitive deficit and neuropathic pain associated with diabetes mellitus.
- 20 164. The method of embodiment 163, wherein the drug-induced cognitive disorder is corticosteroid-induced cognitive dysfunction, doxorubicin-induced cognitive dysfunction, chemotherapy-induced cognitive dysfunction, alcohol-induced cognitive dysfunction, or substance-induced cognitive dysfunction.
- 25 165. The method according to embodiment 162, wherein the brain injury is a traumatic brain injury, hypoxia-induced brain injury, toxin-induced brain injury, stroke or reperfusion injury following ischemic stroke.
- 30 166. The method according to embodiment 154, wherein the inflammatory disease is asthma, postoperative cognitive dysfunction, arthritis, systemic lupus erythematosus (SLE), myasthenia gravis, diabetes, Guillain-Barre syndrome, Hashimoto's

encephalitis, Hashimoto's thyroiditis, ankylosing spondylitis, psoriasis, Sjogren's syndrome, vasculitis, glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, ichthyosis, Graves' ophthalmopathy, inflammatory bowel disease, Addison's disease, vitiligo, 5 acne vulgaris, celiac disease, chronic prostatitis, pelvic inflammatory disease, reperfusion injury, sarcoidosis, transplant rejection, interstitial cystitis, atherosclerosis or atopic dermatitis.

167. The method according to embodiment 154, wherein the autoimmune disease is 10 Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune 15 orchitis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Balo disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS) 20 or Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential 25 mixed cryoglobulinemia, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), 30 Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammaglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen

sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease
 chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue
 disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor
 Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myositis,
 5 Narcolepsy, Neonatal Lupus, Neuromyelitis optica, Neutropenia, Ocular cicatricial
 pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic
 cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry
 Romberg syndrome, Pars planitis (peripheral uveitis), Parsonnage -Turner syndrome,
 Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia
 10 (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndrome type I,
 Polyglandular syndrome type II, Polyglandular syndrome type III, Polymyalgia
 rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy
 syndrome, primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone
 dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma
 15 gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic
 dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal
 fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome,
 Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff
 person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome,
 20 Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell
 arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS),
 Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated
 connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, Vogt-Koyanagi-
 Harada Disease, or Wegener's granulomatosis (or Granulomatosis with Polyangiitis
 25 (GPA)).

168. The method according to embodiment 154, wherein the infectious illness is a viral infection or post-viral condition.
- 30 169. The method according to embodiment 154, wherein the hearing loss condition is mitochondrial nonsyndromic hearing loss and deafness, hair cell death, age-related hearing loss, noise-induced hearing loss, genetic or inherited hearing loss, hearing loss experienced as a result of ototoxic exposure, hearing loss resulting from disease, or hearing loss resulting from trauma.

170. The method according to embodiment 154, wherein the ocular disease is cataracts, glaucoma, endoplasmic reticulum (ER) stress, autophagy deficiency, age-related macular degeneration (AMD), or diabetic retinopathy.
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171. The method according to embodiment 154, wherein the musculoskeletal disease is muscular dystrophy, multiple sclerosis, amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, spinal muscular atrophy, progressive spinobulbar muscular atrophy, spinal cord spasticity, spinal muscle atrophy, myasthenia gravis, neuralgia, fibromyalgia, Machado-Joseph disease, cramp fasciculation syndrome, Freidrich's ataxia, a muscle wasting disorder, an inclusion body myopathy, motor neuron disease, or paralysis.
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172. The method according to embodiment 154, wherein the metabolic disease is non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes, phenylketonuria, proliferative retinopathy, and Keams-Sayre disease.
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173. The method according to embodiment 154, wherein the mitochondrial disease is Barth syndrome, chronic progressive external ophthalmoplegia (cPEO), Keams-Sayre syndrome (KSS), Leigh syndrome, mitochondrial DNA depletion syndromes (MDDS), mitochondrial encephalomyopathy, mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), myoclonus epilepsy with ragged red fibers (MERRF), neuropathy, ataxia, retinitis pigmentosa (NARP), Leber's hereditary optic neuropathy (LHON), and Pearson syndrome.
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174. The method according to embodiment 154, wherein the cancer is glioblastoma or glioma.
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175. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, in a subject who has experienced high stress, comprising administering to the

subject a therapeutically effective amount of the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of embodiments 136-140, or the N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, or the (R)-enantiomer of N-nitroso-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of embodiments 141-145, or an aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof according to embodiment 146 or 147 or the pharmaceutical composition according to any one of embodiments 148-152.

176. The method according to embodiment 175, wherein the stress is caused by adversity early in life or by childhood trauma.

177. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, while reducing μ -opioid receptor agonism associated with treatment with racemic tianeptine, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of embodiments 136-140, or the N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, or the (R)-enantiomer of N-nitroso-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of embodiments 141-145, or an aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof according to embodiment 146 or 147 or the pharmaceutical composition according to any one of embodiments 148-152.

178. A method of treating a disease, disorder or condition selected from the group consisting of a central nervous system (CNS) disorder, asthma, primary biliary cholangitis, hypertriglyceridemia, cardiac hypertrophy, fibromyalgia, cancer, infectious illness, COVID-19, long COVID, menopause and chronic overlapping pain conditions (COPCs), psychological, physical, metabolic or hormonal stress and COPCs, and obesity, comprising administering to the subject a therapeutically

effective amount of the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of embodiments 136-140, or the N-nitroso-tianeptine, the (S)-enantiomer of N- nitroso-tianeptine, or the (R)-
5 enantiomer of N- nitroso-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of embodiments 141-145, or an aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof according to embodiment 146 or 147 or the pharmaceutical composition according to any one of embodiments 148-152.

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179. The method according to any one of embodiments 153-178, wherein the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, the N-nitroso-tianeptine, the (S)-enantiomer of N- nitroso-tianeptine, the (R)-enantiomer of N-nitroso-tianeptine, or an aryl substituted
15 tianeptine analog, or a pharmaceutically acceptable salt of any of them, or the pharmaceutical composition is administered one or more times daily.

180. The method according to embodiment 179, wherein the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, the N-nitroso-tianeptine, the (S)-enantiomer of N- nitroso-tianeptine, the (R)-enantiomer of N-nitroso-tianeptine, or an aryl substituted tianeptine analog, or a pharmaceutically acceptable salt of any of them, or the pharmaceutical composition is administered once daily.

25 181. The method according to any one of embodiments 153-180, wherein the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, the N-nitroso-tianeptine, the (S)-enantiomer of N- nitroso-tianeptine, the (R)-enantiomer of N-nitroso-tianeptine, or an aryl substituted tianeptine analog, or a pharmaceutically acceptable salt of any of them, or the
30 pharmaceutical composition is administered parenterally, orally, sublingually, buccally, inhalationally, palatally, transdermally, rectally, or vaginally.

182. The method according to embodiment 153-181, wherein the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-

hydroxy-tianeptine, the N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, the (R)-enantiomer of N-nitroso-tianeptine, or an aryl substituted tianeptine analog, or a pharmaceutically acceptable salt of any of them, or the pharmaceutical composition is administered sequentially or concurrently with one or more additional therapeutic agents selected from the group consisting of an antidepressant, an anticonvulsant, an anti-anxiety agent, an antipsychotic agent, a cholinesterase inhibitor, an N-methyl-D-aspartate (NMDA) receptor antagonist, a 5HT2 modulator, a corticosteroid, an anti-amyloid agent, an anti-tau agent and a chemotherapeutic agent.

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183. The method according to embodiment 153-181, wherein the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, the N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, the (R)-enantiomer of N-nitroso-tianeptine, or an aryl substituted tianeptine analog, or a pharmaceutically acceptable salt of any of them, or the pharmaceutical composition is administered as part of a treatment regime also including psychotherapeutic intervention.

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184. A crystalline hemi-oxalate salt of (S)-7-(3-chloro-6-methyl-6,11-dihydrodibenzo[c,f] [1,2]thiazepin-11-ylamino)heptanoic acid 5,5-dioxide ((S)-tianeptine), wherein the salt exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak selected from 8.5, 20.6, 21.0 and 24.2 degrees $2\theta \pm 0.3$ degrees 2θ .

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185. The crystalline (S)-tianeptine hemi-oxalate salt according to embodiment 184, wherein the salt exhibits an XRPD pattern further comprising at least one peak selected from the group consisting of 12.1, 13.3, 16.1, 18.9, 19.1, 22.0 and 22.4 degrees $2\theta \pm 0.3$ degrees 2θ .

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186. A crystalline free acid/free base of the (S)-enantiomer of tianeptine according to embodiment 1, wherein the crystalline (S)-enantiomer of tianeptine exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak selected from 10.6, 13.0, 21.1 and 23.7 degrees $2\theta \pm 0.3$ degrees 2θ .

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187. The crystalline free acid/free base of the (S)-enantiomer of tianeptine according to embodiment 186, wherein the crystalline free acid/free base of the (S)-

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enantiomer of tianeptine exhibits an XRPD pattern further comprising at least one peak selected from the group consisting of 8.7, 9.1, 12.6, 18.1, 20.4, 23.0 and 26.1 degrees $2\theta \pm 0.3$ degrees 2θ .

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BRIEF DESCRIPTION OF THE DRAWINGS

[0013] **Figure 1** is a graph showing the separation of a mixture of tianeptine zwitterion enantiomers derived from a racemic mixture of tianeptine oxalate enantiomers by direct phase preparative high-performance liquid chromatography (HPLC) at a wavelength of 220 nm. AU = absorbance units.

10 [0014] **Figures 2A and 2B** show the crystal structures of the enantiomer of tianeptine which has a (-) optical rotation as the sodium salt, complexed with L-dibenzoyl tartaric acid (DBTA). Figure 2A shows the crystal structure of the salt (S)-tianeptine: 0.5 L-DBTA. Figure 2B shows a different crystalline isoform of (S)-tianeptine enantiomer with L-DBTA ((S)-Tianeptine: 0.5 L-DBTA).

15 [0015] **Figures 3A-3B** show graphs of cyclic adenosine 3,5-monophosphate (cAMP) inhibition using varying concentrations of [D-Ala², NMe-Phe⁴, Gly-ol⁵]-enkephalin (DAMGO), racemic tianeptine, and 99.0%-99.35% pure (S)-tianeptine oxalate or 98.5%-99.35% pure (R)-tianeptine oxalate at the μ -opioid receptor. Figure 3A shows a graph of cAMP inhibition at steady state. Figure 3B shows a graph of the initial rate of cAMP
20 inhibition. NFU is a normalized fluorescence unit.

[0016] **Figures 4A-4B** show graphs of concentration-response curves showing average arrestin recruitment using varying concentrations of DAMGO, racemic tianeptine, and 99.0%-99.35% pure (S)-tianeptine oxalate or 98.5%-99.35% pure (R)-tianeptine oxalate at the μ -opioid receptor. Figure 4A shows arrestin recruitment response at steady state.
25 Figure 4B shows arrestin recruitment initial rate analysis.

[0017] **Figures 5A-5B** show graphs of concentration-response curves of % cAMP inhibition using varying log concentrations (M) of DAMGO, racemic tianeptine, and 99.35% pure (S)-tianeptine sodium or (R)-tianeptine sodium at the μ -opioid receptor. The graphs show % cAMP inhibition initial rate analysis (Figure 5A) and % cAMP inhibition maximum effect analysis (Figure 5B).
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[0018] **Figures 6A-6B** show graphs of concentration-response curves % cAMP inhibition using varying log concentrations (M) of DAMGO, racemic tianeptine, racemic tianeptine sodium, and 99.0%-99.35% pure (S)-tianeptine sodium or 98.5%-99.35% pure (R)-

tianeptine sodium at the μ -opioid receptor. The graphs show % cAMP inhibition initial rate analysis (Figure 6A) and % cAMP inhibition maximum effect analysis (Figure 6B).

[0019] **Figures 7A-7B** show graphs of concentration–response curves of average arrestin recruitment at the μ -opioid receptor using varying log concentrations (M) of DAMGO, tianeptine, racemic tianeptine sodium, and 99.9% pure (S)-tianeptine sodium or (R)-tianeptine sodium. The graphs show arrestin recruitment initial rate analysis (Figure 7A) and arrestin recruitment normalized to baseline (Figure 7B).

[0020] **Figures 8A-8B** show graphs depicting tianeptine agonism at the μ -opioid receptor using varying log concentrations (M) of DAMGO and 99.9% pure (S)-tianeptine sodium or (R)-tianeptine sodium. The graphs show peak cAMP inhibition (Figure 8A) and peak arrestin recruitment (Figure 8B).

[0021] **Figures 9A-9D** show graphs depicting the activity of racemic tianeptine, racemic tianeptine oxalate, (S)-tianeptine and (R)-tianeptine (99.9% chiral purity), the PPAR- β/δ agonist positive control GW0742, the PPAR- β/δ agonist Seladelpar and dimethyl sulfoxide (DMSO, negative control) and at the peroxisome proliferator-activated receptor- β/δ (PPAR- β/δ). **Figures 9B and 9D** show a zoomed in view of PPAR- β/δ activation by (S)-tianeptine at $\sim 3 \mu\text{M}$.

[0022] **Figures 10A and 10B** show graphs depicting the activity of racemic tianeptine, racemic tianeptine oxalate, (S)-tianeptine and (R)-tianeptine (99.9% chiral purity), the PPAR- γ agonist positive control rosiglitazone, the PPAR- β/δ agonist Seladelpar and DMSO (negative control) and at the peroxisome proliferator-activated receptor- γ (PPAR- γ).

[0023] **Figures 11A and 11B** show graphs depicting the activity of racemic tianeptine, racemic tianeptine oxalate, (S)-tianeptine and (R)-tianeptine (99.9% chiral purity), the PPAR- α agonist positive control GW7647, the PPAR- β/δ agonist Seladelpar and DMSO (negative control) and at the peroxisome proliferator-activated receptor- α (PPAR- α).

[0024] **Figure 12** depicts the superposition of the crystal structure of PPAR- δ/β in complex with ligand GW2331 with a computational model of PPAR- δ/β in complex with (S)-tianeptine and a computational model with PPAR- δ/β in complex with (R)-tianeptine.

[0025] **Figures 13A and 13B** show computational modeling of (S)-tianeptine docked into PPAR- δ/β (Figure 13A) and (R)-tianeptine docked into PPAR- δ/β (Figure 13B) depicting the formation of a covalent carbon-sulfur (C-S) bond between (S)-tianeptine and cysteine 285 of PPAR- δ/β . The bond-length between (S)-tianeptine and Cys285 of PPAR- δ/β

is 5.00Å (Figure 13A) and the bond-length between (R)-tianeptine and Cys285 of PPAR- δ/β is 7.92Å (Figure 13B).

[0026] **Figures 14A-14F** show graphs depicting the effects of (S)-tianeptine and (R)-tianeptine zwitterion (99.9% chiral purity) on neurite outgrowth of cultured glutamatergic neurons. Figures 14A and 14B depict the average neurite length (μm) at 24 hours (Figure 14A) and 72 hours (Figure 14B) post treatment. Figures 14C and 14D depict the total neurite length (μm) (Figure 14C) and average neurite width (nm) (Figure 14D) at 5 days post treatment with (S)-tianeptine zwitterion (99.9% chiral purity). Figures 14E and 14F depict the total neurite length (μm) (Figure 14E) and average neurite width (nm) (Figure 14F) at 5 days post treatment with (R)-tianeptine zwitterion (99.9% chiral purity). Data normalized to 1% PBS control and compared using strictly standardized mean difference (SSMD). P-value: * $p < 0.05$

[0027] **Figures 15A-15D** show graphs depicting the effects of (S)-tianeptine and (R)-tianeptine zwitterion (99.9% chiral purity) on mitochondrial staining (MitoTracker) in cultured glutamatergic neurons at 5 days post treatment. Figures 15A and 15B depict the mitochondrial staining in cell bodies (Figure 15A) and neurites (Figure 15B) post treatment with (S)-tianeptine zwitterion (99.9% chiral purity). Figures 15C and 15D depict the mitochondrial staining in cell bodies (Figure 15C) and neurites (Figure 15D) post treatment with (R)-tianeptine zwitterion (99.9% chiral purity). Data normalized to 1% PBS control and compared using strictly standardized mean difference (SSMD). p-value: * $p < 0.05$. RFU = Relative Fluorescence Units

[0028] **Figures 16A-16C** show graphs depicting the effects of racemic tianeptine sodium (Figure 16A), (S)-tianeptine sodium (99.9% chiral purity, Figure 16B) and (R)-tianeptine sodium (99.9% chiral purity, Figure 16C) in a novel object recognition (NOR) test. ANOVA p-values: *** $p < 0.001$, ** $p < 0.1$, * $p < 0.05$.

[0029] **Figures 17A-17F** show graphs depicting the effects of racemic tianeptine sodium (Figure 17A-17B), (R)-tianeptine sodium (99.9% chiral purity, Figure 17C-17D) and (S)-tianeptine sodium (99.9% chiral purity, Figure 17E-17F) in a forced swim test (FST). Figures 17A, 17C and 17E show the timeline of the time spent immobile over 6 minutes. Figures 17B, 17D and 17F show the total time spent immobile during the 6-minute test. ANOVA p-values: *** $p < 0.001$, * $p < 0.05$.

[0030] **Figures 18A-18D** show graphs depicting the XRPD patterns of crystalline (S)-tianeptine (Figure 18A), crystalline (S)-tianeptine hemi-oxalate (Figure 18B), amorphous (S)-

tianeptine sodium (Figure 18C) and a comparison of the three XRPDs with the XRPD of racemic tianeptine hemi-oxalate (Figure 18D).

DETAILED DESCRIPTION

5 [0031] This disclosure provides in some embodiments, the (S)-enantiomer of 7-(3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepine-11-ylamino) heptanoic acid ((S)-tianeptine), the zwitterion, ester or amide thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer or a crystalline form thereof, or a pharmaceutically acceptable salt of an ester or amide thereof, or a cocrystal of the (S)-enantiomer or the zwitterion thereof. In
10 other embodiments, this disclosure provides the (S)-enantiomer of deuterated tianeptine (11-D-(S)-tianeptine), the zwitterion, ester or amide thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, or a crystalline form thereof, or a pharmaceutically acceptable salt of an ester or amide thereof, or a cocrystal of the 11-D-(S)-enantiomer or the zwitterion thereof. In both embodiments, the (S)-enantiomers, zwitterions, cocrystals, esters, amides and
15 salts are characterized by comprising $\leq 2\%$ of the corresponding (R)-enantiomer, its zwitterions, esters, amides or salts. In both embodiments, the (S)-enantiomers, zwitterions, esters, amides and salts are characterized by comprising $\leq 0.1\%$ of the corresponding (R)-enantiomer, its zwitterions, esters, amides or salts.

[0032] In other embodiments, this disclosure provides tianeptine analogs including N-hydroxy-tianeptine, the (S)- and (R)-enantiomers of N-hydroxy-tianeptine (*i.e.*, N-hydroxy-(S)-tianeptine or N-hydroxy-(R)-tianeptine), N-nitroso-tianeptine, the (S)- and (R)-enantiomers of N-nitroso-tianeptine (*i.e.*, N-nitroso-(S)-tianeptine or N-nitroso-(R)-tianeptine), an aryl substituted tianeptine analog and pharmaceutically acceptable salts thereof. In some embodiments, the (S)-enantiomers of N-hydroxy-tianeptine or N-nitroso-tianeptine
25 are characterized by comprising $\leq 2\%$ of the corresponding (R)-enantiomer. In some embodiments, the (S)-enantiomers of N-hydroxy-tianeptine or N-nitroso-tianeptine are characterized by comprising $\leq 0.1\%$ of the corresponding (R)-enantiomer. In some embodiments, the (R)-enantiomers of N-hydroxy-tianeptine or N-nitroso-tianeptine are characterized by comprising $\leq 2\%$ of the corresponding (S)-enantiomer. In some
30 embodiments, the (R)-enantiomers of N-hydroxy-tianeptine or N-nitroso-tianeptine are characterized by comprising $\leq 0.1\%$ of the corresponding (S)-enantiomer.

[0033] In some embodiments, this disclosure provides a pharmaceutical composition comprising one or more of the (S)-enantiomers or crystalline form thereof, zwitterions,

cocrystals, esters, amides, analogs or salts of this disclosure, the compositions comprising $\leq 2\%$ of the corresponding (R)-enantiomer. In some embodiments, the pharmaceutical composition comprises $\leq 0.1\%$ of the corresponding (R)-enantiomer.

[0034] In some embodiments, this disclosure provides methods for treating diseases, disorders or conditions selected from the group consisting of a central nervous system (CNS) disorder, inflammatory disease, autoimmune disease, infectious illness, a hearing loss condition, ocular disease, musculoskeletal disease, metabolic disease, mitochondrial disease, hypertriglyceridemia, cancer, menopause and chronic overlapping pain conditions (COPCs), and psychological, physical, metabolic or hormonal stress and COPCs and associated symptoms in a subject in need thereof by administering the (S)-enantiomers (*i.e.*, the (S)-enantiomer of tianeptine and/or the 11-D-(S)-enantiomer of tianeptine) or crystalline forms thereof, zwitterions, esters, amides, salts, analogs and compositions of this disclosure. In some embodiments, diseases, disorders or conditions are modulated by, exacerbated by, or associated with altered activity of PPAR- β/δ and/ or PPAR- γ . In some embodiments, diseases, disorders or conditions are modulated by, exacerbated by, or associated with high levels of S-nitrosylation of PPAR- β/δ and/ or PPAR- γ . In some embodiments, diseases, disorders or conditions are modulated by, exacerbated by, or associated with excessive levels of metal ions in circulation. In some embodiments, diseases, disorders or conditions are modulated by, exacerbated by, or associated with stress.

[0035] In some embodiments, the methods minimize the potential for opioid abuse as the result of administration of the (S)-enantiomers (*i.e.*, the (S)-enantiomer of tianeptine and/or the 11-D-(S)-enantiomer of tianeptine) or crystalline forms thereof, their zwitterions, esters, amides, analogs or pharmaceutically acceptable salts, or compositions comprising them of this disclosure.

[0036] In other embodiments, the disclosure provides methods of producing the (S)-enantiomer of tianeptine and/or the 11-D-(S)-enantiomer of tianeptine of this disclosure.

[0037] Practice of the methods of various embodiments disclosed herein employ, unless otherwise indicated, conventional techniques in molecular biology, biochemistry, chromatin structure and analysis, computational chemistry, cell culture, recombinant DNA and related fields as are within the skill of the art. These techniques are fully explained in the literature.

Definitions

[0038] The term “herein” means the entire application.

[0039] Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. In case of conflict, the present specification, including definitions, will control.

[0040] It should be understood that any of the embodiments described herein, including those described under different aspects of the disclosure and different parts of the specification (including embodiments described only in the Examples) can be combined with one or more other embodiments of this disclosure, unless explicitly disclaimed or improper, and are so disclosed as embodiments to the disclosure. Combination of embodiments are not limited to those specific combinations described in the multiple dependent embodiments of this disclosure.

[0041] All of the publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

[0042] Throughout this specification, the word “comprise” or variations such as “comprises” or “comprising,” which is synonymous with “including,” “containing,” or “characterized by,” is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

[0043] Any example(s) following the term “e.g.” or “for example” is not meant to be exhaustive or limiting.

[0044] The term “including” or “includes” is used to mean “including but not limited to.” “Including” and “including but not limited to” are used interchangeably.

[0045] Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[0046] The articles “a,” “an” and “the” are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article.

[0047] As used herein, the meaning of the term “about” depends upon the context in which it is used. When used with respect to modifying the quantity of an ingredient, parameter, calculation, or measurement in the compositions employed in the methods of the disclosure refers to the variation in the numerical quantity that can occur, for example, through typical measuring and liquid handling procedures used for making the compounds of this disclosure or pharmaceutical compositions in the real world; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of the ingredients employed to make the enantiomer or compositions of this disclosure or to carry out the methods; and the typical +/- of any amount or use without having a substantial effect on the

chemical or physical attributes of the compounds, compositions or methods of the disclosure. Such variation can be typically within 10%, more typically within 5%, of a given value or range. In some embodiments the variation can be within 1%. The term “about” also encompasses amounts that differ due to different equilibrium conditions for a composition
5 resulting from a particular initial mixture. Whether or not modified by the term “about,” the paragraphs include equivalents to the quantities. Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X.” Numeric ranges are inclusive of the numbers defining the range. When used with respect to the
10 position of a peak on an X-ray powder diffraction (XRPD) pattern, the term “about” includes peaks within an associated tolerance of ± 0.3 degrees 2θ . For example, as used herein, an XRPD peak at “about 10.0 degrees 2θ ” means that the stated peak occurs from 9.7 to 10.3 degrees 2θ . When used with respect to the position of a peak on a solid state ^{13}C NMR spectrum, the term “about” includes peaks within ± 0.2 ppm of the stated position. For
15 example, as used herein, a ^{13}C NMR spectrum peak at “about 100.0 ppm” means that the stated peak occurs from 99.8 to 100.2 ppm.

[0048] As used herein, the term “substantially” in reference to an XRPD pattern refers to a spectrum having at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 peaks (perhaps differing in amplitude) in common with the referenced pattern; or a pattern having a tolerance
20 of ± 0.3 degrees 2θ within the referenced peaks. In reference to an NMR pattern, “substantially” refers to a spectrum having at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 peaks (perhaps differing in amplitude) in common with the referenced pattern; or a pattern having a tolerance of ± 0.2 ppm within the referenced peaks. In reference to an FT-IR pattern, “substantially” refers to a spectrum having at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15
25 peaks (perhaps differing in amplitude) in common with the referenced pattern; or a pattern having a tolerance of $\pm 0.5\text{ cm}^{-1}$ within the referenced peaks.

[0049] The term “or” as used herein should be understood to mean “and/or,” unless the context clearly indicates otherwise.

[0050] Notwithstanding that the disclosed numerical ranges and parameters are
30 approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Moreover, all ranges disclosed herein are to be understood to encompass any and all subranges subsumed therein. For example, a stated range of “1 to 10” should be

considered to include any and all subranges between (and inclusive of) the minimum value of 1 and the maximum value of 10; that is, all subranges beginning with a minimum value of 1 or more, *e.g.*, 1 to 6.1, and ending with a maximum value of 10 or less, *e.g.*, 5.5 to 10.

[0051] Where aspects or embodiments are described in terms of a Markush group or other grouping of alternatives, the present application encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group, and also the main group absent one or more of the group members, notwithstanding such individuals and subgroups are not specifically referred to in this disclosure.

[0052] Exemplary methods and materials are described herein, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the various aspects and embodiments. The materials, methods, and examples are illustrative only and not intended to be limiting.

[0053] In order that the disclosure may be more readily understood, certain terms are first defined. These definitions should be read in light of the remainder of the disclosure as understood by a person of ordinary skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art. Additional definitions are set forth throughout the detailed description.

[0054] As used herein, the term “treat” and its cognates refer to a full or partial amelioration or modulation of the symptoms or pathology of a disease, disorder or condition, particularly those that can be effected utilizing the compounds and compositions of this disclosure, and may include, but are not limited to, even minimal changes or improvements in one or more measurable markers of the disease, disorder or condition being treated. “Treat” also refers to delaying the onset of, retarding or reversing the progress of, reducing the severity of, or alleviating or preventing either the disease, disorder or condition to which the term applies, or one or more symptoms of such disease, disorder or condition, for example, and without limitation, delaying or reducing the rate of a decline in cognitive function in age-related cognitive decline.

[0055] “Treating cognitive impairment” refers to taking steps to improve cognitive function in a subject with cognitive impairment so that the subject’s performance in one or more cognitive tests is improved to any detectable degree or is prevented from further decline or the rate of such decline is reduced. Preferably, that subject’s cognitive function, after treatment of cognitive impairment, more closely resembles the function of a normal,

unimpaired subject. Treatment of cognitive impairment in humans may improve cognitive function to any detectable degree, but is preferably improved sufficiently to allow the impaired subject to carry out daily activities of normal life at a similar level of proficiency as a normal, unimpaired subject. In some cases, “treating cognitive impairment” refers to taking

5 steps to improve cognitive function in a subject with cognitive impairment so that the subject’s performance in one or more cognitive tests is improved to any detectable degree, is prevented from further decline, or the rate of such decline is reduced. Preferably, that subject’s cognitive function, after treatment of cognitive impairment, more closely resembles the function of a normal, unimpaired subject. In some cases, “treating cognitive impairment”

10 in a subject affecting by age-related cognitive impairment refers to takings steps to improve cognitive function in the subject so that the subject’s cognitive function, after treatment of cognitive impairment, more closely resembles the function of an age matched normal, unimpaired subject, or the function of a young adult subject. In some cases, “treating cognitive impairment” in a subject refers to taking steps to delay or slow the progression of

15 cognitive impairment in a subject with cognitive impairment. In some cases, “treating cognitive impairment” in a subject refers to taking steps to reduce the rate of decline of cognitive function in a subject with cognitive impairment.

[0056] As used herein, the term “subject”, “patient”, or “individual” are used interchangeably and includes humans and non-human mammals. Non-human mammals

20 include bovines, ovines, porcines, equines, canines, felines, and rodents (*e.g.*, rat, mouse, guinea pig and rabbit). Preferably, the subject is a human.

[0057] As used herein the term “(S)-enantiomers of tianeptine” refers to the (S)-enantiomer of tianeptine or crystalline forms thereof, the zwitterion thereof, a pharmaceutically acceptable salt of the (S)-enantiomer or crystalline forms thereof, a co-

25 crystal of the (S)-enantiomer or the zwitterion thereof, an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or 11-D-(S)-enantiomer, crystalline forms thereof, the zwitterion thereof, a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, a co-

30 crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof.

[0058] As used herein, “therapeutically effective amount” of the (S)-enantiomers of tianeptine of this disclosure, or compositions of this disclosure refers to the amount used to treat, prevent, or alleviate one or more symptoms of a disease or disorder of this disclosure.

In some embodiments the disease or disorder or one or more symptoms of a disease or disorder is modulated by, exacerbated by, or associated with altered activity of PPAR- β/δ and/ or PPAR- γ . In some embodiments, some of the diseases or disorders are associated with stress or the presence of excess metal ions. One skilled in the art can readily determine a therapeutically effective amount of the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer) of this disclosure, zwitterions, pharmaceutically acceptable salts of the (S)-enantiomers of this disclosure to be administered, by taking into account factors such as the size, weight, age and sex of the subject, the extent of disease penetration or persistence and severity of symptoms, and the route of administration. Generally, a therapeutically effective amount of the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer) of this disclosure, zwitterions, pharmaceutically acceptable salts of the (S)-enantiomers of this disclosure administered to a subject is between about 1 mg/day to about 5000 mg/day, between about 1 mg/day to about 4000 mg/day between, between about 1 mg/day to about 3000 mg/day, between about 1 mg/day to about 2000 mg/day, between about 1 mg/day to about 1000 mg/day, between about 2 mg/day to about 600 mg/day, between about 10 mg/day to about 400 mg/day, or between about 25 mg/day to 300 mg/day. Higher or lower doses are also contemplated.

[0059] As used herein, “pharmaceutically acceptable carrier” refers to any diluent or excipient that is compatible with the other ingredients of the formulation, and which is not deleterious to the recipient. The pharmaceutically acceptable carrier can be selected on the basis of the desired route of administration, in accordance with standard pharmaceutical practices.

[0060] As used herein, “enantiomer” refers to each of the two nonsuperimposable isomers of a compound having at least one chiral/asymmetric atom. Each enantiomer is optically active in the context of its ability to rotate light. Single enantiomers are designated according to the Cahn-Ingold-Prelog system, which is a well-known set of priority rules for ranking the four groups attached to an asymmetric carbon. See, *e.g.*, March, *Advanced Organic Chemist.* 4. Th Ed., (1992), p. 109, the entire disclosure of which is herein incorporated by reference.

[0061] As used herein, “optically active” refers to a property whereby a material rotates the plane of plane-polarized light. An isomer or enantiomer that is optically active is nonsuperimposable on its mirror image. As used herein, the property of nonsuperimposability of an object on its mirror image is called “chirality.” The most

common structural feature producing chirality is an asymmetric carbon atom, *i.e.*, a carbon atom having four nonequivalent groups attached thereto.

[0062] As used herein, “racemate” or “racemic compound” refers to a 50-50 mixture of two enantiomers such that the mixture does not rotate plane-polarized light, and can, in many cases, be separated into 2 peaks of equal weights by various means, including chromatography.

[0063] As used herein, the term “substantially pure” or “pure” refers to an enantiomer or composition comprising it comprising no more than 2% of the counterpart enantiomer. In some embodiments, the substantially pure (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or the 11-D-(S)-enantiomer) of this disclosure, the zwitterions thereof, pharmaceutically acceptable salts of the (S)-enantiomers or compositions of this disclosure comprise no more than about 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% of the counterpart (R)-enantiomers of tianeptine (*i.e.*, the (R)-enantiomer or 11-D-(R)-enantiomer), zwitterions or pharmaceutically acceptable salts of the (R)-enantiomers.

[0064] As used herein, the term “chiral purity” refers to the extent to which a mixture of enantiomers comprises one enantiomer over the other.

[0065] As used herein, the term “co-crystal” is distinct from a salt and refers to a solid crystalline supramolecular complex composed of two or more components within the same crystal lattice, wherein the components are in a neutral state and interact via non-ionic interactions. The ability of an active pharmaceutical ingredient (API) and co-former to form a co-crystal can be predicted by determining the ΔpK_a value. When the ΔpK_a of the API and co-former is negative (<0), there is no proton transfer, which indicates that the system will form a co-crystal; in contrast, when the ΔpK_a is above 3, there is full proton transfer, indicating that the system forms a salt. Often, the ΔpK_a is between 0 and 3, in which only a partial proton transfer occurs, so the system is commonly referred to as a salt co-crystal (Nugrahani & Jessica. *Molecules*. 2021).

[0066] As used herein, the term “ μ -opioid receptor assay” or “MOR assay” refers to a methodology of analyzing the activity of the G-protein coupled receptor signaling pathway in response to a ligand binding at the μ -opioid receptor.

[0067] As used herein, the terms “ G_i ” refers to the G_i subunit in the G-protein coupled receptor signaling pathway.

[0068] As used herein, the terms “ G_s ” refers to the G_s subunit in the G-protein coupled receptor signaling pathway.

[0069] As used herein, the terms “ β -arrestin” and “arrestin” are used interchangeably.

[0070] As used herein, the term “m/z” refers to the mass-to-charge ratio.

[0071] As used herein, the term “t_R” or “retention time” refers to the interval between the injection of the sample and the detection of the substances in that sample.

[0072] As used herein, the term “neurite outgrowth” refers to the process in which
5 developing neurons produce new projections, called neurites, in response to guidance cues.

[0073] As used herein, the term “aryl” refers to any functional group or substituent derived from an aromatic ring, having from 5 to 7 ring atoms, including 1 to 4 heteroatoms selected from the group consisting of carbon, nitrogen, sulfur, or oxygen. The aryl group may be added at any possible position on the (S)- or (R)- tianeptines of this disclosure.

10 [0074] As used herein, the term “alkyl” refers to a saturated linear or branched-chain monovalent hydrocarbon radical of any length from one to six carbon atoms (C₁–C₆), wherein the alkyl radical may be optionally substituted independently with one or more substituents.

[0075] As used herein, the term “analog” refers to a compound related to tianeptine, but
15 having an altered chemical structure. For example, the tianeptine analog may comprise additional functional groups including hydroxyl, nitroso or aryl groups. The analogs of tianeptine of this disclosure include N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof, aryl-substituted tianeptine analogs or pharmaceutically acceptable salts thereof.

20

(S)-Tianeptine Enantiomers

[0076] In some aspects, this disclosure provides the (S)-enantiomer of 7-(3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepine-11-ylamino)heptanoic acid ((S)-enantiomer of tianeptine) or the zwitterion thereof or a pharmaceutically acceptable salt of
25 the (S)-enantiomer, or a mixture of two or more of these species, wherein the (S)-enantiomer, zwitterion or pharmaceutically acceptable salt are characterized by comprising no more than about 2% (*i.e.*, ≤ about 2%) of the (R)-enantiomer or the zwitterion thereof or a pharmaceutically acceptable salt of the (R)-enantiomer. In some embodiments, the (S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the (S)-enantiomer are
30 characterized by comprising no more than about 1% (*i.e.*, ≤ about 1%) of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the (S)-enantiomer are characterized by comprising no more than about

0.9% (*i.e.*, $\leq$ about 0.9%) of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the (S)-enantiomer are characterized by comprising no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the (S)-enantiomer are characterized by comprising no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the (S)-enantiomer are characterized by comprising no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the (S)-enantiomer are characterized by comprising no more than about 0.5% (*i.e.*, $\leq$ about 0.5%) of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the (S)-enantiomer are characterized by comprising no more than about 0.4% (*i.e.*, $\leq$ about 0.4%) of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the (S)-enantiomer are characterized by comprising no more than about 0.3% (*i.e.*, $\leq$ about 0.3%) of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the (S)-enantiomer are characterized by comprising no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the (S)-enantiomer are characterized by comprising no more than about 0.1% (*i.e.*, $\leq$ about 0.1%) of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer.

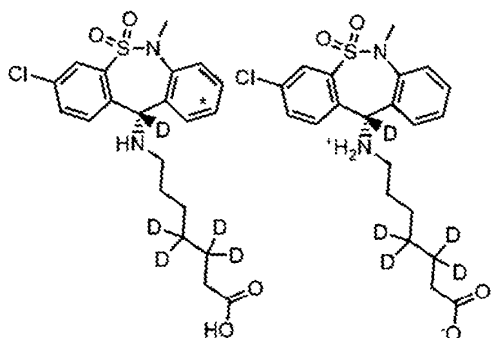
[0077] In some embodiments, the (S)-enantiomer of this disclosure is in the form of a pharmaceutically acceptable salt or a crystalline form thereof. In some embodiments, the (S)-tianeptine of this disclosure is in the form of a zwitterion.

[0078] In some aspects, this disclosure provides an (S)-enantiomer of 7-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepine-11-yl-11-d)amino)heptanoic acid (11-D-(S)-enantiomer of tianeptine), the zwitterion thereof or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, or a mixture of two or more of these species, wherein the 11-D-(S)-enantiomer, zwitterion or pharmaceutically acceptable salt are characterized by comprising no more than about 2% (*i.e.*, $\leq$ about 2%) of the 11-D-(R)-enantiomer or the zwitterion thereof or a pharmaceutically acceptable salt of the 11-D-(R)-enantiomer. In some embodiments, the 11-D-(S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer are characterized by comprising no more than about 1% (*i.e.*, $\leq$ about 1%) of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the 11-D-(S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer are characterized by comprising no more than about 0.9% (*i.e.*, $\leq$ about 0.9%) of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the 11-D-(S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer are characterized by comprising no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the 11-D-(S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer are characterized by comprising no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the 11-D-(S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer are characterized by comprising no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the 11-D-(S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer are characterized by comprising no more than about 0.5% (*i.e.*, $\leq$ about 0.5%) of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the 11-D-(S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer are characterized by comprising no more than about 0.4% (*i.e.*, $\leq$ about 0.4%) of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the 11-D-(S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of

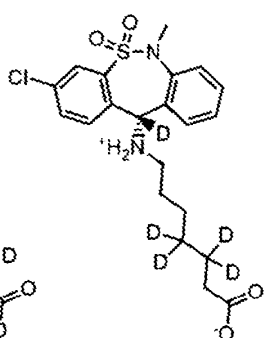
the 11-D-(S)-enantiomer are characterized by comprising no more than about 0.3% (*i.e.*, $\leq$ about 0.3%) of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the 11-D-(S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer are characterized by comprising no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the 11-D-(S)-enantiomer, zwitterion or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer are characterized by comprising no more than about 0.1% (*i.e.*, $\leq$ about 0.1%) of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the 11-D-(S)-tianeptine, zwitterion thereof, or pharmaceutically acceptable salt of either is characterized by reduced racemization at position 11 as compared to the 11-D-(S)-tianeptine, zwitterion thereof or a pharmaceutically acceptable salt of either.

[0079] In some embodiments, the 11-D-(S)-tianeptine of this disclosure is in the form of a pharmaceutically acceptable salt or a crystalline form thereof. In some embodiments, the 11-D-(S)-tianeptine of this disclosure is in the form of a zwitterion.

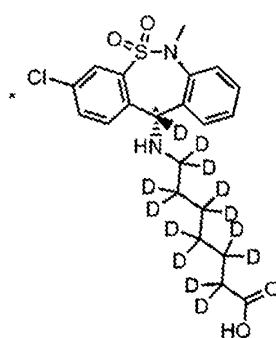
[0080] In some embodiments, the 11-D-(S)-enantiomer, the zwitterion thereof or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is deuterated at the two 3' positions, and optionally deuterated at other positions on the aminoheptanoic side chain. In some embodiments, the 11-D-(S)-enantiomer is 3', 3', 4', 4', 11- pentadeuterotianeptine of the general Formula (IIIa) or the zwitterion thereof of Formula (IIIb); 2', 2', 3', 3', 4', 4', 5', 5', 6', 6', 7', 7', 11-tridecadeuterotianeptine (of the general Formula (IVa)) or the zwitterion thereof of Formula (IVb); 3', 3', 4', 4', tetradeuterotianeptine of the general formula (Va) or the zwitterion thereof of Formula (Vb) or 2', 2', 3', 3', 4', 4', 5', 5', 6', 6', 7', 7', dodecadeuterotianeptine of the general formula (VIa) or the zwitterion thereof of formula (VIb). In some embodiments, the 11-D-(S)-enantiomer is 3', 3', 4', 4', 11-pentadeuterotianeptine of the general Formula (IIIa) or the zwitterion thereof of Formula (IIIb). In some embodiments, the 11-D-(S)-enantiomer is 2', 2', 3', 3', 4', 4', 5', 5', 6', 6', 7', 7', 11-tridecadeuterotianeptine of the general Formula (IVa) or the zwitterion thereof of Formula (IVb). In some embodiments, the 11-D-(S)-enantiomer is 3', 3', 4', 4', tetradeuterotianeptine of the general formula (Va) or the zwitterion thereof of Formula (Vb). In some embodiments, the 11-D-(S)-enantiomer is 2', 2', 3', 3', 4', 4', 5', 5', 6', 6', 7', 7', dodecadeuterotianeptine of the general formula (VIa) or the zwitterion thereof of the general formula (VIb).



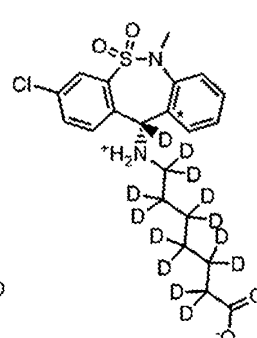
Formula (IIIa)



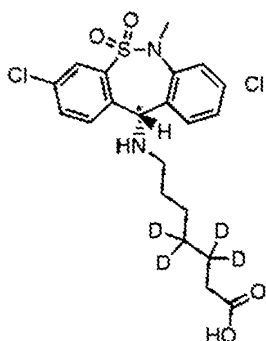
Formula (IIIb)



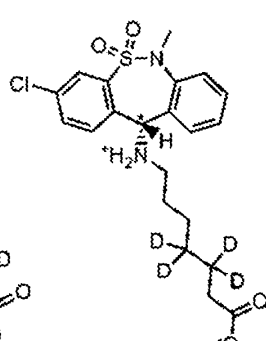
Formula (IVa)



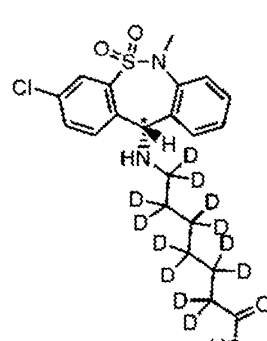
Formula (IVb)



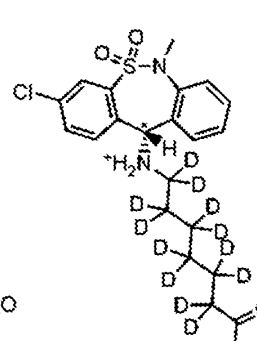
Formula (Va)



Formula (Vb)



Formula (VIa)



Formula (VIb)

[0081] Methods of producing the compounds described herein as pharmaceutically acceptable salts of the (S)-enantiomers of this disclosure, and the like are well known to those of skill in the art. For example, salts can be prepared from the free base using conventional methodology that typically involves reaction with a suitable acid. Suitable acids for preparing acid addition salts include, but are not limited to both organic acids, *e.g.*, acetic, propionic, glycolic, gluconic, glucuronic, glutamic, pyruvic, oxalic, lactic, malic, malonic, succinic, maleic, fumaric, formic, tartaric, citric, aspartic, ascorbic, benzoic, cinnamic, mandelic, methanesulfonic, ethanesulfonic, *p*-toluenesulfonic, benzenesulfonic, salicylic, orotic, hippuric, anthranilic, mesylic, 4-hydroxybenzoic, 2-hydroxyethanesulfonic, phenylacetic, mandelic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, beta-hydroxybutyric, camphorsulfonic, galactaric and galacturonic acid and the like, as well as inorganic acids, *e.g.*, hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, phosphoric, and the like. Conversely, preparation of basic salts of the S-enantiomers described herein can be prepared in a similar manner using a pharmaceutically acceptable base. Suitable

pharmaceutically acceptable base addition salts of the (S)-enantiomers of this disclosure, include metallic salts made from calcium, magnesium, potassium, sodium, ammonium and zinc or the like, or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), procaine and trimethylamine or the like.

[0082] In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomers and crystalline forms thereof of this disclosure is (S)-tianeptine benzenesulfonate (1:1), (S)-tianeptine fumarate (1:1), (S)-tianeptine fumarate (2:1), (S)-tianeptine hippurate (1:1), (S)-tianeptine maleate (1:1), (S)-tianeptine maleate (2:1), (S)-tianeptine p-toluenesulfonate (1:1), (S)-tianeptine orotate (1:1), (S)-tianeptine camphorsulfonate (1:1), (S)-tianeptine N-acetyl-L-tyrosinate (1:1), (S)-tianeptine polisterix, (S)-tianeptine: L-DBTA (2:1), (S)-tianeptine sodium, (S)-tianeptine oxalate, or (S)-tianeptine oxalate (2:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine benzenesulfonate (1:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine fumarate (1:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine fumarate (2:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine hippurate (1:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine maleate (1:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine maleate (2:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine p-toluenesulfonate (1:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine orotate (1:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine camphorsulfonate (1:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine N-acetyl-L-tyrosinate (1:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine polisterix. In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine: L-DBTA (2:1). In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine sodium. In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine oxalate. In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is (S)-tianeptine oxalate (2:1) (*i.e.*, (S)-tianeptine hemi-oxalate). In some embodiments, the hemi-oxalate salt is in a crystalline form.

[0083] In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer and crystalline forms thereof of this disclosure is 11-D-(S)-tianeptine benzenesulfonate (1:1), 11-D-(S)-tianeptine fumarate (1:1), 11-D-(S)-tianeptine fumarate (2:1), 11-D-(S)-tianeptine hippurate (1:1), 11-D-(S)-tianeptine maleate (1:1), 11-D-(S)-tianeptine maleate (2:1), 11-D-(S)-tianeptine p-toluenesulfonate (1:1), 11-D-(S)-tianeptine orotate (1:1), 11-D-(S)-tianeptine camphorsulfonate (1:1), 11-D-(S)-tianeptine N-acetyl-L-tyrosinate (1:1), 11-D-(S)-tianeptine polisterix, 11-D-(S)-tianeptine: L-DBTA (2:1), 11-D-(S)-tianeptine sodium, 11-D-(S)-tianeptine oxalate, or 11-D-(S)-tianeptine oxalate (2:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine benzenesulfonate (1:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine fumarate (1:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine fumarate (2:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine hippurate (1:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine maleate (1:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine maleate (2:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine p-toluenesulfonate (1:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine orotate (1:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine camphorsulfonate (1:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine N-acetyl-L-tyrosinate (1:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine polisterix. In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer is 11-D-(S)-tianeptine: L-DBTA (2:1). In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine sodium. In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine oxalate. In some embodiments, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is 11-D-(S)-tianeptine oxalate (2:1) (*i.e.*, 11-D-(S)-tianeptine hemi-oxalate). In some embodiments the hemi-oxalate salt is in crystalline form.

[0084] In some embodiments, *e.g.*, fumaric acid and maleic acid act as a monoanions or a dianion, leading to different salt stoichiometries (*i.e.*, a 1:1 or 2:1 ratio of tianeptine to

fumaric acid/ maleic acid). These salts may also comprise additional deuterium substitutions at one or more positions on the aminoheptanoic side chain.

[0085] In some embodiments, the pharmaceutically acceptable salt or crystalline forms thereof of the (S)-enantiomer of this disclosure or the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or crystalline forms thereof of this disclosure is formed from the benzenesulfonic, fumaric, hippuric, maleic, or p-toluenesulfonic acid in acetone and 2-propanol. In some embodiments, the pharmaceutically acceptable salt of the (S)-enantiomer or crystalline forms thereof of this disclosure or the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or crystalline forms thereof of this disclosure is formed from orotic acid in 58% water/42% tetrahydrofuran (THF).

[0086] In some aspects, this disclosure provides a co-crystal of the (S)-enantiomer of this disclosure, wherein the (S)-enantiomer or the zwitterion thereof forms a complex with L-tyrosine, L-tryptophan, L-phenylalanine, or another L-amino acid. In some embodiments, the (S)-enantiomer or the zwitterion thereof forms a complex with L-tyrosine. In some embodiments, the (S)-enantiomer or the zwitterion thereof forms a complex with L-tryptophan. In some embodiments, the (S)-enantiomer or the zwitterion thereof forms a complex with L-phenylalanine. In some embodiments, the (S)-enantiomer or the zwitterion thereof forms a complex with another L-amino acid. In some embodiments, the ratio of the (S)-enantiomer or the zwitterion thereof to the L-amino acid is 1:1, 1:2, or 2:1. In some embodiments, the ratio of the (S)-enantiomer or the zwitterion thereof to the L-amino acid is 1:1. In some embodiments, the ratio of the (S)-enantiomer or the zwitterion thereof to the L-amino acid is 1:2. In some embodiments, the ratio of the (S)-enantiomer or the zwitterion thereof to the L-amino acid is or 2:1. In some embodiments, the co-crystal comprises an inorganic monoacid salt of the (S)-enantiomer and a zwitterion of the L-amino acid. In some embodiments, the co-crystal comprises an inorganic monoacid salt of the L-amino acid and the zwitterion of the (S)-enantiomer. In some embodiments, the inorganic monoacid is hydrochloric acid (HCl).

[0087] In some aspects, this disclosure provides a co-crystal of the 11-D-(S)-enantiomer of this disclosure (and of an 11-D-(S)-enantiomer having at least one deuterium substitution on the aminoheptanoic side chain), wherein the (S)-enantiomer or the zwitterion thereof forms a complex with L-tyrosine, L-tryptophan, L-phenylalanine, or another L-amino acid. In some embodiments, the 11-D-(S)-enantiomer or the zwitterion thereof forms a complex with L-tyrosine. In some embodiments, the 11-D-(S)-enantiomer or the zwitterion thereof forms a complex with L-tryptophan. In some embodiments, the 11-D-(S)-enantiomer

or the zwitterion thereof forms a complex with L-phenylalanine. In some embodiments, the 11-D-(S)-enantiomer or the zwitterion thereof forms a complex with another L-amino acid. In some embodiments, the ratio of the 11-D-(S)-enantiomer or the zwitterion thereof to the L-amino acid is 1:1, 1:2, or 2:1. In some embodiments, the ratio of the 11-D-(S)-enantiomer or the zwitterion thereof to the L-amino acid is 1:1. In some embodiments, the ratio of the 11-D-(S)-enantiomer or the zwitterion thereof to the L-amino acid is 1:2. In some embodiments, the ratio of the 11-D-(S)-enantiomer or the zwitterion thereof to the L-amino acid is or 2:1. In some embodiments, the co-crystal comprises an inorganic monoacid salt of the 11-D-(S)-enantiomer and a zwitterion of the L-amino acid. In some embodiments, the co-crystal comprises an inorganic monoacid salt of the L-amino acid and the zwitterion of the 11-D-(S)-enantiomer. In some embodiments, the inorganic monoacid is hydrochloric acid (HCl).

[0088] In some aspects, this disclosure provides an ester of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, wherein the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 1% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.9% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.8% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.7% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.6% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.5% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.4% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$

about 0.3% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.2% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof.

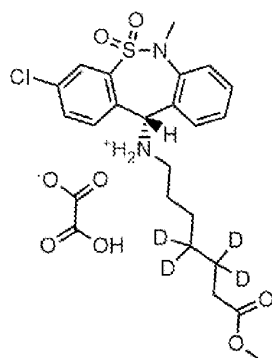
[0089] In some embodiments, this disclosure provides an ester of the 11-D-(S)-enantiomer of this disclosure (and of an 11-D-(S)-enantiomer having at least one deuterium substitution on the aminoheptanoic side chain) or a pharmaceutically acceptable salt thereof, wherein the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 1% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.

In some embodiments, the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.9% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.8% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.7% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.6% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.5% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.4% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.3% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.2% of the

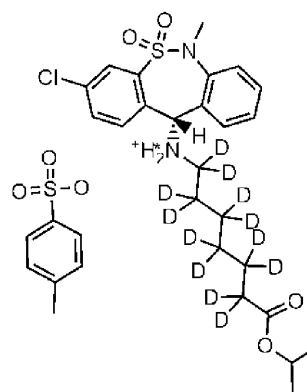
ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.

- 5 [0090] In some embodiments, the esters include C₁-C₆ alkyl, C₃-C₆ branched alkyl, C₃-C₆ cyclic alkyl, and pivaloyloxyethyl esters. The esters are designed such that the salts of the esters, without wishing to be bound by theory, dissolve slowly enough to provide slow release of the esters, and such that the esters can undergo enzymatic cleavage to form the active (S)-enantiomer or 11-D-(S)-enantiomer in the intestine, serum and/or brain at such a
- 10 rate as to provide slow release of the (S)-enantiomer or 11-D-(S)-enantiomer allowing once-a-day dosing of the ester salt.

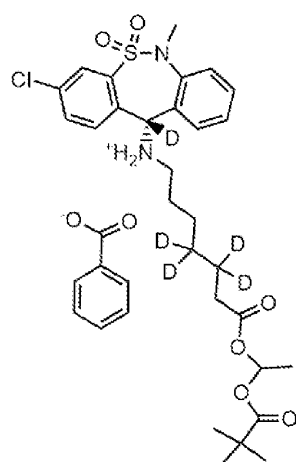
- [0091] Exemplary esters include 3', 3', 4', 4', tetradeutero-(S)-tianeptine methyl ester oxalate 1:1 of Formula (VII), 2', 2', 3', 3', 4', 4', 5', 5', 6', 6', 7', 7' -dodecadeutero(S)-tianeptine isopropyl ester p-toluenesulfonate of Formula (VIII), 3', 3', 4', 4', 11-
- 15 pentadeutero-(S)-tianeptine pivaloyloxyethyl ester benzoate of Formula (IX) and (S)-tianeptine ethyl ester orotate of Formula (X).



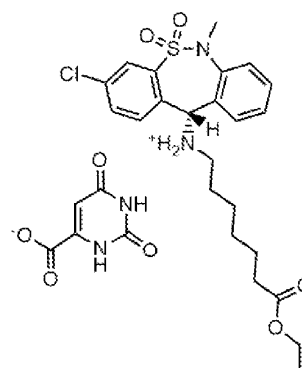
Formula (VII)



Formula (VIII)



Formula (IX)



Formula (X)

[0092] In some aspects, this disclosure provides an amide of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, wherein the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 1% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.9% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.8% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.7% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.6% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.5% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.4% of the amide of the (R)-enantiomer or

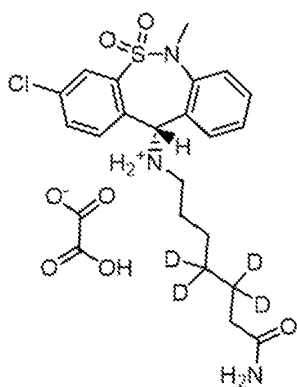
pharmaceutically acceptable salt thereof. In some embodiments, the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.3% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.2% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof.

[0093] In some embodiments, this disclosure provides an amide of the 11-D-(S)-enantiomer of this disclosure (and of an 11-D-(S)-enantiomer having at least one deuterium substitution on the aminoheptanoic side chain) or a pharmaceutically acceptable salt thereof, wherein the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 1% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.9% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.8% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.7% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.6% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.5% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.4% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.3% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.

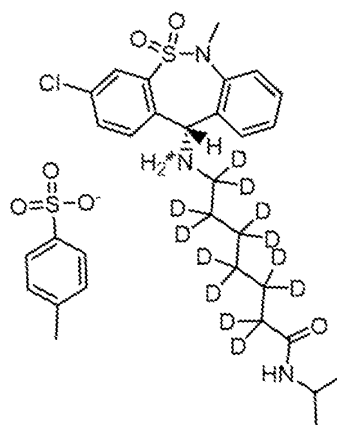
acceptable salt thereof. In some embodiments, the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.2% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.

[0094] In some embodiments, the amides include simple amides, C₁-C₆ alkyl optionally substituted with at least one hydroxyl, C₃-C₆ branched alkyl, and C₃-C₆ cyclic alkyl amides. The amides are designed such that the salts of the amides, without wishing to be bound by theory, provide advantages of improved crystallization in comparison to the (S)-enantiomer or the 11-D-(S)-enantiomer of tianeptine, selected delivery to the CNS due to metabolism by the brain specific fatty acid amide hydrolases (FAAH), and cannabinoid activity through binding of fatty acid amides to cannabinoid receptors which may contribute to pain reduction and antidepressive activity.

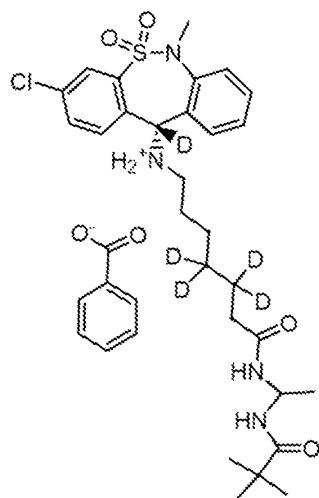
[0095] Exemplary amides include (S)-N-(7-amino-7-oxoheptyl-4,4,5,5-d₄)-3-chloro-6-methyl-6,11-dihydrodibenzo[c,f][1,2]thiazepine-11-aminium 5,5-dioxide oxalate 1:1 of Formula (XI), (S)-3-chloro-N-(7-(isopropylamino)-7-oxoheptyl-1,1,2,2,3,3,4,4,5,5,6,6-d₁₂)-6-methyl-6,11-dihydrodibenzo[c,f][1,2]76hiazepine-11-aminium 5,5-dioxide p-toluenesulfonate of Formula (XII), (11S)-3-chloro-6-methyl-N-(7-oxo-7-((1-pivalamidoethyl)amino)heptyl-4,4,5,5-d₄)-6,11-dihydrodibenzo[c,f][1,2]76hiazepine-11-d-11-aminium 5,5-dioxide benzoate of Formula (XIII) and (S)-3-chloro-N-(7-(ethylamino)-7-oxoheptyl)-6-methyl-6,11-dihydrodibenzo[c,f][1,2]76hiazepine-11-aminium 5,5-dioxide orotate of Formula (XIV).



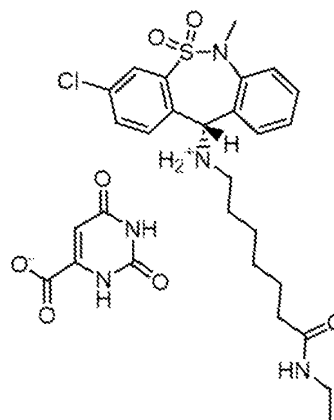
Formula (XI)



Formula (XII)



Formula (XIII)



Formula (XIV)

5 [0096] In some embodiments, this disclosure provides a pharmaceutically acceptable acid salt of the (S)-enantiomers (*e.g.*, (S)-enantiomer or 11-D-(S)-enantiomer) of this disclosure, wherein the nitrogen atom in the sidechain attached to Carbon-11 (C-11) is 100% protonated, the 100% protonated salt being less sensitive to air oxidation in solid or solution forms when compared to the (S)-enantiomer, 11-D-(S)-enantiomer, the zwitterion of either or
10 the sodium salts of either.

[0097] In some aspects, this disclosure provides a crystalline hemi-oxalate salt of (S)-7-(3-chloro-6-methyl-6,11-dihydrodibenzo[c,f] [1,2]thiazepin-11-ylamino)heptanoic acid 5,5-dioxide ((S)-tianeptine). In some embodiments, the crystalline (S)-tianeptine hemi-oxalate salt of this disclosure exhibits an X-ray diffraction pattern (XRPD) comprising at
15 least one peak selected from 8.5, 20.6, 21.0 and 24.2 degrees 2θ ±0.3 degrees 2θ. In some embodiments, the crystalline (S)-tianeptine hemi-oxalate salt further exhibits an XRPD pattern further comprising at least one peak selected from the group consisting of 12.1, 13.3, 16.1, 18.9, 19.1, 22.0 and 22.4 degrees 2θ ±0.3 degrees 2θ.

[0098] In some aspects, this disclosure provides a crystalline free acid/free base of the
20 (S)-enantiomer of tianeptine. In some embodiments, the crystalline (S)-enantiomer of tianeptine exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak selected from 10.6, 13.0, 21.1 and 23.7 degrees 2θ ±0.3 degrees 2θ. In some embodiments, the crystalline (S)-enantiomer of tianeptine exhibits an X-ray diffraction pattern (XRPD) further

comprising at least one peak selected from the group consisting of 8.7, 9.1, 12.6, 18.1, 20.4, 23.0 and 26.1 degrees $2\theta \pm 0.3$ degrees 2θ .

(S)-Tianeptine Analogs

- 5 [0099] In some aspects, this disclosure provides the compound N-hydroxy-tianeptine or a pharmaceutically acceptable salt thereof. In some aspects, this disclosure provides the (S)-enantiomer of N-hydroxy-tianeptine (*i.e.*, N-hydroxy-(S)-tianeptine) or a pharmaceutically acceptable salt thereof. In some aspects, this disclosure provides the (R)-enantiomer of N-hydroxy-tianeptine (*i.e.*, N-hydroxy-(R)-tianeptine) or a pharmaceutically acceptable salt thereof. Without wishing to be bound by theory, N-hydroxy-tianeptine shows no μ -opioid receptor (MOR) agonism and acts as a potent PPAR- β/δ and/or PPAR- γ agonist.
- 10 [00100] In some embodiments, the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof, are characterized by comprising no more than about 2% (*i.e.*, $\leq$ about 2%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of the (R)-enantiomer of N-hydroxy-tianeptine. In some embodiments, the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 1% (*i.e.*, $\leq$ about 1%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.9 % (*i.e.*, $\leq$ about 0.9%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about
- 25
- 30

0.5% (*i.e.*, $\leq$ about 0.5%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.4% (*i.e.*, $\leq$ about 0.4%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

5 In some embodiments, the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.3% (*i.e.*, $\leq$ about 0.3%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

10 In some embodiments, the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.1% (*i.e.*, $\leq$ about 0.1%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

15 [00101] In some embodiments, the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof, are characterized by comprising no more than about 2% (*i.e.*, $\leq$ about 2%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt thereof. In some embodiments, the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 1% (*i.e.*, $\leq$ about 1%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

20 In some embodiments, the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.9 % (*i.e.*, $\leq$ about 0.9%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

25 In some embodiments, the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

30 In some embodiments, the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of the (S)-

enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.5% (*i.e.*, $\leq$ about 0.5%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.4% (*i.e.*, $\leq$ about 0.4%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.3% (*i.e.*, $\leq$ about 0.3%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.1% (*i.e.*, $\leq$ about 0.1%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

[00102] In some embodiments, the (S)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof, are characterized by comprising no more than about 2% (*i.e.*, $\leq$ about 2%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of the (R)-enantiomer of N-nitroso-tianeptine. In some embodiments, the (S)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 1% (*i.e.*, $\leq$ about 1%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.9% (*i.e.*, $\leq$ about 0.9%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of the (R)-enantiomer of N-nitroso-tianeptine or a

pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

5 In some embodiments, the (S)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.5% (*i.e.*, $\leq$ about 0.5%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about

10 0.4% (*i.e.*, $\leq$ about 0.4%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.3% (*i.e.*, $\leq$ about 0.3%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-

15 enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (S)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.1% (*i.e.*, $\leq$

20 about 0.1%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

[00103] In some embodiments, the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof, are characterized by comprising no more than about

25 2% (*i.e.*, $\leq$ about 2%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt thereof. In some embodiments, the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about

1% (*i.e.*, $\leq$ about 1%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no

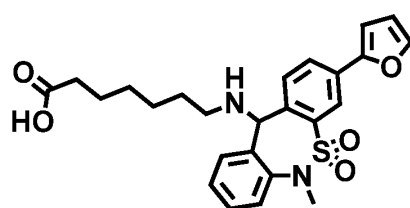
30 more than about 0.9% (*i.e.*, $\leq$ about 0.9%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

In some embodiments, the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.5% (*i.e.*, $\leq$ about 0.5%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.4% (*i.e.*, $\leq$ about 0.4%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.3 % (*i.e.*, $\leq$ about 0.3%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising no more than about 0.1% (*i.e.*, $\leq$ about 0.1%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

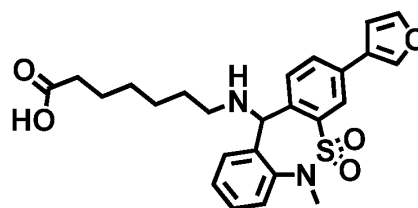
[00104] In some aspects, this disclosure provides the compound N-nitroso-tianeptine or a pharmaceutically acceptable salt thereof. In some aspects, this disclosure provides the (S)-enantiomer of N-nitroso-tianeptine (*i.e.*, N-nitroso-(S)-tianeptine) or a pharmaceutically acceptable salt thereof. In some aspects, this disclosure provides the (R)-enantiomer of N-nitroso-tianeptine (*i.e.*, N-nitroso-(R)-tianeptine) or a pharmaceutically acceptable salt thereof. Without wishing to be bound by theory, N-hydroxy-tianeptine shows no μ -opioid receptor (MOR) agonism and acts as a potent PPAR- β/δ and/or PPAR- γ agonist.

[00105] In some aspects, this disclosure provides aryl-substituted tianeptine derivatives. Exemplary derivatives include 7-((3-(furan-2-yl)-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid of Formula (XXI), 7-((3-(furan-3-yl)-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-

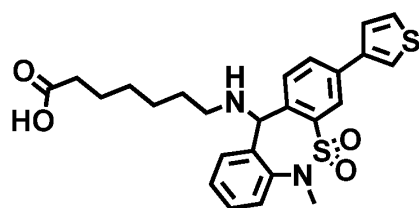
yl)amino)heptanoic acid of Formula (XXII), 7-((6-methyl-5,5-dioxido-3-(thiophen-3-yl)-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid of Formula (XXIII) and 2-(4-(((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)methyl)-2-methylphenoxy)acetic acid of Formula (XXIV). Without being bound to theory, the aryl-substituted tianeptine derivatives exhibit increased membrane penetration compared to tianeptine due to the aromatic ring, and the (R)-enantiomer of the aryl-substituted tianeptine derivatives and the racemic mixture show decreased MOR agonism compared to (R)-tianeptine and racemic tianeptine due to the shape of the molecule.



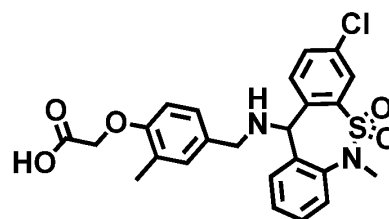
Formula (XXI)



Formula (XXII)



Formula (XXIII)



Formula (XXIV)

Pharmaceutical composition

[00106] The compounds described herein can be administered as the (S)-enantiomer or the 11-D-(S)-enantiomer of this disclosure or, if desired, in the form of a zwitterion, salt (including crystalline salts), ester, ester salt, amide, amide salt or co-crystal of this disclosure, provided the zwitterion, salt, ester, ester salt, amide, amide salt or co-crystal is suitable pharmacologically, *e.g.*, effective in the present method(s). Zwitterions, salts, esters, ester salts or co-crystals of the (S)-enantiomer or the 11-D-(S)-enantiomer of this disclosure can be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry.

[00107] In some embodiments, this disclosure provides a pharmaceutical composition comprising one or more of the (S)-enantiomers of this disclosure, *i.e.*, the zwitterions thereof or pharmaceutically acceptable salts of the (S)-enantiomers of this disclosure, or co-crystals of the (S)-enantiomers (including crystalline salts thereof) of this disclosure or zwitterions

thereof, or esters of the (S)-enantiomers or pharmaceutically acceptable salts thereof of this disclosure, or amides of the (S)-enantiomers or pharmaceutically acceptable salts thereof of this disclosure and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises no more than about 2% (*i.e.*, $\leq$ about 2%) of the (R)-enantiomers, the zwitterions thereof, or pharmaceutically acceptable salts of the (R)-enantiomers, or co-crystals of the (R)-enantiomers or zwitterions thereof, or esters of the (R)-enantiomers or pharmaceutically acceptable salts thereof, or amides of the (R)-enantiomers or pharmaceutically acceptable salts thereof.

[00108] In some embodiments, this disclosure provides a pharmaceutical composition comprising the (S)-enantiomer of tianeptine of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt (including crystalline salts thereof) of the (S)-enantiomer of this disclosure, or a co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises no more than about 2% (*i.e.*, $\leq$ about 2%) of the (R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or the zwitterion thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure. In some embodiments, the composition comprises no more than about 1% (*i.e.*, $\leq$ about 1%) of the (R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or the zwitterion thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure. In some embodiments, the composition comprises no more than about 0.9% (*i.e.*, $\leq$ about 0.9%) of the (R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or the zwitterion thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure. In some embodiments, the composition comprises no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of the (R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or the zwitterion thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (R)-

enantiomer or pharmaceutically acceptable salt thereof of this disclosure. In some embodiments, the composition comprises no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of the (R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or the zwitterion thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure. In some embodiments, the composition comprises no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of the (R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or the zwitterion thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure. In some embodiments, the composition comprises no more than about 0.5% (*i.e.*, $\leq$ about 0.5%) of the (R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or the zwitterion thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure. In some embodiments, the composition comprises no more than about 0.4% (*i.e.*, $\leq$ about 0.4%) of the (R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or the zwitterion thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure. In some embodiments, the composition comprises no more than about 0.3% (*i.e.*, $\leq$ about 0.3%) of the (R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or the zwitterion thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure. In some embodiments, the composition comprises no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of the (R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or the zwitterion thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure. In some embodiments of this disclosure, the composition comprises no more than about 0.1% (*i.e.*, $\leq$ about 0.1%) of the (R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or the zwitterion

thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure.

[00109] In some embodiments, the pharmaceutical composition of this disclosure comprises the (S)-enantiomer of tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable salt (including crystalline salts thereof) of the (S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable co-crystal of the (S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments the pharmaceutical composition comprises the zwitterion of the (S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition comprises an ester of the (S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable salt of the ester of the (S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition comprises an amide of the (S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable salt of the amide of the (S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient.

[00110] In some embodiments, this disclosure provides a pharmaceutical composition comprising the 11-D-(S)-enantiomer of tianeptine of this disclosure (and of an 11-D-(S)-enantiomer having at least one deuterium substitution on the aminoheptanoic side chain), the zwitterion thereof, or a pharmaceutically acceptable salt (including crystalline salts thereof) of an 11-D-(S)-enantiomer of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of an 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure, or an amide of an 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof of this disclosure and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises no more than about 2% (*i.e.*, $\leq$ about 2%) of an 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(R)-enantiomer, or co-crystal of an 11-D-(R)-enantiomer or the zwitterion thereof, or an ester of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of an 11-D-(R)-

enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises no more than about 1% (*i.e.*, $\leq$ about 1%) of an 11-D-(R)-enantiomer of tianeptine, a zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(R)-enantiomer, or co-crystal of an 11-D-(R)-enantiomer or a zwitterion thereof, or an ester of an
5 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises no more than about 0.9% (*i.e.*, $\leq$ about 0.9%) of an 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(R)-enantiomer, or co-crystal of an 11-D-(R)-enantiomer or a zwitterion thereof, or an
10 ester of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of an 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(R)-enantiomer, or co-crystal of an 11-D-(R)-enantiomer or a zwitterion thereof, or an
15 ester of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of an 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(R)-enantiomer, or co-crystal of an 11-D-(R)-enantiomer or a zwitterion thereof, or an
20 ester of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of an 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(R)-enantiomer, or co-crystal of an 11-D-(R)-enantiomer or a zwitterion thereof, or an
25 ester of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises no more than about 0.5% (*i.e.*, $\leq$ about 0.5%) of an 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(R)-enantiomer, or co-crystal of the 11-D-(R)-enantiomer or a zwitterion thereof, or an
30 ester of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises no more than about 0.4% (*i.e.*, $\leq$ about 0.4%) of an 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(R)-enantiomer, or co-crystal of an 11-D-(R)-enantiomer or a zwitterion thereof, or an

ester of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises no more than about 0.3% (*i.e.*, $\leq$ about 0.3%) of an 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(R)-enantiomer, or co-crystal of an 11-D-(R)-enantiomer or a zwitterion thereof, or an ester of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of an 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(R)-enantiomer, or co-crystal of an 11-D-(R)-enantiomer or a zwitterion thereof, or an ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof. In some embodiments of this disclosure, the composition comprises no more than about 0.1% (*i.e.*, $\leq$ about 0.1 %) of an 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(R)-enantiomer, or co-crystal of an 11-D-(R)-enantiomer or a zwitterion thereof, or an ester of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of an 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.

[00111] In some embodiments, the pharmaceutical composition of this disclosure comprises an 11-D-(S)-enantiomer of tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable salt (including crystalline salts thereof) of an 11-D-(S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable co-crystal of an 11-D-(S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments the pharmaceutical composition comprises a zwitterion of an 11-D-(S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition comprises an ester of an 11-D-(S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable salt of the ester of an 11-D-(S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition comprises an amide of the 11-D-(S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical

composition comprises a pharmaceutically acceptable salt of the amide of the 11-D-(S)-enantiomer of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient.

[00112] In some embodiments, the composition comprises a mixture of two or more pharmaceutically acceptable salts (including crystalline salts thereof) or co-crystals of the (S)-enantiomer or the 11-D-(S)-enantiomer (and of an 11-D-(S)-enantiomer having at least one deuterium substitution on the aminoheptanoic side chain), wherein the mixture of the pharmaceutically acceptable salts or co-crystals is characterized by an enhanced extended release when administered orally as compared to administering a composition comprising a single pharmaceutically acceptable salt or co-crystal of the (S)-enantiomer or the 11-D-(S)-enantiomer of this disclosure. In some embodiments, the enhanced extended release of the mixture of the pharmaceutically acceptable salts or co-crystals is due, without being bound by theory, to the different dissolution rates of each of the salt or co-crystal forms in the intestinal track.

[00113] In some embodiments, the pharmaceutical composition of this disclosure comprises one or more of the tianeptine analogs of this disclosure, *i.e.*, N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, the (R)-enantiomer of N-nitroso-tianeptine, or an aryl-substitute analog of tianeptine of this disclosure or a pharmaceutically acceptable salt of any of them and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises the N-hydroxy-tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises a pharmaceutically acceptable salt of the N-hydroxy-tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises the (S)-enantiomer of N-hydroxy-tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises a pharmaceutically acceptable salt of the (S)-enantiomer of the N-hydroxy-tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises the (R)-enantiomer of N-hydroxy-tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises a pharmaceutically acceptable salt of the (R)-enantiomer of the N-hydroxy-tianeptine of this

disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises the N-nitroso-tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises a pharmaceutically acceptable salt of the N-nitroso-tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises the (S)-enantiomer of N-nitroso-tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises a pharmaceutically acceptable salt of the (S)-enantiomer of the N-nitroso-tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises the (R)-enantiomer of N-nitroso-tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises a pharmaceutically acceptable salt of the (R)-enantiomer of the N-nitroso-tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises an aryl-substitute analog of tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the pharmaceutical composition of this disclosure comprises a pharmaceutically acceptable salt of aryl-substitute analog of tianeptine of this disclosure and a pharmaceutically acceptable carrier, diluent or excipient.

[00114] In some embodiments, this disclosure provides a pharmaceutical composition comprising the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof of this disclosure, and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises no more than about 2% (*i.e.*, $\leq$ about 2%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of the (R)-enantiomer of N-hydroxy-tianeptine. In some embodiments, the composition comprises no more than about 1% (*i.e.*, $\leq$ about 1%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.9% (*i.e.*, $\leq$ about 0.9%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some

embodiments, the composition comprises no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.5% (*i.e.*, $\leq$ about 0.5%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.4% (*i.e.*, $\leq$ about 0.4%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.3% (*i.e.*, $\leq$ about 0.3%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.1% (*i.e.*, $\leq$ about 0.1%) of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

[00115] In some embodiments, this disclosure provides a pharmaceutical composition comprising the (R)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof of this disclosure, and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises no more than about 2% (*i.e.*, $\leq$ about 2%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises no more than about 1% (*i.e.*, $\leq$ about 1%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.9% (*i.e.*, $\leq$ about 0.9%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.5% (*i.e.*, $\leq$ about 0.5%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that

enantiomer. In some embodiments, the composition comprises no more than about 0.4% (*i.e.*, $\leq$ about 0.4%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.3% (*i.e.*, $\leq$ about 0.3%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.1% (*i.e.*, $\leq$ about 0.1%) of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

- 10 [00116] In some embodiments, this disclosure provides a pharmaceutical composition comprising the (S)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof of this disclosure, and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises no more than about 2% (*i.e.*, $\leq$ about 2%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of the (R)-enantiomer of N-nitroso-tianeptine. In some embodiments, the composition comprises no more than about 1% (*i.e.*, $\leq$ about 1%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.9% (*i.e.*, $\leq$ about 0.9%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.5% (*i.e.*, $\leq$ about 0.5%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.4% (*i.e.*, $\leq$ about 0.4%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.3% (*i.e.*, $\leq$ about 0.3%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some

embodiments, the composition comprises no more than about 0.1% (*i.e.*, $\leq$ about 0.1%) of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

[00117] In some embodiments, this disclosure provides a pharmaceutical composition comprising the (R)-enantiomer of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof of this disclosure, and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises no more than about 2% (*i.e.*, $\leq$ about 2%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises no more than about 1% (*i.e.*, $\leq$ about 1%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.9% (*i.e.*, $\leq$ about 0.9%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.8% (*i.e.*, $\leq$ about 0.8%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.7% (*i.e.*, $\leq$ about 0.7%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.6% (*i.e.*, $\leq$ about 0.6%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.5% (*i.e.*, $\leq$ about 0.5%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.4% (*i.e.*, $\leq$ about 0.4%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.3% (*i.e.*, $\leq$ about 0.3%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.2% (*i.e.*, $\leq$ about 0.2%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer. In some embodiments, the composition comprises no more than about 0.1% (*i.e.*, $\leq$ about 0.1%) of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of that enantiomer.

Dosages Forms and Modes of Administration

[00118] Any suitable route of administration may be employed for administering the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer) of this disclosure, zwitterions, pharmaceutically acceptable salts, co-crystals, esters and pharmaceutically acceptable salts of these esters, amides and pharmaceutically acceptable salts of these amides, and the analogs of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or the aryl-substituted tianeptine analogs, or pharmaceutically acceptable salts thereof) and pharmaceutical compositions thereof of this disclosure. Exemplary routes of administration of the (S)-enantiomer of tianeptine of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer and crystalline forms thereof of this disclosure, or a co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof, or an 11-D-(S)-enantiomer of tianeptine of this disclosure, a zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(S)-enantiomer and crystalline forms thereof of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or a zwitterion thereof, or an ester of an 11-D-(S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof, or an amide of the 11-D-(S)-enantiomer, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or the aryl-substituted tianeptine analogs) or pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof of this disclosure or a pharmaceutical composition of this disclosure include, but are not limited to parenteral, oral, sublingual, buccal, inhalational, palatal, transdermal, rectal, and vaginal administration.

[00119] In some embodiments, dosage forms useful for administering the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer) of this disclosure, zwitterions, pharmaceutically acceptable salts, co-crystals, esters and pharmaceutically acceptable salts of these esters, amides, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or the aryl-substituted tianeptine analogs or pharmaceutically acceptable salts thereof), and pharmaceutical compositions of this disclosure may include, but are not limited to tablets, such as scored tablets, coated tablets, mini-tablets, chewable tablets, orodispersible tablets or dissolving tablets; thin films; powders (*e.g.*, a lung powder or dry powder inhaler);

caplets; capsules (*e.g.*, hard gelatin capsules); soft gels; suppositories; nasal and other forms of inhalational sprays. In some embodiments, the dosage form is a tablet. In some embodiments, the dosage form is a thin film. In some embodiments, the dosage form is a powder. In some embodiments, the dosage form is a caplet. In some embodiments, the dosage form is a capsule. In some embodiments, the dosage form is a suppository. In some embodiments, the dosage form is an inhalational spray. In some embodiments, the spray is a nasal spray. In some embodiments, the spray is an oral spray.

[00120] The dosage form of this disclosure for parenteral administration in some embodiments can take the form of an aqueous or nonaqueous solution, dispersion, suspension or emulsion. For example, in preparing the dosage forms of this disclosure for parenteral administration, at least one of the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer) of this disclosure, zwitterions, co-crystals, esters or pharmaceutically acceptable salts, amides, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog) or pharmaceutically acceptable salts thereof are mixed with a suitable pharmaceutically acceptable carrier such as water, oil (particularly a vegetable oil), ethanol, saline solutions (*e.g.*, normal saline), aqueous dextrose (glucose) and related sugar solutions, glycerol, or glycols such as propylene glycol or polyethylene glycol. For parenteral administration, these dosage forms preferably contain a water-soluble salt of at least one of the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer), zwitterions, co-crystals, esters, amides, the N-hydroxy-tianeptine, the (S)- or (R)- enantiomer thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analogs) or pharmaceutically acceptable salts thereof of this disclosure. Stabilizing agents, antioxidizing agents and preservatives can also be added to the for parenteral dosage forms. Suitable antioxidizing agents include sulfite, ascorbic acid, citric acid and its salts, and sodium EDTA. Suitable preservatives include benzalkonium chloride, methyl- or propyl-paraben, and chlorbutanol.

[00121] For oral administration, in some embodiments the dosage forms of this disclosure comprise at least one of the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer), zwitterions, co-crystals, esters, amides, or analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog) and salts of this disclosure combined with one or more solid or liquid inactive ingredients to form tablets,

capsules, pills, powders, or other suitable oral dosage forms. For example, at least one of the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer), zwitterions, esters, amides, salts or co-crystals, or analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog) and salts of this disclosure is combined with at least one pharmaceutically acceptable carrier such as a solvent, filler, binder, humectant, disintegrating agent, solution retarder, absorption accelerator, wetting agent absorbent or lubricating agent. In one embodiment, at least one of the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer), zwitterions, esters, amides, salts or co-crystals or analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog) and salts of this disclosure is combined with carboxymethylcellulose calcium, magnesium stearate, mannitol and starch, and is formed into tablets by conventional tableting methods. In one embodiment, the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer), zwitterions, esters, amides, salts or co-crystals, or analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog) and salts of this disclosure is formulated into a tablet comprising cellulose and a calcium salt, as described in U.S. Pat. No. 5,888,542, the entire disclosure of which is herein incorporated by reference.

[00122] In some embodiments, the dosage form of the (S)-enantiomer or an 11-D-(S)-enantiomer, zwitterions, salts, co-crystals, esters or amides thereof, or analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog) and salts of this disclosure are formulated for immediate release, controlled release, sustained release, extended release, or slow release. In some embodiments, the dosage form of this disclosure is formulated for immediate release of the (S)-enantiomer, zwitterion, salt, ester, amide or co-crystal thereof, or analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog) and salts thereof of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for immediate release of an 11-D-(S)-enantiomer, zwitterion, salt, ester, amide or co-crystal thereof of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for immediate release of an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine

analog or a pharmaceutically acceptable salt thereof) of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for controlled release of the (S)-enantiomer, zwitterion, salt, ester, amide or co-crystal thereof of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for controlled release of an 11-D-(S)-enantiomer, zwitterion, salt, ester, amide or co-crystal thereof of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for controlled release of an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure. In some embodiments, the composition of this disclosure is formulated for sustained release of the (S)-enantiomer, zwitterion, salt, ester, amide or co-crystal thereof of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for sustained release of an 11-D-(S)-enantiomer, zwitterion, salt, ester, amide or co-crystal thereof of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for sustained release of an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for extended release of the (S)-enantiomer, zwitterion, salt, ester, amide or co-crystal thereof of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for extended release of an 11-D-(S)-enantiomer, zwitterion, salt, ester, amide or co-crystal thereof of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for extended release of an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts) of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for slow release of the (S)-enantiomer, zwitterion, salt, ester, amide or co-crystal thereof of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for slow release of an 11-D-(S)-enantiomer, zwitterion, salt, ester, amide or co-crystal thereof of this disclosure. In some embodiments, the dosage form of this disclosure is formulated for slow release of an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure.

[00123] Preferably, a controlled-release dosage form of this disclosure is capable of

releasing at least one of the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer), zwitterions, esters, amides, salts, or co-crystals thereof, or analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure into a subject at a desired rate, so as to maintain a substantially constant pharmacological activity over a given period of time. Formulation of controlled-release pharmaceutical compositions of the invention is within the skill in the art. Controlled release formulations suitable for use in the present invention are described in, for example, U.S. Pat. No. 5,674,533 (liquid dosage forms), U.S. Pat. No. 5,591,767 (liquid reservoir transdermal patch), U.S. Pat. No. 5,120,548 (device comprising swellable polymers), U.S. Pat. No. 5,073,543 (ganglioside-liposome vehicle), U.S. Pat. No. 5,639,476 (stable solid formulation coated with a hydrophobic acrylic polymer), the entire disclosures of which are herein incorporated by reference.

[00124] Biodegradable microparticles can also be used to formulate controlled-release dosage forms of this disclosure, for example, as described in U.S. Pat. Nos. 5,354,556 and 5,733,566, the entire disclosures of which are herein incorporated by reference.

[00125] In one embodiment, controlled-release dosage form of this disclosure comprises at least one the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer), zwitterions thereof, pharmaceutically acceptable salts of the (S)-enantiomers, cocrystals of the (S)-enantiomers or their zwitterions, esters of the (S)-enantiomers or pharmaceutically acceptable salts thereof, or amides of the (S)-enantiomers or pharmaceutically acceptable salts thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)-enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) and a controlled-release component. As used herein, a “controlled-release component” is a compound, such as a polymer, polymer matrix, gel, permeable membrane, liposome and/or microsphere, that induces the controlled-release of the at least one of the (S)-enantiomers, zwitterions, cocrystals, esters, amides and salts of this disclosure into the subject upon exposure to a certain physiological compound or condition. For example, the controlled-release component can be biodegradable, activated by exposure to a certain pH or temperature, by exposure to an aqueous environment, or by exposure to enzymes. An example of a controlled-release component which is activated by exposure to a certain temperature is a sol-gel. In this embodiment, at least one of the (S)-enantiomers of tianeptine (*i.e.*, the (S)-enantiomer or 11-D-(S)-enantiomer) of this disclosure, zwitterions thereof,

pharmaceutically acceptable salts of the (S)-enantiomers, cocrystals of the (S)-enantiomers or their zwitterions, esters of the (S)-enantiomers or pharmaceutically acceptable salts thereof, or amides of the (S)-enantiomers, the N-hydroxy-tianeptine, the (S)- or (R)- enantiomer thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) is incorporated into a sol-gel matrix that is a solid at room temperature. When the sol-gel matrix is implanted into a subject having a body temperature high enough to induce gel formation of the sol-gel matrix, the tianeptine is released into the subject.

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Exemplary Disorders of this Disclosure

[00126] Diseases, disorders or conditions of this disclosure include but are not limited to a central nervous system (CNS) disorder, inflammatory disease, autoimmune disease, infectious illness, a hearing loss condition, ocular disease, musculoskeletal disease, metabolic disease, mitochondrial disease, hypertriglyceridemia (*e.g.*, statin-resistant hypertriglyceridemia, mixed-hypertriglyceridemia and familial hypertriglyceridemia), cancer (*e.g.*, glioblastoma or glioma), menopause and chronic overlapping pain conditions (COPCs), and psychological, physical, metabolic or hormonal stress and COPCs.

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[00127] CNS disorders of this disclosure include but are not limited to mood disorders (*e.g.*, major depressive disorder (MDD), bipolar disorder, or substance-induced disorder), trauma and stressor related disorders (*e.g.*, post-traumatic stress disorder (PTSD), acute stress disorder (ASD), adjustment disorder, or reactive attachment disorder), anxiety disorders (*e.g.*, panic disorder, generalized anxiety disorder (GAD), a specific phobia, agoraphobia or social phobia), obsessive compulsive disorder, neurodegenerative or neuroinflammatory disorders (*e.g.*, Mild Cognitive Impairment, Alzheimer's Disease, dementia, Parkinson's disease, Huntington's disease, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), traumatic brain injury, neuromyelitis optica, myasthenia gravis, autoimmune encephalitis, prion disease, transverse myelitis or pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)), neurodevelopmental disorders (*e.g.*, attention-deficit/ hyperactivity disorder (ADHD), schizophrenia, Prader-Willi Syndrome (including hyperphagia and other symptoms (*e.g.*, depression and anxiety) or autism), leukodystrophy (*e.g.*, leukoencephalopathy, a hypomyelinating or demyelinating disease, an intellectual disability syndrome (*e.g.*, Fragile X syndrome), a cognitive impairment (*e.g.*, cognitive

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impairment associated with a disease, disorder or condition (*e.g.*, Mild Cognitive Impairment, prodromal Alzheimer's Disease or Alzheimer's Disease, prodromal fronto-temporal dementia (FTD) or FTD, prodromal posterior cortical atrophy (PCA) or PCA, cognitive impairment associated with schizophrenia, a drug-induced cognitive disorder – such as corticosteroid-induced cognitive dysfunction, doxorubicin-induced cognitive dysfunction, chemotherapy-induced cognitive dysfunction, alcohol-induced cognitive dysfunction, or substance-induced cognitive dysfunction, radiotherapy-induced cognitive dysfunction, space travel-related cognitive decline (*e.g.*, spaceflight-associated neuro-ocular syndrome (SANS) or cognitive decline associated with elevated space radiation exposure), or cognitive deficit and neuropathic pain associated with diabetes mellitus), cognitive impairment associated with aging (*e.g.*, age-related cognitive impairment, age-related cognitive decline (ARCD), age-associated memory impairment (AAMI)), a glial cell dysfunction, or a brain injury (*e.g.*, a traumatic brain injury, hypoxia-induced brain injury, toxin-induced brain injury, stroke or reperfusion injury following ischemic stroke), and CNS oxidative stress.

[00128] Inflammatory diseases of this disclosure include but are not limited to postoperative cognitive dysfunction, arthritis (*e.g.*, rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis), systemic lupus erythematosus (SLE), myasthenia gravis, diabetes (*e.g.*, juvenile onset diabetes or diabetes mellitus type 1), Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, ankylosing spondylitis, psoriasis, Sjogren's syndrome, vasculitis, glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, ichthyosis, Graves' ophthalmopathy, inflammatory bowel disease, Addison's disease, vitiligo, asthma (*e.g.*, allergic asthma), acne vulgaris, celiac disease, chronic prostatitis, pelvic inflammatory disease, reperfusion injury, sarcoidosis, transplant rejection, interstitial cystitis, atherosclerosis and atopic dermatitis.

[00129] Autoimmune diseases of this disclosure include but are not limited to Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune orchitis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Balo disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, Chronic inflammatory

demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Cocksackie myocarditis, CREST syndrome, Crohn's disease, Dermatitis herpetiformis, Dermatomyositis,

5 Devis's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's

10 thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammaglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki

15 disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neonatal Lupus,

20 Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis (peripheral uveitis), Parsonage-Turner syndrome, Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis

25 nodosa, Polyglandular syndrome type I, Polyglandular syndrome type II, Polyglandular syndrome type III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex

30 sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis,

Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, Vogt-Koyanagi-Harada Disease, and Wegener's granulomatosis (or Granulomatosis with Polyangiitis (GPA)).

5 [00130] Infectious illnesses of this disclosure include but are not limited to viral infection (*e.g.*, COVID-19, influenza, human immunodeficiency virus (HIV) and herpes) or post-viral condition (*e.g.*, long COVID).

[00131] Hearing loss conditions of this disclosure include but are not limited to mitochondrial nonsyndromic hearing loss and deafness, hair cell death, age-related hearing
10 loss, noise-induced hearing loss, genetic or inherited hearing loss, hearing loss experienced as a result of ototoxic exposure, hearing loss resulting from disease, and hearing loss resulting from trauma.

[00132] Ocular diseases of this disclosure include but are not limited to cataracts, glaucoma, endoplasmic reticulum (ER) stress, autophagy deficiency, age-related macular
15 degeneration (AMD), and diabetic retinopathy.

[00133] Musculoskeletal diseases of this disclosure include but are not limited to muscular dystrophy (*e.g.*, Duchenne muscular dystrophy, Becker muscular dystrophy, distal muscular dystrophy, congenital muscular dystrophy, Emery-Dreifuss muscular dystrophy, facioscapulohumeral muscular dystrophy, myotonic muscular dystrophy type 1, or myotonic
20 muscular dystrophy type 2), multiple sclerosis, amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, spinal muscular atrophy, progressive spinobulbar muscular atrophy, spinal cord spasticity, spinal muscle atrophy, myasthenia gravis, neuralgia, fibromyalgia, Machado-Joseph disease, cramp fasciculation syndrome, Friedreich's ataxia, a muscle wasting disorder (*e.g.*, muscle
25 atrophy, sarcopenia, cachexia), an inclusion body myopathy, motor neuron disease, and paralysis.

[00134] Metabolic diseases of this disclosure include but are not limited to non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity (*e.g.*, diet induced obesity), heart disease (*e.g.*, cardiac hypertrophy), atherosclerosis, arthritis,
30 cystinosis, diabetes (*e.g.*, Type I diabetes, Type II diabetes, or gestational diabetes), phenylketonuria, proliferative retinopathy, and Keams-Sayre disease.

[00135] Mitochondrial diseases of this disclosure include but are not limited to Barth syndrome, chronic progressive external ophthalmoplegia (cPEO), Keams-Sayre syndrome (KSS), Leigh syndrome (*e.g.*, MILS, or maternally inherited Leigh syndrome), mitochondrial

DNA depletion syndromes (MDDS, *e.g.*, Alpers syndrome), mitochondrial encephalomyopathy (*e.g.*, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), myoclonus epilepsy with ragged red fibers (MERRF), neuropathy, ataxia, retinitis pigmentosa (NARP), Leber's hereditary optic neuropathy (LHON), and Pearson syndrome.

[00136] In some embodiments the diseases, disorders or conditions exemplified in this disclosure are modulated by, exacerbated by, or associated with altered activity of PPAR- β/δ and/ or PPAR- γ . In some embodiments the diseases, disorders or conditions exemplified in this disclosure are modulated by, exacerbated by, or associated with high levels of S-nitrosylation of PPAR- β/δ and/or PPAR- γ . In some embodiments the diseases, disorders or conditions exemplified in this disclosure are modulated by, exacerbated by, or associated with excessive levels of metal ions (*e.g.*, iron or copper) in circulation.

CNS Disorders

[00137] Exemplary clinical symptoms of CNS disorders, diseases and conditions include, but are not limited to, changes in cognitive function, including age-related decline in cognitive function, which is similar to or not as robust as age-matched controls, changes in attention and memory; difficulty with speaking, understanding, reading or writing; inability to process thoughts; anxiety; irritability or aggressiveness; muscle fatigue; muscle wasting; difficulty with walking; headache; hearing loss; seizures; spasticity; speech and swallowing disorders; tremors; paralysis; blindness; and loss of sensation.

Major Depressive Disorder

[00138] Major depressive disorder (MDD), also referred to as “clinical depression,” is a mood disorder in which symptoms that affect how a person feels, thinks, and handles daily activities are present almost every day for at least two weeks. Symptoms associated with MDD include (1) persistent sad, anxious, or “empty” mood; (2) feeling of hopelessness, or pessimism; (3) irritability; (4) feelings of guilt, worthlessness, or helplessness; (5) loss of interest or pleasure in hobbies and activities (*e.g.*, anhedonia); (6) decreased energy or fatigue; (7) moving or talking more slowly; (8) psychomotor agitation or retardation; (9) feeling restless or having trouble sitting still; (10) difficulty concentrating, remembering, or making decisions; (11) difficulty sleeping, early-morning awakening, or oversleeping (*e.g.*, insomnia or hypersomnia); (12) appetite and/or weight changes (*e.g.*, a change of more than 5% of body weight in a month); (13) recurring thoughts of death or suicide; (14) suicide

attempts; (15) aches or pains, headaches, cramps, or digestive problems without a clear physical cause and/or that do not ease even with treatment.

[00139] MDD can be diagnosed based on (1) a physical exam; (2) laboratory tests (e.g., blood test of complete blood count and/or assessing thyroid function); (3) psychiatric evaluation (e.g., health professional asks about symptoms, thoughts, feelings and behavior patterns and/or patient fills out a questionnaire, such as the Hospital Anxiety and Depression Scale (HADS), the Hamilton Depression Rating Scale (HDRS, HAM-D), and the Montgomery-Åsberg Depression Rating Scale (MADRS)); (4) Diagnostic and Statistical Manual of Mental Disorders (e.g., DSM-5 lists criteria for depression published by the American Psychiatric Association).

[00140] DSM-5 criteria for diagnosing MDD include at least 5 symptoms that are present during the same 2-week period, with at least one of the symptoms being diminished interest and pleasure or depressed mood. The symptoms associated with the DSM-5 criteria for MDD include (1) depressed mood (for children and adolescents, this can also be an irritable mood); (2) diminished interest or loss of pleasure in almost all activities (e.g., anhedonia); (3) significant weight change or appetite disturbance (for children, this can be failure to achieve expected weight gain); (4) sleep disturbance (e.g., insomnia or hypersomnia); (5) psychomotor agitation or retardation; (6) fatigue or loss of energy; (7) feelings of worthlessness; (8) diminished ability to think or concentrate; indecisiveness; (9) recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Age-related Cognitive Impairment

[00141] “Age-related cognitive impairment” refers to cognitive impairment in aged subjects, wherein their cognitive function is not as robust as that expected in an age-matched normal subject or as that expected in young adult subjects. In some cases, cognitive function is reduced by about 5%, about 10%, about 30%, or more, compared to cognitive function expected in an age-matched normal subject. In some cases, cognitive function is as expected in an age-matched normal subject, but reduced by about 5%, about 10%, about 30%, about 50% or more, compared to cognitive function expected in a young adult subject. Age-related impaired cognitive function may be associated with Mild Cognitive Impairment (MCI) (including amnesic MCI and non-amnesic MCI), Age-Associated Memory Impairment (AAMI), and Age-related Cognitive Decline (ARCD).

[00142] “Age-Associated Memory Impairment (AAMI)” refers to a decline in memory

due to aging. A patient may be considered to have AAMI if he or she is at least 50 years old and meets all of the following criteria: a) The patient has noticed a decline in memory performance, b) The patient performs worse on a standard test of memory compared to young adults, c) All other obvious causes of memory decline, except normal aging, have been ruled out (in other words, the memory decline cannot be attributed to other causes such as a recent heart attack or head injury, depression, adverse reactions to medication, Alzheimer's disease, etc.).

[00143] "Age-Related Cognitive Decline (ARCD)" refers to declines in memory and cognitive abilities that are a normal consequence of aging in humans (e.g., Craik & Salthouse, 1992). This is also true in virtually all mammalian species. Age-Associated Memory Impairment refers to older persons with objective memory declines relative to their younger years, but cognitive functioning that is normal relative to their age peers (Crook et al., 1986). Age-Consistent Memory Decline is a less pejorative label which emphasizes that these are normal developmental changes (Crook, 1993; Larrabee, 1996), are not pathophysiological (Smith et al., 1991), and rarely progress to overt dementia (Youngjohn & Crook, 1993). The DSM-IV (1994) has codified the diagnostic classification of ARCD, which has continued in DSM-5 (2013) under code 780.9 for ARCD.

Drug-induced Cognitive Dysfunction

Corticosteroid-induced Cognitive Dysfunction

[00144] Due to their anti-inflammatory properties, corticosteroids are used in the treatment of many diseases and conditions including asthma, systematic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, nephritic syndrome, cancer, organ transplantation, autoimmune hepatitis, hypersensitivity reactions, cardiogenic and septic shock, glucocorticoid deficiency diseases (Addison's disease and panhypopituitarism), and multiple sclerosis. When the body experiences stress, the adrenal glands release corticosteroids, such as cortisol. Synthetic corticosteroids work by mimicking steroid hormones naturally produced by the adrenal glands. Upon release into the body's circulatory system, these hormones help to regulate inflammation as well as the body's immune response. Common synthetic corticosteroids include prednisone, cortisone, hydrocortisone, and methylprednisone. Supplementing the body's normal hormone levels with synthetic corticosteroids induces a genomic cascade that reduces inflammation and suppresses the immune response. This genomic cascade is initiated by the binding of steroids to intracellular glucocorticoid receptors (GRs) (Datson, NA et al. *European Journal of Neuroscience*. 2001).

[00145] Despite their widespread use and therapeutic benefit, synthetic corticosteroids often cause numerous adverse psychological, metabolic, and somatic side effects (Warrington TP *et al. Mayo Clinic Proceedings*. 2006). Examples of such somatic side effects include hypertension, accelerated atherosclerosis, acne, alopecia, hirsutism, striae, skin atrophy, purpura, obesity, diabetes mellitus, adrenal-pituitary axis suppression, hyperlipidemia, fluid and sodium retention, loss of potassium, calcium and nitrogen, delayed growth, pseudotumor cerebri, peptic ulcer disease, pancreatitis, fatty liver, leukocytosis, neutrophilia, lymphopenia, oral candidiasis, increased risk of systemic infection, myopathy, osteoporosis, avascular necrosis, cataracts and glaucoma. Psychological side effects include mood and anxiety disorders, behavioral disturbance, cognitive impairment, and psychosis.

[00146] Cognitive impairment, anxiety and mood disorders are among the most common psychological side effects of corticosteroid use. Especially for patients who require long-term steroid treatment, these effects result in a diminished quality of life. For example, 33% of individuals taking corticosteroids (about 13 million) are reported to exhibit deficits in working or short-term memory, declarative memory, attention span and concentration (academic and occupational performance), and executive functioning (Stoudemire A *et al. Gen Hosp Psychiatry*. 1984). In extreme cases, steroids can even induce delirium, dementia (persistent memory impairment), and mania (Varney NR *et al., Am J Psychiatry*. 1984). Currently, there is no FDA approved drug designated for the treatment of the cognitive impairment and similar psychiatric disorders, such as anxiety and mood disorders, associated with corticosteroid use. In addition, there are no alternatives to corticosteroids for the treatment of inflammatory disorders – corticosteroids must be used.

Chemotherapy-induced Cognitive Dysfunction

[00147] Chemotherapy-related cognitive dysfunction, also known as chemotherapy-related cognitive impairment or chemo fog or chemo brain, is referred to as a decline in a variety of neuropsychological tasks following chemotherapy or other anticancer treatments, such as radiation therapy or surgery, in patients with non-central nervous system cancers. Post-chemotherapy, the domains most impaired are memory, processing speed, attention, and executive functions (Lange M, *et al. Ann Oncol*. 2019).

Asthma

[00148] Asthma is a chronic inflammatory disease of the airways of the lung caused by a combination of genetic and environmental factors, including exposure to air pollution and

allergens. Other potential triggers include medications such as aspirin and beta blockers. Among other events, eosinophilic inflammation has been reported in the airways of asthma patients. The pathophysiology of the disease is characterized by variable airflow obstruction, airway inflammation, mucus hypersecretion, and subepithelial fibrosis. Clinically, patients
5 may present with cough, wheezing, and shortness of breath.

Primary Biliary Cholangitis

[00149] Primary biliary cholangitis (PBC) is an organ-specific autoimmune disease characterized by the chronic progressive destruction of small bile ducts of the liver coupled
10 with portal inflammation. The destruction of the bile ducts leads to the buildup of bile and other toxins in the liver resulting in scarring, fibrosis, and eventually cirrhosis. PBC is a relatively rare disease, affecting up to one in 3,000–4,000 people, but predominantly affects middle-aged women. Early symptoms of PBC include fatigue and itchy skin, while symptoms of advanced disease include dry eyes and mouth, pain in the upper right abdomen,
15 splenomegaly, musculoskeletal pain, edema, ascites, fatty deposits (xanthomas) on the skin, jaundice, hyperpigmentation, osteoporosis, high cholesterol, diarrhea and hypothyroidism (Boonstra K *et al.*, *J Hepatol.* 2012).

Hypertriglyceridemia

20 [00150] Hypertriglyceridemia (HTG) is a common metabolic disorder marked by an elevated concentration of triglycerides in plasma (*i.e.*, levels above 150 mg/dl), which increases the risk for the development of cardiovascular disease. While most people with hypertriglyceridemia are asymptomatic, people with severe HTG may develop xanthomas. Severe HTG (*i.e.*, levels above 500 mg/dl) has also been associated with and increased risk of
25 pancreatitis. Both genetic and lifestyle factors play significant roles in the pathophysiology of HTG. Medications including corticosteroids, thiazides, nonselective beta-blockers, estrogen, tamoxifen, bile acid sequestrants, cyclophosphamide, antiretroviral drugs, and second-generation antipsychotic agents can also elevate TG levels. The initial and most valuable approach to treating HTG, is an adjustment in lifestyle contributors to HTG
30 including management of diet, weight, and the non-TG components of the metabolic syndrome, however these approaches are often unreliable due to poor patient adherence. Medications such as fibrates (*e.g.*, fenofibrate (PPAR- α agonist), prescription omega-3 fatty acids (*e.g.*, Vascepa (R) (icosapent ethyl, IPE)) and statins are also used to treat TG, but are associated with side effects such as musculoskeletal pain, general weakness, edema,

headaches, drowsiness, rash, constipation and changes in libido (Santos-Baez LS & Ginsberg HN. *Front Endocrinol.* 2020).

Fibromyalgia, Long COVID, Menopause and Chronic Overlapping Pain Conditions (COPCs)

[00151] Fibromyalgia is a condition characterized by widespread pain, fatigue, sleep disorders and cognitive dysfunction or “brain fog”. It is a member of the group of conditions originally called “Overlapping Chronic Pain Conditions” (OCPCs), but now more commonly called “Chronic Overlapping Pain Conditions” (COPCs), further including the temporomandibular disorder (TMD), irritable bowel syndrome (IBS), vulvodynia, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, chronic tension-type headache, migraine headache, and chronic lower back pain. Epidemiological studies, estimates that the prevalence of the individual COPCs ranges from approximately 4 million (myalgic encephalomyelitis/chronic fatigue syndrome) to 44 million (IBS). Many COPCs are defined as being idiopathic, arising spontaneously with no specific cause. However, central sensitization is currently thought to contribute to these conditions (Maixner W, et al., *J Pain.* 2016). Exemplary clinical symptoms of fibromyalgia and other COPCs include, but are not limited to, widespread pain, fatigue, sleep disorders and cognitive dysfunction.

[00152] Post-Acute Sequelae of (SARS)-CoV-2 Infection (PASC) (colloquially known as “long COVID”) is a term used to describe a set of symptoms experienced by people with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 infection with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. PASC symptoms span multiple organ systems, can occur within symptom clusters (*i.e.*, neurologic, non-neurologic, and systemic) and may also fluctuate or relapse over time (Davis et al. *EclinicalMedicine.* 2021, Crook et al. *BMJ.* 2021, Bierle et al. *J Prim Care Community Health.* 2021, WHO 2021). The lack of a standardized definition of PASC makes it difficult to determine the exact epidemiology, incidence rates, and the impact of the condition on long-term disability. A conservative estimate based on data collected from numerous countries is that on average 30% of people with COVID-19 will experience PASC (Nalbandian et al. *Nat Med.* 2021).

[00153] PASC is a multi-faceted condition affecting multiple body systems. Symptoms of PASC may be new onset (*e.g.*, new onset of pain), following initial recovery from an acute, or even mild, COVID-19 episode, or persist from the initial illness. While the

symptoms of PASC vary, pain, fatigue and sleep disturbances were found to be the main symptoms affecting quality of life and the ability to return to full time work (Alonso-Matielo et al. *Front Physiol.* 2021, Davis et al. *EclinicalMedicine.* 2021, Sahin et al. *Eur Neurol.* 2021).

- 5 [00154] Exemplary clinical symptoms of long COVID include, but are not limited to, fatigue, muscle weakness, diaphoresis, myalgia, arthralgia, chills, limb edema, dizziness, post-exertional malaise, cognitive dysfunction, respiratory symptoms (polypnea, chest pain, cough, sputum, sore throat), cardiovascular abnormalities, alopecia, olfactory abnormalities, neurocognitive difficulties including memory and concentration problems, psychological
10 symptoms such as sleep difficulties, depression, anxiety, feelings of inferiority, and generally a worse quality of life.

- [00155] Menopause is that period after the cessation of normal ovulation cycles, during which normal menstruation ceases. This period is marked by a decrease in hormone production (e.g., estradiol (E2)) in the ovaries resulting in a shift in hormone balance in the
15 body, which often gives rise to a variety of symptoms associated with menopause. Peri-menopause, which is also known as pre-menopause or the climacteric, is that period prior to menopause during which normal ovulation cycles gradually give way to cessation of menses. The symptoms of peri-menopause, menopause and post-menopause include physical symptoms such as hot flashes, chills and sweating secondary to vasomotor instability.
20 Additionally, psychological and emotional symptoms may accompany onset of climacteric, such as fatigue, irritability, insomnia, inability to concentrate, depression, memory loss, headache, anxiety and nervousness. Additional symptoms can include intermittent dizziness, paresthesias, palpitations and tachycardia as well as nausea, constipation, diarrhea, arthralgia, myalgia, cold hands and feet and weight gain. In addition, changes to the genitals, urinary
25 incontinence, vaginal dryness, loss of pelvic muscle tone, increased risk of cardiovascular disease and osteoporosis increase with onset of menopause.

Obesity

- [00156] Obesity, defined by the United States Centers for Disease Control and
30 Prevention (CDC) as an excessively high amount of body fat or adipose tissue in relation to lean body mass, is now a world-wide epidemic, and is one of the most serious contributors to increased morbidity and mortality. Obesity is associated with the leading causes of death, including deaths from diabetes, heart disease, stroke, and some types of cancer.

[00157] In some embodiments, the (S)-enantiomers of this disclosure (*i.e.*, (S)-tianeptine or 11-D-(S)-tianeptine) are used to treat obesity and weight gain, particularly in individuals who tend to gain body weight and fat content despite a lack of hyperphagia and a mid- or low-fat diet. In some embodiments, the (S)-enantiomers of this disclosure (*i.e.*, (S)-tianeptine or 11-D-(S)-tianeptine) or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) are used to treat obesity and weight gain in individuals with low levels of PPAR- β/δ and/or PPAR- γ expression and/or activity in neurons.

10

Methods of Treating

[00158] In some aspects, the present disclosure provides a method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor- β/δ (PPAR- β/δ) and/or PPAR- γ and one or more associated symptoms thereof, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an 11-D-(S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(S)-enantiomer of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of an 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure, or a pharmaceutical composition of this disclosure comprising one or more of them.

30 [00159] In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ - modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt (including crystalline forms thereof)

of the (S)-enantiomer, or co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer of this disclosure, or an amide of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable salt thereof. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of the zwitterion of the (S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder, or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of the (S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable co-crystal of the (S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable co-crystal of the zwitterion of the (S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of an ester of the (S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of the ester of the (S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of an amide of the (S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of an amide of the (S)-enantiomer of this disclosure.

[00160] In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at

risk thereof a therapeutically effective amount of an 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of an 11-D-(S)-enantiomer of this disclosure, or an amide of an 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of an 11-D-(S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of the zwitterion of an 11-D-(S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of an 11-D-(S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable co-crystal of an 11-D-(S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable co-crystal of a zwitterion of an 11-D-(S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of an ester of an 11-D-(S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of the ester of an 11-D-(S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of an amide of an 11-D-(S)-enantiomer of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of the amide of an 11-D-(S)-enantiomer of this disclosure.

[00161] In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, or the N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, or the (R)-enantiomer of N-nitroso-tianeptine, or a pharmaceutically acceptable salt thereof. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of the N-hydroxy-tianeptine of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of the N-hydroxy-tianeptine of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer of the N-hydroxy-tianeptine of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of the (S)-enantiomer of the N-hydroxy-tianeptine of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of the (R)-enantiomer of the N-hydroxy-tianeptine of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of the (R)-enantiomer of the N-hydroxy-tianeptine of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of the N-nitroso-tianeptine of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of the N-nitroso-tianeptine of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective

amount of the (S)-enantiomer of the N-nitroso-tianeptine of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of the (S)-enantiomer of the N-nitroso-tianeptine of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of the (R)-enantiomer of the N-nitroso-tianeptine of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of an aryl-substituted tianeptine analog of this disclosure. In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutically acceptable salt of an aryl-substituted tianeptine analog of this disclosure.

[00162] In some embodiments, the method of treating the PPAR- β/δ and/or PPAR- γ -modulated disease, disorder or condition comprises administering to a subject in need or at risk thereof a therapeutically effective amount of a pharmaceutical composition of this disclosure.

[00163] In some aspects, the present disclosure provides a method of treating a disease, disorder or condition and one or more associated symptoms thereof, in a subject who has experienced high stress. In some embodiments, the disease, disorder or condition is caused by adversity prenatally or early in life, or by childhood trauma, which disease, disorder or condition in some embodiments is manifested by subsequent violent behavior. In some embodiments, the disease, disorder or condition in a subject who has experienced high stress is modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor- β/δ (PPAR- β/δ) and/or PPAR- γ . Without wishing to be bound by theory, prolonged stress (prenatal, postnatal, or both) leads to an increase in the production of free radicals, particularly in the brain. The (S)-enantiomers of this disclosure (*i.e.*, (S)-tianeptine or 11-D-(S)-tianeptine) are activated in the presence of free radicals forming a tianeptine C11-free radical intermediate (which radical may be delocalized over 13 carbon

atoms, 2 nitrogen atoms, 2 oxygen atoms and 1 sulfur atom) capable of covalent interaction with and irreversible activation of PPAR- δ/β and/ or PPAR- γ . These free radicals can form while the (S)-tianeptine enantiomer is bound to the PPAR ligand binding site (LBS), leading to preferential covalent linkage of the (S)-tianeptine to a PPAR LBS because of the chiral geometry of the site.

[00164] In some aspects, the present disclosure provides a method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with high levels of receptor S-nitrosylation. In some aspects, the present disclosure provides a method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with high levels of S- nitrosylation of PPAR- β/δ and/or PPAR- γ , comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof or an 11-D-(S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(S)-enantiomer of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of an 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of this disclosure comprising one or more of them. Without wishing to be bound by theory, the (S)-enantiomer of this disclosure (*i.e.*, (S)-tianeptine or 11-D-(S)-tianeptine) reacts with S-nitroso-PPAR- β/δ and/or S-nitroso-PPAR- γ to form S-nitroso-(S)-enantiomer and unnitrosylated PPAR- β/δ and/or PPAR- γ .

[00165] In some aspects, the methods of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor- β/δ (PPAR- β/δ) and/or PPAR- γ of this disclosure are improved over methods using racemic mixtures of the enantiomers of tianeptine, their zwitterions, salts, co-crystals and esters in that the methods of this disclosure result in reduced agonism of the μ -opioid receptors. The reduced μ -opioid receptor agonism of the (S)-enantiomers of this disclosure (*i.e.*, (S)-tianeptine or 11-D-(S)-tianeptine) compared to racemic mixtures of the enantiomers of tianeptine minimizes the potential for opioid abuse, opioid toxicity and opioid overdose (*e.g.*, by opiate-induced respiratory depression (OIRD)).

[00166] In some aspects, the present disclosure provides a method of treating a disease, disorder or condition selected from the group consisting of a central nervous system (CNS) disorder, inflammatory disease, autoimmune disease, infectious illness, a hearing loss condition, ocular disease, musculoskeletal disease, metabolic disease, mitochondrial disease, hypertriglyceridemia, cancer, menopause and chronic overlapping pain conditions (COPCs), and psychological, physical, metabolic or hormonal stress and COPCs, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof or an 11-D-(S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(S)-enantiomer of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of an 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the 11-D-(S)-enantiomer, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure or a pharmaceutical composition of this disclosure comprising one or more of them.

[00167] In some aspects, the present disclosure provides a method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with excessive levels of metal ions in circulation, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof or an 11-D-(S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(S)-enantiomer of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of an 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the 11-D-(S)-enantiomer of this disclosure, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-

substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure, or a pharmaceutical composition of this disclosure comprising one or more of them. In some embodiments, the metal ion is iron or copper. In some embodiments, the (S)-enantiomer of this disclosure (*i.e.*, (S)-tianeptine or 11-D-(S)-tianeptine) or analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salt) is administered to a subject with elevated levels of iron or copper ion determined by a blood test or a test of cerebrospinal fluid (CSF). Without wishing to be bound by theory, the (S)-enantiomers of this disclosure (*i.e.*, (S)-tianeptine or 11-D-(S)-tianeptine) or analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) are activated in the presence of free radicals (*e.g.*, hydroxyl radicals), produced by the reaction of free iron or copper with oxygen and hydrogen peroxide, forming a tianeptine C11-free radical intermediate (which radical may be delocalized over 13 carbon atoms, 2 nitrogen atoms, 2 oxygen atoms and 1 sulfur atom) capable of covalent interaction with and irreversible activation of PPAR- δ/β and/or PPAR- γ . These free radicals can form while the (S)-tianeptine enantiomer is bound to the PPAR ligand binding site (LBS), leading to preferential covalent linkage of the (S)-tianeptine to a PPAR LBS because of the chiral geometry of the site. In some embodiments, the disease, disorder or condition modulated by, exacerbated by, or associated with excessive levels of metal ions in circulation is a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor- β/δ (PPAR- β/δ) and/or PPAR- γ .

[00168] In some aspects, the present disclosure provides a method of reducing violent or aggressive behavior associated with a CNS disorder, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof or an 11-D-(S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(S)-enantiomer of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of an 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the 11-D-(S)-

enantiomer of this disclosure or a pharmaceutically acceptable salt thereof or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure, or a pharmaceutical composition
5 of this disclosure comprising one or more of them.

[00169] In some aspects, the present disclosure provides a method of reducing the potential of being committed to a psychiatric hospital or being incarcerated due to behavior or actions associated with a CNS disorder, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer of this disclosure, the
10 zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof or an 11-D-(S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt
15 of an 11-D-(S)-enantiomer of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of an 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-
20 tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure, or a pharmaceutical composition of this disclosure comprising one or more of them.

[00170] In some embodiments, the methods of treating of this disclosure comprise administering the (S)-enantiomer of tianeptine of this disclosure, the zwitterion thereof, or a
25 pharmaceutically acceptable salt of the (S)-enantiomer of this disclosure, or a co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof, or an 11-D-(S)-enantiomer of tianeptine of this disclosure, a zwitterion thereof, or a pharmaceutically
30 acceptable salt of an 11-D-(S)-enantiomer of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or a zwitterion thereof, or an ester of an 11-D-(S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof, or an amide of the 11-D-(S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-

tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure, or a pharmaceutical composition of this disclosure comprising one or more of them one or more times daily. In some embodiments, the method of treating of this disclosure comprises administering the (S)-
5 enantiomer of tianeptine of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer of this disclosure, or a co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof or an 11-D-(S)-enantiomer of
10 tianeptine of this disclosure, a zwitterion thereof, or a pharmaceutically acceptable salt of an 11-D-(S)-enantiomer of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or a zwitterion thereof, or an ester of an 11-D-(S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof, or an amide of the 11-D-(S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof, or an analog of tianeptine (*i.e.*, N-
15 hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure, or a pharmaceutical composition of this disclosure comprising one or more of them once daily.

[00171] In some embodiments, the methods of treating of this disclosure comprise
20 administering the (S)-enantiomers of this disclosure, their zwitterions, or a pharmaceutically acceptable salts or co-crystals of the (S)-enantiomers of this disclosure or esters of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or amides of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salt thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-
25 tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure or pharmaceutical compositions of this disclosure comprising them in compositions or combinations comprising them with one or more of an additional therapeutic agent selected from the group consisting of an antidepressant, an anticonvulsant, an anti-anxiety agent, an antipsychotic agent, a
30 cholinesterase inhibitor, an N-methyl-D-aspartate (NMDA) receptor antagonist, a 5-HT₂ modulator, a corticosteroid, an anti-amyloid agent, an anti-tau agent and a chemotherapeutic agent. In some embodiments, the methods of treating of this disclosure comprise administering the (S)-enantiomers of this disclosure, their zwitterions, or a pharmaceutically acceptable salts or co-crystals of the (S)-enantiomers of this disclosure, or esters of the (S)-

enantiomers of this disclosure, or amides of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure, or pharmaceutical compositions of this disclosure comprising them sequentially with one or more of an additional therapeutic agent. In some embodiments, the methods of treating of this disclosure comprise administering the (S)-enantiomers of this disclosure, their zwitterions, or a pharmaceutically acceptable salts, or co-crystals of the (S)-enantiomers of this disclosure, or esters of the (S)-enantiomers of this disclosure, or amides of the (S)-enantiomers of this disclosure, or pharmaceutically acceptable salts thereof or pharmaceutically acceptable salts thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog or pharmaceutically acceptable salts thereof) of this disclosure, or pharmaceutical compositions of this disclosure comprising them concurrently with one or more of an additional therapeutic agent. Exemplary antidepressants include, but are not limited to, citalopram, fluoxetine, paroxetine, trazodone or sertraline. Exemplary anticonvulsants include, but are not limited to, carbamazepine, divalproex, or dextromethorphan. Exemplary anti-anxiety agents include, but are not limited to, lorazepam, oxazepam, or buspirone. Exemplary antipsychotic agents include, but are not limited to, quetiapine, promazine, aripiprazole, ziprasidone, olanzapine, or risperidone. Exemplary cholinesterase inhibitors include, but are not limited to, donepezil, rivastigmine, galantamine, or tacrine. Exemplary NMDA receptor antagonists include, but are not limited to, amantadine or memantine. Exemplary 5-HT₂ modulators include, but are not limited to, pimavanserin or cyclobenzaprine. Exemplary corticosteroids include, but are not limited to prednisone, methylprednisolone and dexamethasone. Exemplary anti-amyloid agents include, but are not limited to, aducanumab (Aduhelm®), bapineuzumab, solanezumab, or verubecestat. In some embodiments, the anti-amyloid agent and/or anti-tau agent is one or more of the agents as described by Cummings et al. incorporated herein by reference (Cummings et al. *Alzheimers Dement* (NY), 2017). Exemplary chemotherapeutic agents include, but are not limited to, temozolomide, carmustine, bevacizumab, or lomustine.

[00172] In some embodiments of the combinations of this disclosure, the (S)-enantiomers of this disclosure, their zwitterions, or a pharmaceutically acceptable salts of the (S)-enantiomers of this disclosure, or co-crystals of the (S)-enantiomers of this disclosure or zwitterions thereof, or esters of the (S)-enantiomers of this disclosure or pharmaceutically

acceptable salts thereof, or amides of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof, or an aryl-substituted tianeptine analog) or pharmaceutically acceptable salts thereof of this disclosure, or pharmaceutical compositions of this disclosure comprising them and the one or more additional therapeutic agents are formulated separately. In some embodiments of the combinations of this disclosure, the (S)-enantiomers of this disclosure, their zwitterions, or a pharmaceutically acceptable salts of the (S)-enantiomers of this disclosure, or co-crystals of the (S)-enantiomers of this disclosure or zwitterions thereof, or esters of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or amides of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof, or an aryl-substituted tianeptine analog) or pharmaceutically acceptable salts thereof of this disclosure, or pharmaceutical compositions of this disclosure comprising them and the one or more additional therapeutic agents are formulated together. In certain such embodiments, the (S)-enantiomers of this disclosure, their zwitterions, or a pharmaceutically acceptable salts of the (S)-enantiomers of this disclosure, or co-crystals of the (S)-enantiomers of this disclosure or zwitterions thereof, or esters of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or amides of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof, or an aryl-substituted tianeptine analog) or pharmaceutically acceptable salts thereof of this disclosure, or pharmaceutical compositions of this disclosure comprising them and the one or more additional therapeutic agents are packaged together. In some of such embodiments, the (S)-enantiomers of this disclosure, their zwitterions, or a pharmaceutically acceptable salts of the (S)-enantiomers of this disclosure, or co-crystals of the (S)-enantiomers of this disclosure or zwitterions thereof, or esters of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or amides of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog) or pharmaceutically acceptable salts thereof of this disclosure, or pharmaceutical compositions of this disclosure comprising them and the one or more additional therapeutic agents are packaged separately.

- [00173] In some embodiments of this disclosure, the (S)-enantiomers of this disclosure, their zwitterions, or a pharmaceutically acceptable salts of the (S)-enantiomers of this disclosure, or co-crystals of the (S)-enantiomers of this disclosure or zwitterions thereof, or esters of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or amides of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog) or pharmaceutically acceptable salts thereof of this disclosure or pharmaceutical compositions of this disclosure comprising them and the one or more additional therapeutic agents in a combination (where they are not formulated together) of this disclosure are administered simultaneously or concurrently (*i.e.*, with a time separation of no more than about 15 minutes and in some embodiments no more than 10 minutes) or sequentially (*i.e.*, with a time separation of more than about 15 minutes and in some embodiments more than one hour or up to 12-24 hours).
- [00174] In some embodiments, the method of treating of this disclosure comprises administering the (S)-enantiomers of this disclosure, their zwitterions, or a pharmaceutically acceptable salts of the (S)-enantiomers of this disclosure, or co-crystals of the (S)-enantiomers of this disclosure or zwitterions thereof, or esters of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or amides of the (S)-enantiomers of this disclosure or pharmaceutically acceptable salts thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog) or pharmaceutically acceptable salts thereof of this disclosure, or pharmaceutical compositions of this disclosure comprising them as part of a treatment regime also including psychotherapeutic intervention.
- In some embodiments, the psychotherapeutic intervention includes psychotherapeutic therapies including, but not limited to, exposure therapies, eye movement desensitization and reprocessing therapy, somatic therapies, cognitive behavioral therapy, and ecotherapy.

Methods of Reducing Racemization of the (S)-enantiomer

- [00175] In some aspects, the present disclosure provides a method of reducing the racemization of the (S)-enantiomer of this disclosure, the zwitterion thereof, a pharmaceutically acceptable salt of the (S)-enantiomer of this disclosure, a co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer

of this disclosure or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer of this disclosure or pharmaceutically acceptable salt thereof comprising the step of deuterating the (S)-enantiomer, the zwitterion thereof, a pharmaceutically acceptable salt of the (S)-enantiomer, a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer pharmaceutically acceptable salt thereof, at position C-11.

Methods of Producing

[00176] In some aspects, the present disclosure provides a method of producing the (S)-enantiomer of this disclosure, said method comprising the steps of resolving a racemic or other mixture of the (S)- and (R)-enantiomers of a chiral amine tianeptine intermediate (see, *e.g.*, Compound 3 of Table 2), which mixtures are characterized by more than 0.1% (*i.e.*, $\geq 0.1\%$) of the (R)-enantiomer of the chiral amine tianeptine intermediate (see, *e.g.*, Compound 5 of Table 2) by enantioselective crystallization using L- or D- enantiomeric selective conformers in a solvent to produce an (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer, the (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer being crystallized from the solvent mixture and being characterized in that it comprises $\leq 2\%$ (in some embodiments $\leq 0.1\%$) of the (R)-amine tianeptine intermediate:D- conformer (see, *e.g.*, Compounds 4 or 5 of Table 2), reacting the (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer with a 7-bromoheptanoate alkyl ester to produce an (S)-tianeptine alkyl ester intermediate:(S)-enantiomer-selective-conformer and reacting that intermediate with a base to remove the conformer to produce an (S)-tianeptine alkyl ester intermediate (see, *e.g.*, Compound 6 of Table 2), and saponifying the (S)-tianeptine alkyl ester intermediate to produce the (S)-enantiomer of tianeptine (see, *e.g.*, Compound 8 of Table 2).

[00177] In some embodiments, the chiral amine tianeptine intermediate is 3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-amine, (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer is (11S)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzo 123hiazepine-11-amine: (S)-enantiomer-selective-conformer and the (S)-tianeptine ester intermediate:(S)-enantiomer-selective-conformer is ethyl 7-[[[(11S)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate:(S)-enantiomer-selective-conformer.

[00178] In some aspects, the present disclosure provides a method of producing the 11-D-(S)-enantiomer of this disclosure, said method comprising the steps of resolving a

racemic or other mixture of the (S)- and (R)-enantiomers of a chiral amine 11-D-tianeptine intermediate (see, *e.g.*, Compound 11 of Table 3), which mixtures are characterized by more than 0.1% (*i.e.*, $\geq 0.1\%$) of the (R)-enantiomer of the chiral amine 11-D-tianeptine intermediate (see, *e.g.*, Compound 12 of Table 3) by enantioselective crystallization using L- or D- enantiomeric selective conformers in a solvent to produce an (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer, the (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer being crystallized from the solvent mixture and being characterized in that it comprises $\leq 2\%$ (in some embodiments $\leq 0.1\%$) of the (R)-amine 11-D-tianeptine intermediate:D- conformer (see, *e.g.*, Compounds 12 or 13 of Table 3), reacting the (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer with a 7-bromoheptanoate alkyl ester to produce an 11-D-(S)-tianeptine alkyl ester intermediate:(S)-enantiomer-selective-conformer and reacting that intermediate with a base to remove the conformer to produce an 11-D-(S)-tianeptine alkyl ester intermediate (see, *e.g.*, Compound 15 of Table 3), and saponifying the 11-D-(S)-tianeptine alkyl ester intermediate to produce the 11-D-(S)-enantiomer of tianeptine (see, *e.g.*, Compound 17 of Table 3).

[00179] In some embodiments, the chiral amine 11-D-tianeptine intermediate is 11-amino-3-chloro-6-methyl-6,11-dihydrodibenzo[*c,f*][1,2]thiazepine 5,5-dioxide-11-d, the (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer is (S)-11-amino-3-chloro-6-methyl-6,11-dihydrodibenzo[*c,f*][1,2]thiazepine 5,5-dioxide-11-*d*: (S)-enantiomer-selective-conformer, and the 11-D-(S)-tianeptine ester intermediate:(S)-enantiomer-selective-conformer is ethyl (S)-7-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[*c,f*][1,2]thiazepine-11-yl-11-*d*)amino)heptanoate:(S)-enantiomer-selective-conformer.

[00180] In some aspects, the present disclosure provides a method of producing the (S)-enantiomer of this disclosure or zwitterion thereof, said method comprising the steps of: (i) resolving a racemic or other mixture of the (S)- and (R)-enantiomers of a tianeptine alkyl ester (see, *e.g.*, Compound 18 of Table 4) using an L- or D- enantiomeric selective conformer in a solvent, which mixtures are characterized by more than 0.1% (*i.e.*, $\geq 0.1\%$) of the (R)-enantiomer of the tianeptine alkyl ester (see, *e.g.*, Compound 19 of Table 4) by enantioselective crystallization to produce crystalline (R)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer salt, the (S)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer (see, *e.g.*, Compound 20 of Table 4) remaining in solution, the (S)-tianeptine alkyl ester (R)-enantiomer-selective-conformer being characterized in that it comprises $\leq 2\%$

(in some embodiments $\leq 0.1\%$) of the (R)-tianeptine alkyl ester: (R)-enantiomer-selective-conformer, (ii) hydrolyzing the (S)-tianeptine alkyl ester: (R)-enantiomer-selective-conformer with a strong acid to produce the (S)-tianeptine acid salt, which tianeptine acid salt comprises $\leq 2\%$ of the (R)-tianeptine acid salt; and (iii) neutralizing the (S)-tianeptine acid salt with a base to produce the zwitterion of the (S)-enantiomer of tianeptine (see, *e.g.*, Compound 22 of Table 4).

[00181] In some aspects, the present disclosure provides a method of producing the 11-D-(S)-enantiomer of this disclosure or zwitterion thereof, said method comprising the steps of: (i) resolving a racemic or other mixture of the (S)- and (R)-enantiomers of an 11-D-tianeptine alkyl ester (see, *e.g.*, Compound 23 of Table 5) using an L- or D- enantiomeric selective conformer in a solvent, which mixtures are characterized by more than 0.1% (*i.e.*, $\geq 0.1\%$) of the (R)-enantiomer of the 11-D-tianeptine alkyl ester (see, *e.g.*, Compound 24 of Table 5) by enantioselective crystallization to produce crystalline 11-D-(R)-tianeptine alkyl ester: (R)-enantiomer-selective-conformer salt, the 11-D-(S)-tianeptine alkyl ester: (R)-enantiomer-selective-conformer (see, *e.g.*, Compound 25 of Table 5) remaining in solution, the 11-D-(S)-tianeptine alkyl ester (R)-enantiomer-selective-conformer being characterized in that it comprises $\leq 2\%$ (in some embodiments $\leq 0.1\%$) of the 11-D-(R)-tianeptine alkyl ester: (R)-enantiomer-selective-conformer, (ii) hydrolyzing the 11-D-(S)-tianeptine alkyl ester: (R)-enantiomer-selective-conformer with a strong acid to produce the 11-D-(S)-tianeptine acid salt, which 11-D-tianeptine acid salt comprises $\leq 2\%$ of the 11-D-(R)-tianeptine acid salt; and (iii) neutralizing the 11-D-(S)-tianeptine acid salt with a base to produce the zwitterion of the 11-D-(S)-enantiomer of tianeptine (see, *e.g.*, Compound 27 of Table 5).

[00182] In some embodiments of any of the above embodiments the tianeptine alkyl ester is a methyl ester, an ethyl ester or another straight or branched chain C_1 - C_6 alkyl ester.

[00183] In some embodiments, the enantioselective crystallization, including those of the above embodiments, may be repeated to increase the enantiomeric purity or chiral purity of a resolved tianeptine or ester thereof. Optionally, supercritical fluid chromatography (or in some embodiments high performance liquid chromatography (HPLC)) can be used to initially resolve the enantiomeric mixtures or can be used to increase the enantiomeric purity or chiral purity of a resolved (S)-tianeptine of this disclosure.

[00184] In some embodiments, the enantioselective crystallization used in the methods of producing of this disclosure comprises using a conformer. Non-limiting examples of conformers include L-dibenzoyl tartaric acid (DBTA), D-DBTA, Di-*o*-toluoyl-

L-tartaric acid (L-D(2-Me)BTA), D-D(2-Me)BTA, other DBTA derivatives, (S)-1,1'-Bi-2-naphthol-2,2'-diyl hydrogen phosphate, (R)-1,1'-Bi-2-naphthol-2,2'-diyl hydrogen phosphate, (S)-(R)-mandelic acid, (R)-(S)-mandelic acid, (S)-(S)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid, (R)-(S)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid, (1S)-(R)-10-camphorsulfonic acid and (1R)-(R)-10-camphorsulfonic acid.

[00185] In some embodiments, the solvent comprises a mixture of benzene, acetone and trichloromethane. In some embodiments, the solvent comprises benzene, acetone and trichloromethane in a ratio of 2:1:1. In some embodiments, enantiomeric crystallization further comprises slow evaporation of the solvent mixture.

10 [00186] In some embodiments, the hydrolysis is performed using a strong acid. Non-limiting examples of strong acids include hydrochloric acid, sulfuric acid and phosphoric acid.

[00187] In some embodiments, other known methods of producing the (S)-enantiomers of this disclosure may be used, for example, chirality pools and asymmetric synthesis.

Methods of Inducing Neurite Outgrowth

[00188] In some aspects, the present disclosure provides a method of enhancing neurite outgrowth comprising administering to a subject in need thereof the (S)-enantiomer of this disclosure, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an 11-D-(S)-enantiomer of this disclosure, the zwitterion thereof, 20 or a pharmaceutically acceptable salt of an 11-D-(S)-enantiomer of this disclosure, or a co-crystal of an 11-D-(S)-enantiomer of this disclosure or the zwitterion thereof, or an ester of an 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an amide of the 11-D-(S)-enantiomer of this disclosure or a pharmaceutically acceptable salt thereof, or an analog of tianeptine (*i.e.*, N-hydroxy-tianeptine, the (S)- and (R)- enantiomers thereof, the N-nitroso-tianeptine, the (S)- and (R)- enantiomers thereof or an aryl-substituted tianeptine analog) or pharmaceutically acceptable salts thereof, or a pharmaceutical composition of this disclosure comprising one or more of them. In some embodiments, the neurite outgrowth is observed in a glutamatergic neuron.

EXAMPLES

[00189] Some of the embodiments of this disclosure will further be described in more detail by the following examples which describe the methods whereby the (S)-enantiomers of tianeptine of this disclosure may be prepared, purified, analyzed and tested. These examples are not to be construed as limiting the disclosure. The skilled worker will readily appreciate that the following examples are merely illustrative and can be modified according to methods and techniques commonly known in the art.

Example 1: Preparation and Analysis of Chiral Tianeptine

[00190] A racemic mixture of tianeptine oxalate (9.6 g, 18.3 mmol) was converted into a racemic mixture of tianeptine zwitterion and separated by direct phase preparative high-performance liquid chromatography (HPLC) using a ChiralPak IG 4.6 x 250 mm column and a solvent gradient of 5-60% [ACN/EtOH in 10 mM aq. AmForm] in supercritical CO₂ with a run time of 10 min, and flow rate of 3 mL/min to yield (S)-tianeptine zwitterion (Figure 1, Peak 1) and (R)-tianeptine zwitterion (Figure 1, Peak 2). Analytical HPLC was performed using ChiralPak IG 4.6 x 250 mm, 5-60% [ACN/EtOH in 10 mM aq. AmForm], Run time = 10 min, Flow = 3 mL/min. The chiral purity of the two enantiomers was assessed by analytical SFC using a ChiralPak IG 4.6 x 250 mm column and a solvent gradient of 5-60% [MeCN/EtOH in 10 mM AmForm] with a run time of 10 min, and flow rate of 3 mL/min. (S)-tianeptine: t_R = 4.19 min, 99.8% chiral purity; (R)-tianeptine: t_R = 4.53 min, 97.6% chiral purity. Residual ammonium formate was removed via lyophilization.

[00191] In another method, a racemic mixture of tianeptine sodium (20 g, 42.3 mmol) was converted to a racemic mixture of tianeptine zwitterion and separated by preparative SFC using a ChiralPak AD 21 x 250 mm column and a solvent mixture of 35% [MeCN/EtOH in 10 mM AmForm] in supercritical CO₂ with a flow rate of 50 mL/min to yield (S)-tianeptine zwitterion and (R)-tianeptine zwitterion. The separation was discontinued when 3 g of each enantiomer were isolated. Both enantiomers of zwitterionic tianeptine (> 98% chiral purity, each) were separately submitted to a second purification under the conditions identical to the first purification. Fractions were separately concentrated, and the residues were diluted with DCM (300 mL). The organic phases were washed with water (3 x 300 mL) and brine (300 mL), dried over Na₂SO₄, filtered and concentrated. The residues were dried under vacuum at 50 °C to yield 1.9 g of (S)-tianeptine zwitterion and 2.2 g of (R)-tianeptine zwitterion. The

chiral purity of the two enantiomers was assessed by analytical SFC using a ChiralPak AD 4.6 x 150 mm column and a solvent mixture of 5-60% [MeCN/EtOH in 10 mM AmForm] with a run time of 10 min and a flow rate of 3 mL/min. (S)-tianeptine: $t_R = 3.38$ min, >99.9% chiral purity; (R)-tianeptine: $t_R = 3.76$ min, > 99.9% chiral purity.

5 [00192] For ammonium-formate-free separation, a racemic mixture of tianeptine sodium (6.00 g, 12.7 mmol) was converted into a racemic mixture of tianeptine zwitterion and separated by preparative supercritical fluid chromatography (SFC) using a Phenomenex Lux Amylose-1 21.2x250 mm column and a solvent mixture of 35% [MeCN/EtOH] in supercritical CO₂ with a run time of 10 min and a flow rate of 17.5 mL/min to yield 2.2 g of
10 (S)-tianeptine zwitterion and 2.0 g of (R)-tianeptine zwitterion. The chiral purity of the two enantiomers was assessed by analytical SFC using a ChiralPak IG 4.6 x 250 mm column with a solvent mixture of 5-60% [MeCN /EtOH in 10 mM AmForm] with a run time of 10 min and a flow rate of 3 mL/min. (S)-tianeptine: $t_R = 4.18$ min, >99.9% chiral purity; (R)-tianeptine: $t_R = 4.51$ min, 99.1% chiral purity.

15 [00193] The absolute stereochemistry of the tianeptine sodium enantiomers was determined based on X-ray crystallography. In one experiment, dibenzoyl-L-tartaric acid (L-DBTA) (12.3 mg, 0.0343 mmol) was added to a mixture of (S)-tianeptine sodium (>99.9% chiral purity, 15.0 mg, 0.0343 mmol) in EtOH (0.500 mL). The clear solution was allowed to slowly evaporate to dryness. EtOH (0.500 mL) was added, and the process was repeated to
20 provide crystalline material, which was suitable for X-ray crystallography. Crystallization studies using 2:1 tianeptine sodium: L-DBTA determined with 93% certainty (Flack X parameter = 0.07) that the absolute stereochemistry of (-)-tianeptine sodium salt is the (S)-enantiomer (Figure 2A).

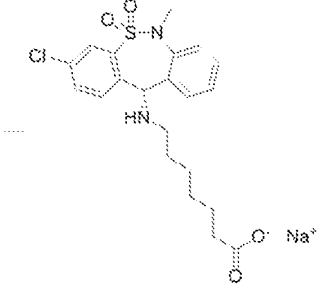
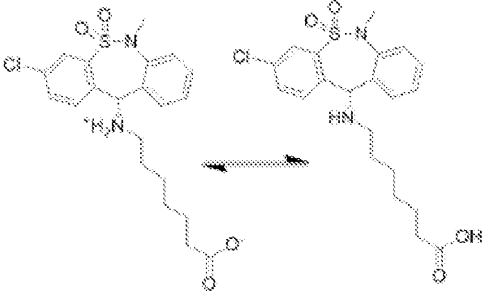
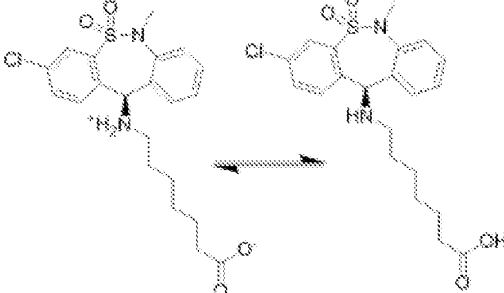
[00194] In a separate experiment, L-DBTA (12.3 mg, 0.0343 mmol) was added to a
25 mixture of (S)-tianeptine sodium (>99.9% chiral purity, 15.0 mg, 0.0343 mmol) in EtOH (0.250 mL). The clear solution was slowly diluted with methyl tert-butyl ether (MTBE) by vapor diffusion to provide crystalline material, which was suitable for X-ray crystallography. Crystallization studies performed using 2:1 tianeptine sodium: L-DBTA also confirmed with 96.5% certainty (Flack X parameter = 0.035) that the absolute stereochemistry of (-)-
30 tianeptine sodium salt is the (S)-enantiomer (Figure 2B).

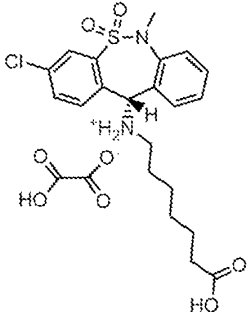
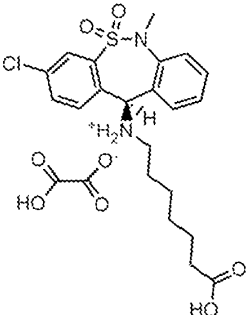
[00195] The optical rotations of various tianeptine enantiomers of this disclosure and various of their salts are listed in **Table 1**. In methanol, the optical rotation for (S)-tianeptine depends on the type and concentration of the counterion (*i.e.*, the pH). For example, at pH ~ 7 the optical rotation of the for (S)-tianeptine zwitterion is $[\alpha]_D^{26} = +18.00^\circ$, while at pH < 7,

the optical rotation of the 1:1 (S)-tianeptine oxalate salt is $[\alpha]_D^{23.2} = +77.0^\circ$. In contrast, at pH > 12 (S)-tianeptine sodium with 3 equivalents (eq.) of sodium hydroxide (NaOH) in methanol has an optical rotation of $[\alpha]_D^{26.9} = -4.40^\circ$. As shown in Table 1, similar pH dependency is had for the (R) enantiomers of tianeptine.

5

Table 1. Optical Rotation of Various Tianeptine Enantiomers

Compound	Structure	Optical Rotation
(S)-Tianeptine sodium with 3.00eq. NaOH		$[\alpha]_D^{26.9} = -4.40^\circ$ (C = 0.25 in MeOH)
(S)-Tianeptine zwitterion		$[\alpha]_D^{27.2} = +18.00^\circ$ (C = 0.10 in MeOH)
(R)-Tianeptine zwitterion		$[\alpha]_D^{27.2} = -34.00^\circ$ (C = 0.1 MeOH)

(S)-Tianeptine oxalate 1:1		$[\alpha]_D^{23.2} = +77.0^\circ$ (C = 0.2 in MeOH)
(R)-Tianeptine oxalate 1:1		$[\alpha]_D^{23.6} = -72.0^\circ$ (C = 0.2 in MeOH)

Example 2. Stereospecific Synthesis of Tianeptine (S) and (R) Enantiomers

General Methods

[00196] Silica gel chromatography was performed on Teledyne Isco instruments using
5 pre-packaged disposable SiO₂ stationary phase columns with eluent flow rate range of 15 mL/min to 200 mL/min, UV detection (200-300, 254 and 280 nm).

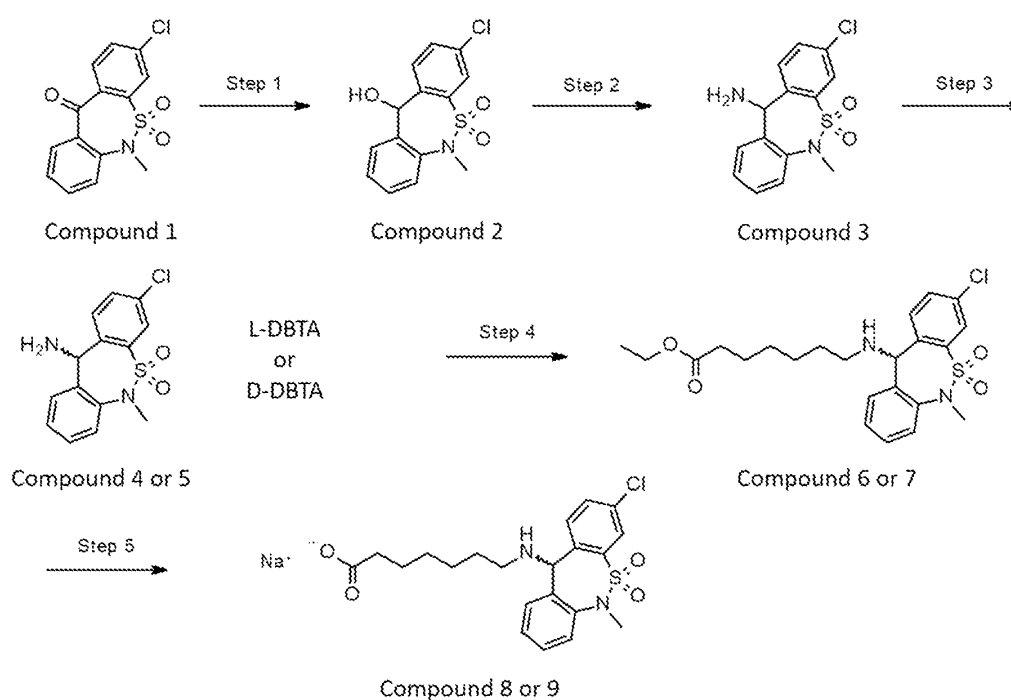
[00197] Reverse phase preparative HPLC was carried out using C18 columns, UV
detection (214 nm and 254 nm) eluting with gradients of MeCN in H₂O (0.03% (NH₄)₂CO₃/
0.375% NH₄OH) (high pH), MeCN in H₂O (0.1% HCOOH) (low pH) or MeCN in H₂O
10 (neutral pH).

[00198] The analytical HPLC chromatograms were performed using an Agilent 1100
series instrument with DAD detector (190 nm to 300 nm). The mass spectra were recorded
with a Waters Micromass ZQ detector at 130 °C. The mass spectrometer was equipped with
an electrospray ion source (ESI) operated in a positive ion mode and was set to scan between
15 *m/z* 150-750 with a scan time of 0.3 s.

[00199] Products and intermediates were analyzed by HPLC/MS on a Gemini-NX (5
μM, 2.0 × 30 mm) using a high pH buffer gradient of 5% to 100% of MeCN in H₂O (0.03%

(NH₄)₂CO₃/ 0.375% NH₄OH) over 10 minutes at 1.8 mL/min for a 10 minute run (B05), EVO C18 (5 μM, 3.0 × 50 mm) using a low pH buffer gradient of 5% to 100% of MeCN in H₂O (0.1% HCOOH) over 2.5 min at 2.2 mL/min for a 3.5 min run (A05). The ¹H NMR spectra were recorded on a Bruker UltraShield 500 MHz/54 mm instrument (BZH 43/500/70B, D221/54-3209) or on a 300 MHz instrument. The chemical shifts are referenced to solvent peaks, which in ¹H NMR appears at 7.26 ppm for CDCl₃, 2.50 for DMSO-*d*₆, and 3.31 ppm for CD₃OD.

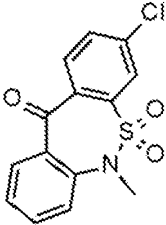
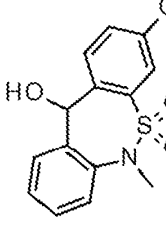
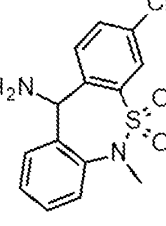
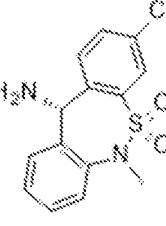
Scheme 1: Exemplary Synthetic Scheme for Tianeptine Enantiomers

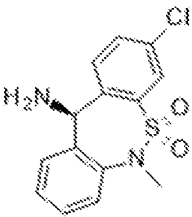
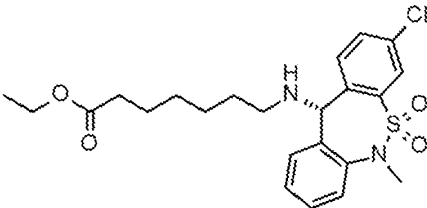
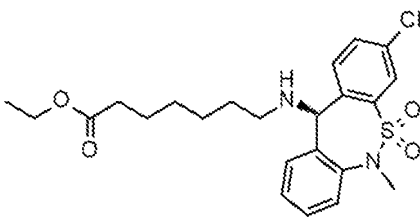
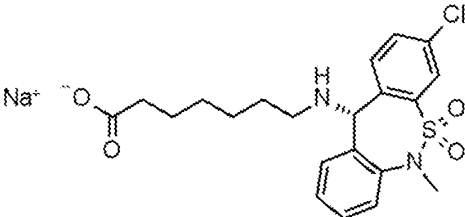


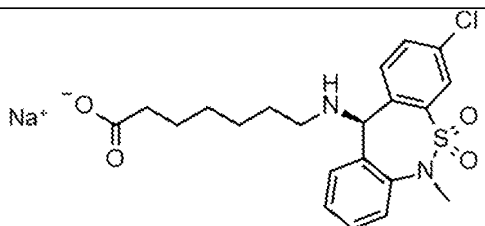
10

[00200] The compounds of Scheme 1 are shown in **Table 2**.

Table 2. Compounds of Scheme 1

Compound Number	Compound Structure and Name
1	 3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-one
2	 3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-ol
3	 3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-amine
4	 (11S)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-amine

5	 (11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-amine
6	 ethyl 7-([(11S)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate
7	 ethyl 7-([(11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate
8	 sodium; 7-([(11S)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate

9	 sodium;7-[(11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepine-11-yl]amino]heptanoate
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[00201] In Step 1 (Scheme 1), 3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-ol (compound 2) was prepared according to International Patent Application Publication No. WO2003/051276 A2, incorporated herein by reference.

5 NaBH₄ (4.61 g, 122 mmol) was added to a mixture of a chiral 3-chloro-6-methyl-5,5-dioxo-benzo[c][1,2]benzothiazepin-11-one (compound 1) (15.0 g, 48.7 mmol) in methanol (MeOH) (133 mL) and dichloromethane (DCM) (444 mL) at 22 °C under nitrogen. The mixture was stirred at 22 °C for 2 hours and concentrated. The residue was diluted with DCM (400.0 mL). The organic phase was washed with saturated aqueous (sat. aq.) NaHCO₃

10 (300 mL), water (300 mL) and brine (300 mL), dried over Na₂SO₄, filtered and concentrated to provide the title compound as a solid (11.0 g, 73%). m/z (ES+) [M+Na]⁺ = 332.02; LCMS (A05); t_R = 0.57 min.

[00202] In step 2 (Scheme 1), 3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-amine (compound 3) (a chiral amine tianeptine intermediate)

15 was prepared according to WO2003/051276 A2 with modifications. Dimethylformamide (DMF) (0.356 mL, 4.84 mmol) was added to compound 2 (3.00 g, 9.68 mmol) and cobalt chloride (CoCl)₂ (4.15 mL, 48.4 mmol) in DCM (100 mL) and the mixture was stirred at 22 °C for 1 hour and concentrated. The residue was diluted with toluene (20.0 mL) and concentrated. The residue was diluted with DCM (176 mL) and placed under an atmosphere

20 of NH₃. The mixture was stirred at 22°C for 18 hours and diluted with DCM (50.0 mL). The organic phase was washed with sat. aq. NaHCO₃ (2 x 200 mL) and brine (200 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (24 g cartridge) with DCM and MeOH (0-10%) to provide compound 3 as a solid (1.88 g, 63%). ¹H NMR (300 MHz, DMSO-d₆) δ 7.84 (d, J = 8.3 Hz, 1H), 7.79 – 7.65 (m, 2H), 7.62 – 7.56 (m, 1H), 7.52 – 7.47 (m, 1H), 7.37 (td, J = 6.2, 3.2 Hz, 2H), 5.60 (s, 1H), 3.36 (s, 3H), 2.63 (s, 2H); m/z: [M-NH₂]⁺ = 292.0; LCMS (A05); t_R = 1.85 min.

25

[00203] In step 3 (Scheme 1), (11S)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-amine: L-2,3-dibenzoyloxybutanedioic acid (compound 4:L-DBTA) was prepared according to European Patent Application Publication No. EP0671173A1, incorporated herein by reference. Compound 3 (6.09 mmol, 1.88 g) was added to L-2,3-dibenzoyloxybutanedioic acid (L-DBTA) (6.08 mmol, 2.18 g) in ethanol (EtOH) (35.0 mL) at 22 °C. The mixture was stirred at 70 °C for 2 hours and the precipitated solid was filtered and washed with EtOH (5.00 ml). The solid was dried and re-crystallized 3 times from EtOH (35.0 ml, 25.0 mL, and 15.0 mL, respectively). The final solid of compound 4 was dried to provide enantiomerically pure material (chiral purity > 99 %, 362 mg, 12 %). m/z: $[M-NH_2]^+$ = 292.0; LCMS (A05); t_R = 1.74 min; enantiopurity determined using ChiralPak IG 4.6 x 250 mm, 5-60% MeOH in 10 mM aq. AmForm, 10 min, t_R = 4.53 min.

[00204] (11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-amine: dibenzoyl- D-tartaric acid (compound 5:D-DBTA) is prepared by washing the combined filtrates with sat. aq. $NaHCO_3$, dried over Na_2SO_4 , filtered and concentrated. Then the residue is dissolved in EtOH and D-DBTA (1.0 eq) is added, followed by fractional crystallization as described above (chiral purity >99%).

[00205] In step 4 (Scheme 1), Ethyl 7-[(11S)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate (compound 6) was prepared according to EP0671173A1 with modifications. Compound 4:L-DBTA (294 mg, 0.952 mmol) was diluted with DCM (10.0 mL) and aq. Sodium carbonate (5M, 10.0 mL). The organic phase was separated and dried over Na_2SO_4 , filtered, and concentrated. The residue was dissolved in MeCN (5.88 mL), and ethyl 7-bromoheptanoate (339 mg, 1.43 mmol), NaI (143 mg, 0.952 mmol), and dipotassium carbonate (263 mg, 1.90 mmol) were added at 22 °C under nitrogen. The mixture was stirred at 75 °C for 3 days and cooled to room temperature. The mixture was filtered through Celite, washing with MeCN (3.00 mL), and the filtrate was concentrated. The residue was diluted with ethyl acetate (EtOAc) (10.0 mL) and sat. aq. $NaHCO_3$ (10.0 mL) to remove the L-DBTA conformer. The organic phase was washed with brine (10.0 mL), dried over Na_2SO_4 , filtered and concentrated to provide compound 6 as an oil (95% pure, 245 mg, 55.3%). m/z: $[M+H]^+$ = 465.7; LCMS (A05); t_R = 2.85 min.

[00206] Alternatively, the reaction can be run using KI as a promoter, and Na_2CO_3 or $KHCO_3$ can be used as alternative bases to remove the L-DBTA conformer.

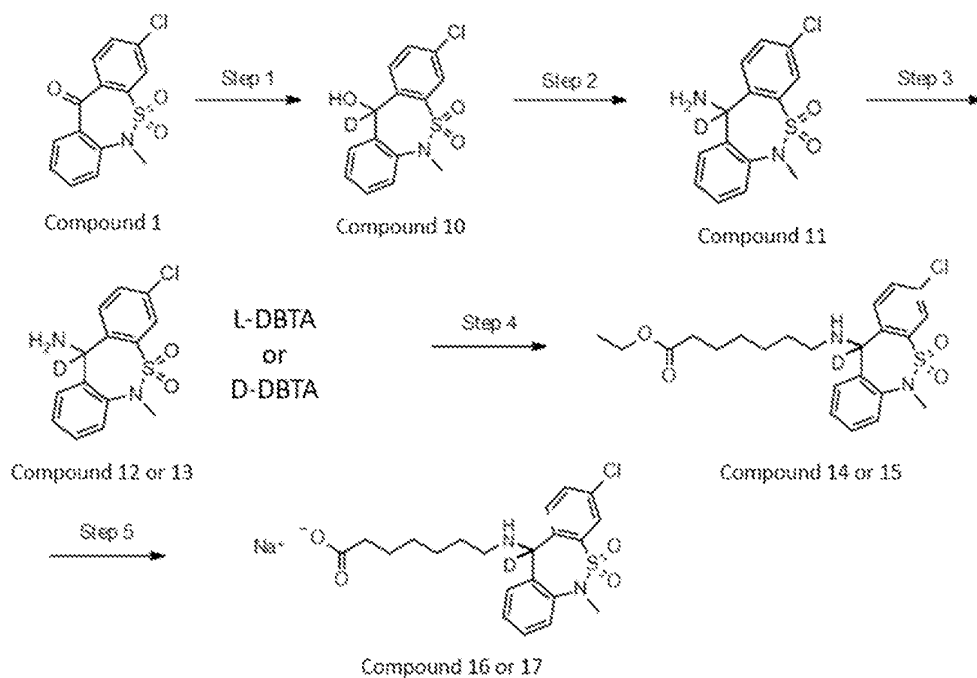
[00207] Ethyl 7-[(11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate (compound 7) is prepared using

compound 5:D-DBTA and the same steps as described above.

[00208] In step 5 (Scheme 1), sodium 7-[[[(11S)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate (compound 8) was prepared according to EP0671173A1 by mixing NaOH (0.3M, 9.95 mL) with compound 6 (869 mg, 1.86 mmol) in EtOH (9.95 mL) at 22 °C. After stirring the mixture at 22 °C for 5 hours, the mixture was worked up by diluting the aqueous phase with HCl (1N) to reach pH 7, extracting with DCM, drying the organic phase over Na₂SO₄, filtering, and concentrating. The residue was purified further by silica gel chromatography (24 g cartridge) with DCM and MeOH (0%-5%). The sodium salt can be obtained by diluting with aq. NaOH (1N, 1.00 eq) and stirring the mixture until it is homogeneous. Water (20.0 mL) was added, and the mixture was lyophilized to provide compound 8 as a solid.

[00209] Alternatively, the compound is prepared by cleaving the ester with acetic acid/hydrochloride (AcOH/HCl), diluting with water, adding Na₂CO₃ to reach pH 7, and extracting with DCM. The purification is done as described above.

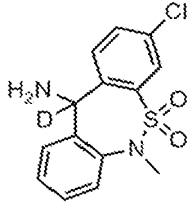
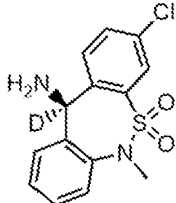
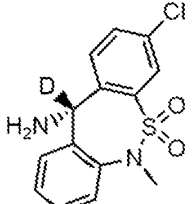
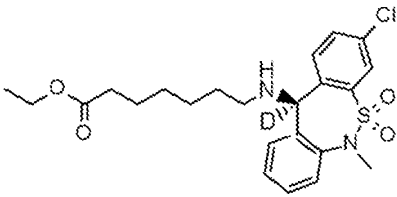
[00210] Sodium 7-[[[(11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate (compound 9) is prepared using compound 7 and following the steps as described above.

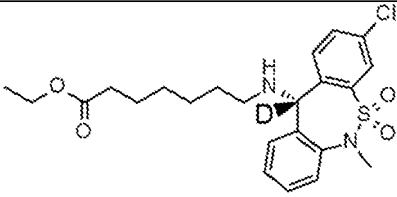
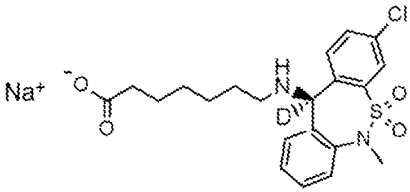
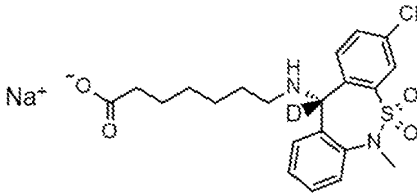
Scheme 2: Exemplary Synthetic Scheme for Deuterated Tianeptine Enantiomers

[00211] In Scheme 2, the deuterated form of sodium 7-[[[(11S)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl-11-d]-amino]heptanoate or sodium 7-[[[(11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl-11-d]-amino]heptanoate is prepared according to Steps 1 to 5 as described above for Scheme 1, but in Step 1, the reductant NaBH₄ is replaced with NaBD₄. The compounds of Scheme 2 are shown in **Table 3**.

10 **Table 3. Compounds of Scheme 2**

Compound Number	Compound Structure and Name
10	3-chloro-11-hydroxy-6-methyl-6,11-dihydrodibenzo[c,f][1,2]thiazepine 5,5-dioxide-11-d

11	 11-amino-3-chloro-6-methyl-6,11-dihydrodibenzo[c,f][1,2]thiazepine 5,5-dioxide-11-<i>d</i>
12	 (R)-11-amino-3-chloro-6-methyl-6,11-dihydrodibenzo[c,f][1,2]thiazepine 5,5-dioxide-11-<i>d</i>
13	 (S)-11-amino-3-chloro-6-methyl-6,11-dihydrodibenzo[c,f][1,2]thiazepine 5,5-dioxide-11-<i>d</i>
14	 ethyl (R)-7-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepine-11-yl-11-<i>d</i>)amino)heptanoate

15	 ethyl (S)-7-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepine-11-yl-11-α)amino)heptanoate
16	 sodium (R)-7-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl-11-α)amino)heptanoate
17	 sodium (S)-7-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl-11-α)amino)heptanoate

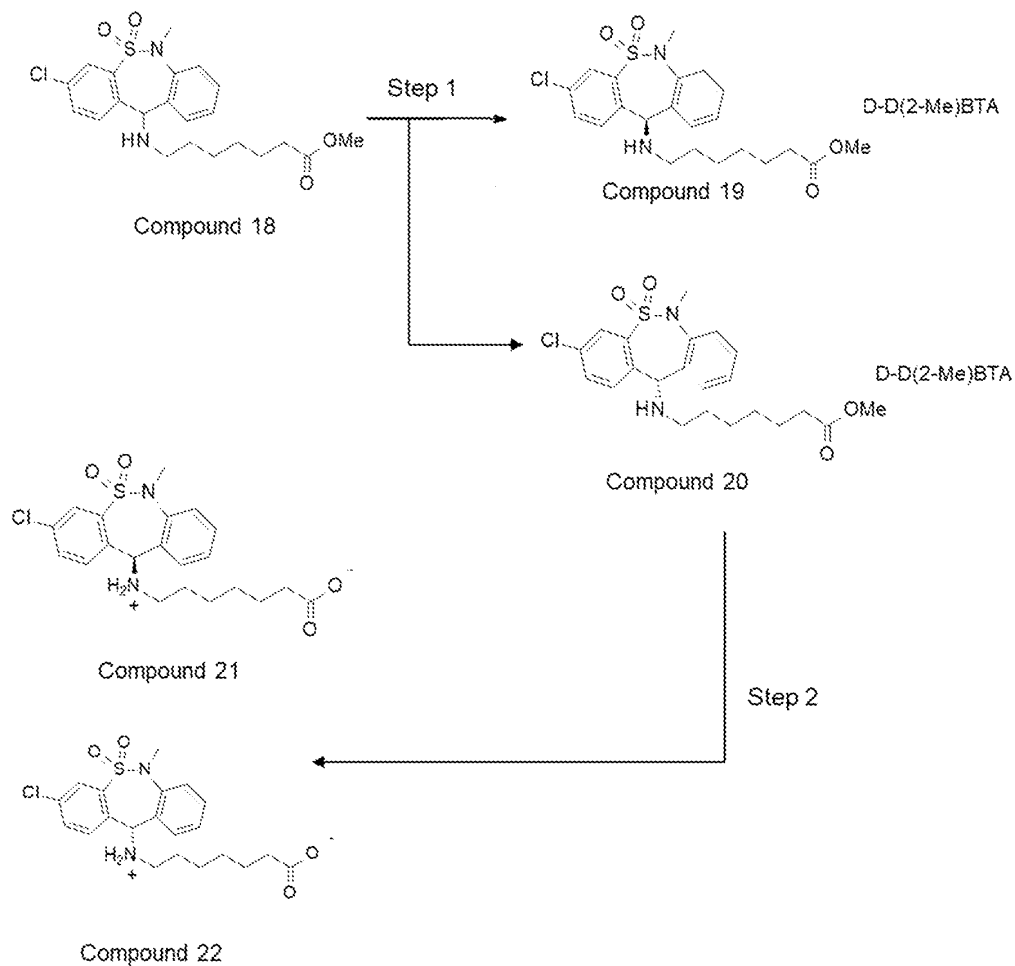
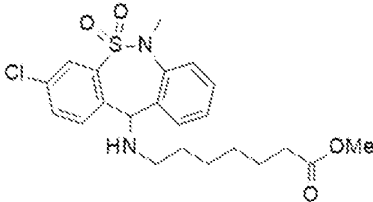
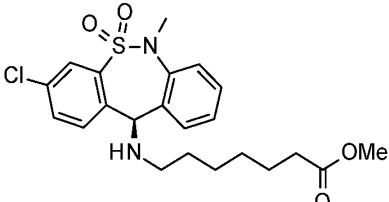
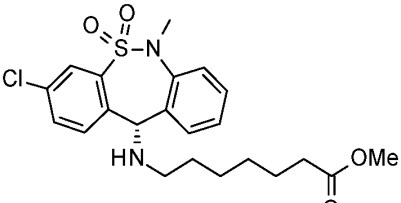
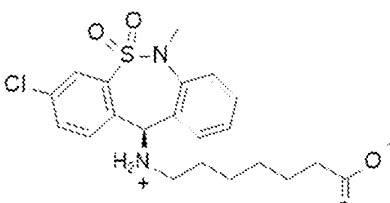
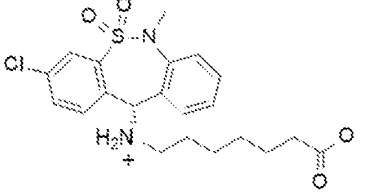
*Synthesis of Tianeptine (S) and (R) Enantiomers from Tianeptine Methyl Ester***Scheme 3: Exemplary Synthetic Scheme for Tianeptine Enantiomers from Tianeptine Methyl Ester**

Table 4. Compounds of Scheme 3

Compound Number	Compound Structure and Name
18	 methyl 7-[(3-chloro-6-methyl-5,5-dioxo-1H-benzo[c][1,2]benzothiazepin-11-yl)amino]heptanoate
19	 methyl 7-[(1R)-3-chloro-6-methyl-5,5-dioxo-1H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate
20	 methyl 7-[(1S)-3-chloro-6-methyl-5,5-dioxo-1H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate
21	 7-[(1R)-3-chloro-6-methyl-5,5-dioxo-1H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate

22	 7-[[[(1S)-3-chloro-6-methyl-5,5-dioxo-1,1H-benzo[c][1,2]benzothiazepin-11-yl]amino]heptanoate
----	--

[00212] Racemic tianeptine methyl ester (compound 18) is commercially available. In step 1 (Scheme 3) D-D(2-Me)BTA (Di-o-toluoyl-D-tartaric acid = (2S,3S)-2,3-bis[(2-methylbenzoyl)oxy]butanedioic acid) (88.4 mg, 0.229 mmol) was added to a solution of racemic tianeptine methyl ester (compound 18) (103 mg, 0.229 mmol) in acetonitrile (MeCN, 1.2 mL, 0.2M). The reaction mixture was stirred at 22 °C for 15 min and filtered resulting in the preferential precipitation of crystalline (R)-tianeptine methyl ester (compound 19) as the D-D(2-Me)BTA salt (99.8% chiral purity) and leaving (S)-tianeptine methyl ester (compound 20): D-D(2-Me)BTA salt (99.2% chiral purity) in solution in the filtrate. The filtrate was concentrated, and the residue was diluted with sat. aq. NaHCO₃ (15.0 mL) to remove the D-D(2-Me)BTA and extracted with DCM (3 X 15.0 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated to provide (S)-tianeptine methyl ester (compound 20).

[00213] Optionally, subsequent rounds of enantioselective crystallization are applied to further purify the (S)-tianeptine methyl ester. In one embodiment, L-DBTA (44.2 mg, 0.114 mmol) was added to the residue obtained from Step 1 in MeCN (600 µL) at 22 °C. The mixture was cooled to -15 °C for 48 h and filtered. The solid was washed with cold MeCN (0 °C, 3 X 1.00 mL) and dried to provide (S)-tianeptine methyl ester. The chiral purity was assessed by analytical SFC using a Lux Cellulose-4, 4.6 x 250mm, 5µm column and a solvent gradient of 5-60% [MeOH/0.1% NH₄OH as a modifier] with a run time of 7.00 min, and flow rate of 3.00 mL/min. (S)-tianeptine methyl ester: t_R = 4.08 min, chiral purity > 99.8%.

[00214] Alternatively, MeCN (1.08 mL) and toluene (0.120 mL) were added to L-DBTA (81.8 mg, 0.228 mmol) and racemic tianeptine methyl ester (103 mg, 0.228 mmol) at 22 °C. The mixture was stirred at 22 °C until all solids were dissolved and cooled to -15 °C for 72 h and filtered. The solid was washed with cold MeCN (3 x 1.00 mL). The solid was dissolved in MeCN (0.600 mL) at 60 °C, cooled to -15 °C for 72 h, filtered, washing with cold MeCN (3 x 1.00 mL). The recrystallization was repeated another two times with MeCN

(1.20 mL and 1.00 mL) to provide the (S)-tianeptine methyl ester/L-DBTA salt. The chiral purity was assessed by analytical SFC using a Lux Cellulose-4, 4.6 x 250mm, 5 μ m column and a solvent gradient of 5-60% [MeOH/0.1% NH₄OH as a modifier] with a run time of 7.00 min, and flow rate of 3.00 mL/min. (S)-tianeptine methyl ester: t_R = 4.10 min, >99.9% chiral purity.

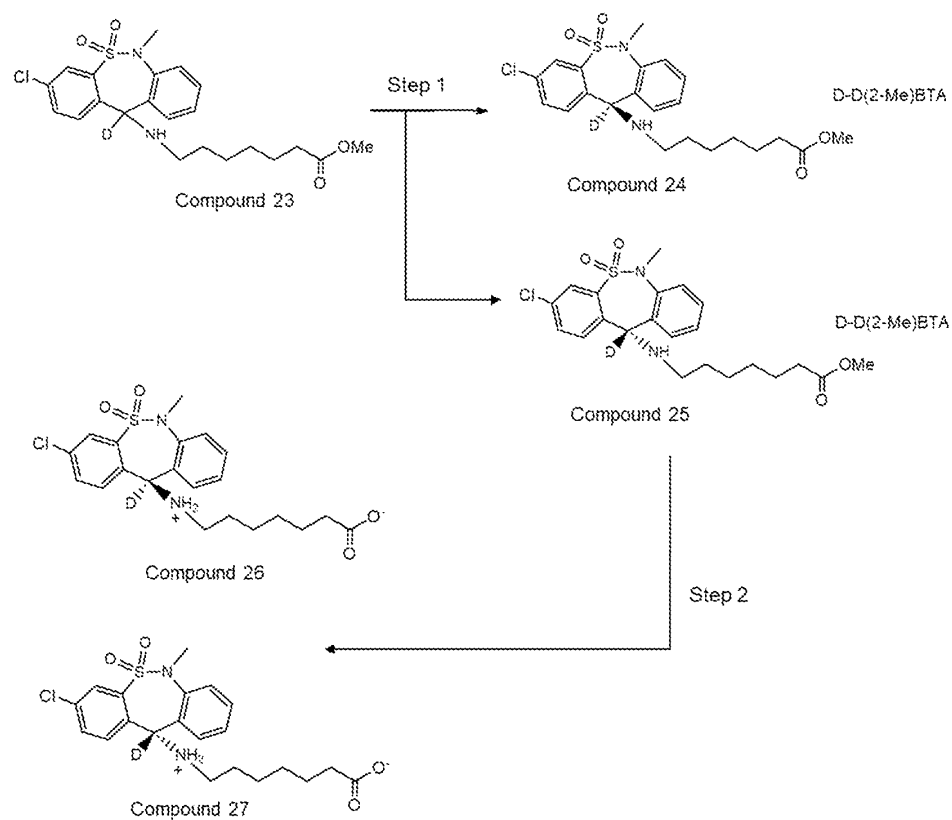
[00215] Optionally, racemic tianeptine methyl ester is separated by preparative supercritical fluid (SFC) using a chiral column to yield (S)-tianeptine methyl ester.

[00216] To prepare the zwitterion of the methyl ester (Compound 22), in step 2 (Scheme 3), 2M HCl (10 mL) is added to the (S)-tianeptine methyl ester: D-D(2-Me)BTA salt (Compound 20: D-D(2-Me)BTA) (1 mmol) at 22 °C. The mixture is stirred at 100 °C until all starting material is consumed, cooled to 22 °C, and neutralized with 2M NaOH. The mixture is filtered and the solid is washed with H₂O and dried to yield (S)-tianeptine zwitterion (Compound 22) in very high optical purity.

[00217] Optionally, other aqueous acids, such as sulfuric or phosphoric acid, are used for hydrolysis. Basic hydrolysis with a strong base, such as NaOH in methanol can also be used, but may result in racemization under some conditions. Hydrolysis is also performed with lithium hydroxide (1 eq.) in methanol/THF.

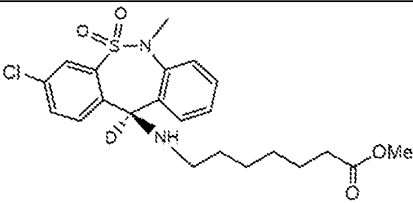
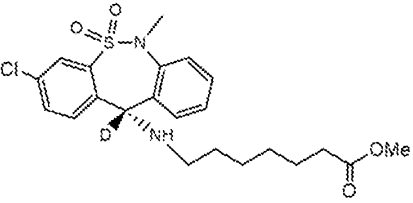
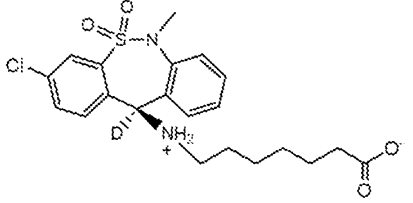
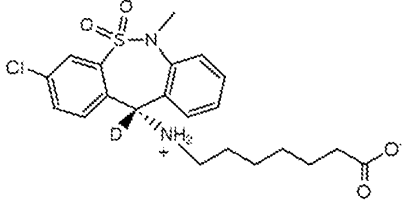
[00218] In Scheme 4, the deuterated form of (S)-tianeptine-HCl or (S)-tianeptine-HCl is prepared according to Steps 1 to 2 as described above for Scheme 3, but in Step 1, the deuterated tianeptine methyl ester is used as the starting product, or in some embodiments, using the alternative methods described above.

Scheme 4: Exemplary Synthetic Scheme for 11-D-Tianeptine Enantiomers from 11-D-Tianeptine Methyl Ester



5 **Table 5. Compounds of Scheme 4**

Compound Number	Compound Structure and Name
23	methyl 7-[(3-chloro-6-methyl-5,5-dioxo-6,11-dihydrodibenzo[<i>c,f</i>][1,2]thiazepin-11-yl)-11-<i>d</i>]amino]heptanoate

24	 methyl (R)-7-[(3-chloro-6-methyl-5,5-dioxo-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl-11-<i>d</i>)amino]heptanoate
25	 methyl (S)-7-[(3-chloro-6-methyl-5,5-dioxo-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl-11-<i>d</i>)amino]heptanoate
26	 (R)-7-[(3-chloro-6-methyl-5,5-dioxo-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl-11-<i>d</i>)ammonio]heptanoate
27	 (S)-7-[(3-chloro-6-methyl-5,5-dioxo-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl-11-<i>d</i>)ammonio]heptanoate

Example 3: Tianeptine Oxalate Activity at the μ -Opioid Receptor

μ -Opioid Receptor (MOR) Assay

- [00219] Fluorescent biosensors (*e.g.*, cADDiS or β -arrestin) from Montana Molecular
 5 were used to measure μ -opioid receptor (MOR) signaling in real-time in live cells (*e.g.*, HEK293T cells) using the Hamamatsu Functional Drug Screening System (FDSS)/ μ Cell

reader. cAMP inhibition, following pre-incubation with forskolin, and β -arrestin2 (arrestin) recruitment were measured. The MOR response at steady state, 60 minutes after compound addition, and the initial rate of MOR signaling were quantified.

[00220] Baseline fluorescence was measured, and after a baseline recording of 4
5 minutes a compound (*e.g.*, [D-Ala², NMe-Phe⁴, Gly-ol⁵]-enkephalin (DAMGO), racemic tianeptine, (S)-tianeptine, or (R)-tianeptine) was added. Control experiments measuring cAMP inhibition and arrestin recruitment were performed using a 10 μ M compound (*e.g.*, DAMGO, racemic tianeptine, and 99.0%-99.35% pure (S)-tianeptine oxalate or 98.5%-99.35% pure (R)-tianeptine oxalate) with or without MOR receptor overexpression and
10 vehicle with MOR receptor overexpression. DAMGO, racemic tianeptine, (S)-tianeptine oxalate, and (R)-tianeptine oxalate were added at various concentrations including 0 nM (vehicle), 0.001 nM, 0.00316 nM, 0.01 nM, 0.0316 nM, 0.1 nM, 0.316 nM, 1 nM, 3.16 nM, 10nM, 31.6 nM, 100 nM, 316 nM, 1000 nM, 3160 nM, 10000 nM and 31600 nM. Data were normalized to the baseline and transferred to GraphPad Prism and represented as a mean $\pm$
15 SEM from 3 replicates. Data were fit to a fall-to-plateau model with baseline drift and the activity at steady state and initial rate of signaling were quantified.

[00221] Racemic tianeptine was a moderate potency full agonist for inhibition of cAMP production (Table 6 and Figures 3A and 3B), and a low potency near-full agonist for arrestin recruitment (Table 7 and Figures 4A and 4B). Comparatively, 99.0%-99.35% pure
20 (S)-tianeptine oxalate was an order of magnitude less potent (EC_{50} of 560 nM and 40nM for (S)-tianeptine oxalate and tianeptine, respectively) and had a similar E_{max} of cAMP inhibition to racemic tianeptine (82% vs. 90% for (S)-tianeptine oxalate and racemic tianeptine, respectively) (Table 6 and Figures 3A, 3B, 4A and 4B) while 98.5%-99.35% pure (R)-tianeptine oxalate had a similar EC_{50} (*i.e.*, potency) and E_{max} to racemic tianeptine (Table 6
25 and Figures 3A, 3B, 4A and 4B). The steady state concentration response and the initial rate analysis of cAMP inhibition (Table 6) and arrestin recruitment (Table 7) are shown below.

Table 6. cAMP Inhibition using (S)-tianeptine oxalate and (R)- tianeptine oxalate

Compound	cAMP Inhibition Maximum Effect		cAMP Inhibition Initial Rate
	EC ₅₀ (nM)	E _{max} (% DAMGO)	E _{max} (% DAMGO)
DAMGO	1.6	100	100
Racemic Tianeptine	40	90	84
(S)-Tianeptine Oxalate (99.0%-99.35%chiral purity)	560	82	90
(R)-Tianeptine Oxalate (98.5%-99.35% chiral purity)	41	91	91

Table 7. Arrestin recruitment using (S)-tianeptine oxalate and (R)-tianeptine oxalate

Compound	cAMP Inhibition Maximum Effect		cAMP Inhibition Initial Rate
	EC ₅₀ (nM)	E _{max} (% DAMGO)	E _{max} (% DAMGO)
DAMGO	160	100	100
Racemic Tianeptine	2,200	83	74
(S)-Tianeptine Oxalate (99.0%-99.35%chiral purity)	>10,000	ND	ND
(R)-Tianeptine Oxalate (98.5%-99.35%chiral purity)	2,400	90	67

Example 4: Tianeptine Sodium Activity at the μ -Opioid Receptor*MOR Assay*

[00222] Fluorescent biosensors (*e.g.*, cADDiS or β -arrestin) from Montana Molecular were used to measure μ -opioid receptor (MOR) signaling in real-time in live cells (*e.g.*,
5 HEK293T cells) using the Hamamatsu Functional Drug Screening System (FDSS)/ μ Cell reader. The signals measured were Gi signaling (*i.e.*, cAMP production or cAMP inhibition in cells pre-incubated with forskolin) and β -arrestin2 (arrestin) recruitment (*i.e.*, arrestin activation). The activity at steady state and initial rate of signaling were quantified. The compounds tested include DAMGO, racemic tianeptine, racemic mixture of tianeptine
10 sodium, and (S)- or (R)-tianeptine sodium. Various concentrations of the compounds include 0 nM, 0.001 nM, 0.003 nM, 0.010 nM, 0.032 nM, 0.1 nM, 0.316 nM, 1 nM, 3.162 nM, 10nM, 31.62 nM, 100nM, 316.2 nM, 1000 nM, 3162 nM, 10000 nM, and 31620 nM.

Gi Signaling

15 [00223] Live HEK293T cells were transduced with cADDiS biosensor, and μ -opioid receptor (MOR) (Gene ID: OPRM1), Dopamine Receptor D2 (Gene ID: DRD2) as a positive control or no receptor as a negative control. Baseline fluorescence was measured for 20 minutes, followed by stimulation with 10 μ M forskolin for 70 minutes. Compounds (*e.g.*, DAMGO, racemic tianeptine, racemic mixture of tianeptine sodium, (S)-tianeptine sodium,
20 and (R)-tianeptine sodium) were added at minute 90. The negative controls (cells with no MOR overexpression) were treated with vehicle-only or forskolin + vehicle treated samples. The positive controls (cells expressing DRD2) were treated with 3.2 μ M quinpirole.

[00224] The time course data after compound addition was normalized to the baseline fluorescence and adjusted to the time course data from forskolin + vehicle treated samples.
25 Data were transferred to GraphPad Prism and is shown as a mean $\pm$ SEM from 4 replicates. Data were best fit to either a fall-and-rise to steady state or a rise-and-fall to steady state model, depending on cAMP production or % cAMP inhibition. Percent inhibition of cAMP data was used to obtain dose-concentration curves.

[00225] (S)-Tianeptine sodium (99.0%-99.35%chiral purity) was a low potency partial
30 MOR agonist as indicated by % cAMP inhibition in two separate experiments, while (R)-Tianeptine sodium (99.35% chiral purity) showed similar potency and efficacy as compared to racemic tianeptine (Table 8, Figures 5A, 5B, 6A and 6B). The potency of the racemic

mixture of tianeptine sodium was approximately 3.5-fold lower than (R)-tianeptine sodium when comparing the EC₅₀ (Table 8).

[00226] The concentration-response and the initial rate analysis of cAMP inhibition is shown in **Table 8**.

5

Table 8. cAMP Inhibition using (S)- and (R)- tianeptine sodium

Experiment 1				
Compound	cAMP Inhibition Initial Rate		cAMP Inhibition Maximum Effect	
	EC ₅₀ (nM)	E _{max} (% DAMGO)	EC ₅₀ (nM)	E _{max} (% DAMGO)
(S)-Tianeptine Sodium (99.35% chiral purity)	>10000	33.1	4402	34.9
(R)-Tianeptine Sodium (99.35% chiral purity)	28.6	95.1	16	96.3
Racemic Tianeptine	45.2	107	13.2	104
DAMGO	0.40	100	0.633	100
Experiment 2				
Compound	cAMP Inhibition Initial Rate		cAMP Inhibition Maximum Effect	
	EC ₅₀ (nM)	E _{max} (% DAMGO)	EC ₅₀ (nM)	E _{max} (% DAMGO)
(S)-Tianeptine Sodium (99.0%-99.35% chiral purity)	2341	47.3	2211	43.4
(R)-Tianeptine Sodium (98.5%-99.35 chiral purity)	11.6	108	10.4	106
Racemic Tianeptine Sodium	27.9	87.7	36.6	90.4
Racemic Tianeptine	22.8	101	14.9	88.0
DAMGO	0.359	100	0.384	100

Arrestin Recruitment

10 [00227] Live HEK293T cells were transduced with β-arrestin (arrestin) biosensor, and OPRM1, angiotensin II type 1 receptor (AT1R; Gene ID: AGTR1) as a positive control, or no receptor as a negative control. Baseline fluorescence was measured for 20 minutes, then

compounds (e.g., DAMGO, racemic tianeptine, racemic mixture of tianeptine, (S)-tianeptine sodium and (R)-tianeptine sodium) were added and fluorescence was measured for 90 minutes. The negative controls (cells with no MOR overexpression) were treated with vehicle-only treated samples. The positive controls (cells expressing AT1R) were treated with 3.2 μ M angiotensin II.

[00228] The time course data after compound addition was normalized to the baseline fluorescence. Data were transferred to GraphPad Prism and is shown as a mean $\pm$ SEM from 4 replicates. Data were best fit to an arrestin recruitment and degradation model. Initial rate and maximum effect at peak arrestin recruitment was used to obtain dose-concentration curves.

[00229] (S)-Tianeptine sodium (99.9% chiral purity) showed no agonist effect at the μ -opioid receptor. However, (R)-Tianeptine sodium (99.9% chiral purity) was near full efficacy as an agonist at the μ -opioid receptor (90% of DAMGO) and showed similar potency as compared to racemic tianeptine (Figures 7A and 7B). The potency of the racemic mixture of tianeptine sodium was approximately 1.8-fold lower than (R)-tianeptine sodium as determined by the EC₅₀ of the arrestin recruitment (maximum effect), showing full efficacy but slightly slower kinetics (82.5% of the (R)-tianeptine sodium initial rate) (Table 9).

[00230] The concentration-response and the initial rate analysis of arrestin recruitment is shown in Table 9.

Table 9. Arrestin Recruitment using 99.9% pure (S)- and (R)- tianeptine sodium

Compound	Arrestin Recruitment Initial Rate		Arrestin Recruitment Maximum Effect	
	EC ₅₀ (nM)	E _{max} (% DAMGO)	EC ₅₀ (nM)	E _{max} (% DAMGO)
(S)-Tianeptine Sodium	>31620	N.D.	>31620	N.D.
(R)-Tianeptine Sodium	2601	84.7	886	89.5
Racemic Tianeptine Sodium	2359	69.9	1576	99.1
Racemic Tianeptine	1888	81.8	827	99.9
DAMGO	187	100	51.7	100

[00231] Overall, (S)-tianeptine and (R)-tianeptine exhibit distinct activities at the μ -opioid receptor, further recapitulated by the analysis of substantially pure tianeptine enantiomers, isolated by chiral chromatography, on MOR agonism. For example, 99.9% pure (S)-tianeptine showed no MOR agonism assessed by cAMP inhibition (Figure 8A) and arrestin recruitment (Figures 7A, 7B and 8B). In contrast, 99.35% pure or lower (S)-tianeptine was a low potency partial MOR agonist assessed by cAMP inhibition (Tables 6, 7 and 8, and Figures 3A, 3B, 4A, 4B, 5A, 5B, 6A and 6B). Therefore, MOR agonism was determined to be entirely due to (R)-tianeptine, where it was about 800-fold more active than (S)-tianeptine, suggesting that the use of pure or substantially pure (S)-tianeptine has the potential to reduce the potential for opioid abuse, or opioid toxicity, or opioid overdose. **Table 10** shows the EC₅₀ of the 99.9% pure tianeptine enantiomers. No activity was observed at any achievable concentration for 99.9% pure (S)-tianeptine (Figures 7A, 7B, 8A and 8B).

Table 10. EC₅₀ of 99.9% pure (S)-tianeptine sodium and (R)-tianeptine sodium

Compound	EC ₅₀ cAMP Inhibition (μ M)	EC ₅₀ Peak Arrestin (μ M)
(S)-Tianeptine	>1000	>1000
(R)-Tianeptine	0.168	1.873

Example 5: Activity of Tianeptine (R)- and (S)- Enantiomers at the peroxisome proliferator-activated receptors (PPAR)

PPAR Activity Assay

[00232] PPAR activity assays were performed using the respective PPAR (*e.g.*, PPAR- α , PPAR- γ or PPAR- β/δ) luciferase reporters from Indigo Biosciences and performed according to the manufacturer's instructions. The luciferase reporter cells were prepared in Cell Recovery Medium provided by the manufacturer and treated with different compounds (*e.g.*, racemic tianeptine, racemic tianeptine oxalate, (S)-tianeptine (99.9% chiral purity), (R)-tianeptine sodium (99.9% chiral purity), DMSO (negative control), PPAR- β/δ positive controls GW072, PPAR- γ positive control rosiglitazone, PPAR- α positive control GW7647 or PPAR- β/δ agonist Seladelpar) under different concentrations. Cells treated with compounds were incubated at 37°C, 5% CO₂ for 22-24 hours. Media contents were then removed, and the cells were incubated with the Luciferase Detection Reagent. The luminescence was quantified using Molecular Devices Spectra Max L- channel. The data were expressed and plotted as Relative Light Unit (RLU).

[00233] (R)-tianeptine showed no agonist effect at PPAR- β/δ . However, (S)-tianeptine, racemic tianeptine and racemic tianeptine oxalate showed a clear effect at 3 μ M (Figures 9A-9D). (S)-tianeptine also showed robust agonism at PPAR- γ (1-3 μ M), while (R)-tianeptine, racemic tianeptine and racemic tianeptine oxalate showed slightly less potent PPAR- γ agonism (3-10 μ M) (Figures 10A and 10B). None of racemic tianeptine, racemic tianeptine oxalate, (S)-tianeptine or (R)-tianeptine was a PPAR- α agonist (Figures 11A and 11B). These data reveal a role of the enantiomers of tianeptine in modulating PPAR- β/δ and PPAR- γ -mediated pathologies.

10 **Example 6: Molecular Modeling of PPAR- β/δ and Tianeptine (R)- and (S)- Enantiomers**

[00234] A crystal structure of PPAR- β/δ in complex with GW2331 ligand (pdb ID: 1Y0S) was used as a starting point for molecular modeling of PPAR- β/δ in complex with (R)- and (S)- enantiomers of tianeptine. GW2331 shares broad structural features, such as size and shape, with tianeptine enantiomers and targets the critical ligand binding site. Two separate models of PPAR- β/δ in complex with (S)-tianeptine or (R)-tianeptine were docked, and energy minimized.

[00235] The results of ligand guided docking followed by molecular dynamics simulations, indicated that only (S)-tianeptine was able to fit into the ligand binding site of PPAR- β/δ while maintaining the overall orientation of GW2331 (Figure 12). The attempts to model (R)-tianeptine resulted in clashes and unfavorable interactions of the ligand with the protein chain. The complex of PPAR- β/δ and (R)-tianeptine was a best-case scenario, if and only if (R)-tianeptine would bind to the critical ligand binding site of PPAR- β/δ . Therefore, comparative analysis of the two computational models suggests that (S)-tianeptine is the preferred enantiomer of tianeptine capable of binding PPAR- β/δ supporting the results of the PPAR- β/δ activity assay.

Example 7: Proposed Mechanism for Bond Formation between (S)-Tianeptine and PPAR- β/δ

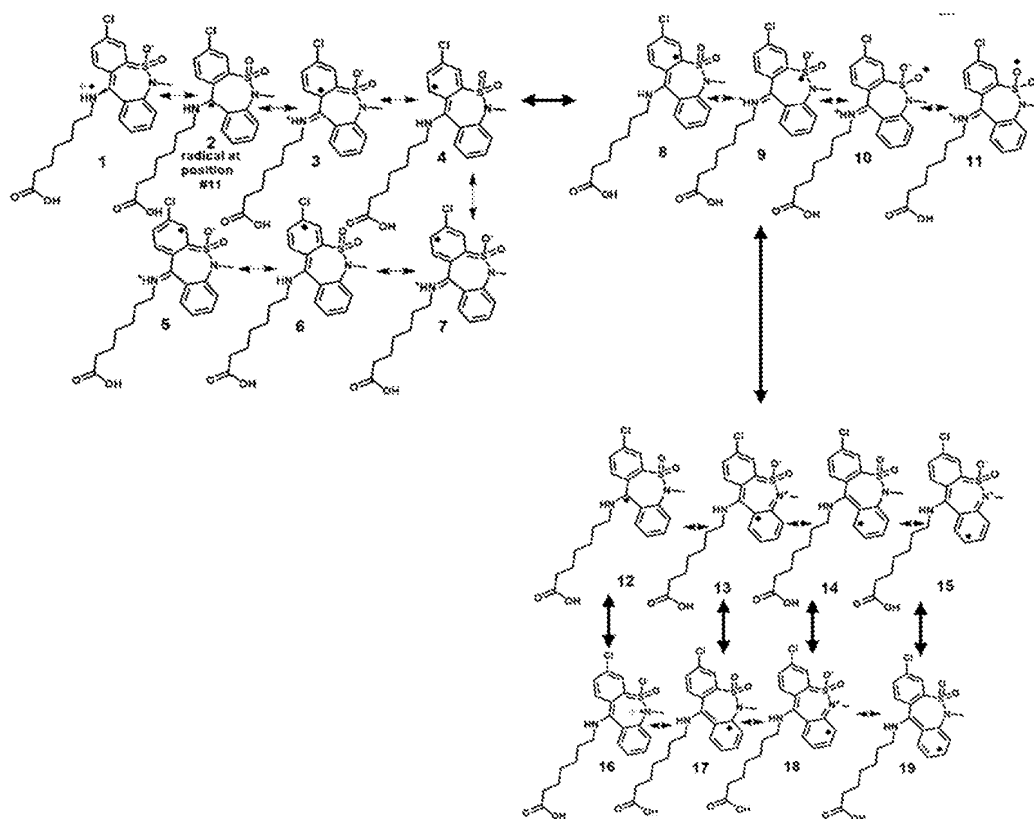
[00236] Reactive oxygen species (ROS) react with fatty acids and esters to form hydroxyalkenals oxidation products (*e.g.*, 4-hydroxyhexenal, 4-hydroxynonenal, and 4-hydroxy-2E,6Z-dodecadienal). These hydroxyalkenals are endogenous PPAR- γ ligands that activate PPAR- γ irreversibly by forming a bond between the 3-carbon of 4-hydroxyalkenols and cysteine 285 (cys285) of PPAR- γ (Gallo et al., *J Physiol Pharmacol.* 2020; Sasson, *Biochimie.* 2017). This derivatization of PPAR- γ at cys285 can serve as a signaling

mechanism for ROS damage, but 4-hydroxyalkenals cause considerable toxicity due to reaction at many other protein sites (Domingues *et al.*, *J. Proteomics*. 2013).

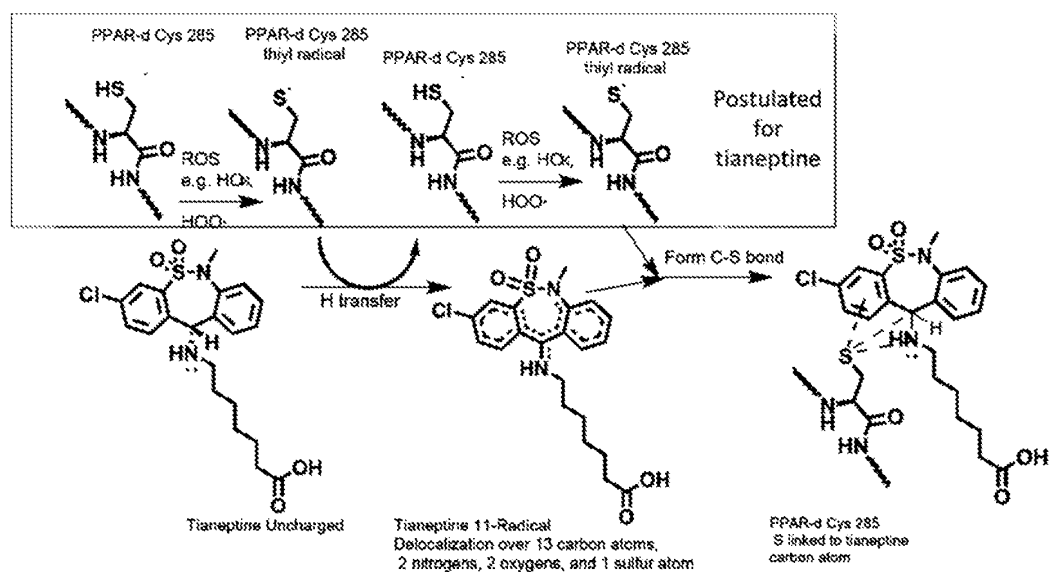
[00237] Tianeptine reacts with oxygen in DMSO at 25°C, forming tianeptine impurity D (C-11 imine), through the loss of 2 hydrogens at C-11 and the side chain amine nitrogen.

- 5 This oxidation is inhibited by radical scavengers glutathione, thiophenol, and hydroquinone, which is consistent with a tianeptine C11-free radical intermediate. This tianeptine 11-radical is delocalized over 13 carbon atoms, 2 nitrogen atoms, 2 oxygen atoms and 1 sulfur atom. The 19 possible isomers of the tianeptine C11-radical depicted in **Scheme 5**, indicate a highly delocalized radical that could form easily and last long enough to undergo reactions with thiol
- 10 radicals to form C-S bonds. Computational modeling of (S)- and (R)- tianeptine to evaluate the potential of C-S bond formation in the PPAR- δ/β binding site revealed a shorter bond-length between (S)-tianeptine and cys285 (5Å, Figure 13A), compared to that of (R)-tianeptine and cys285 (7.9Å, Figure 13B), suggesting that only (S)-tianeptine would be capable of covalent interaction with PPAR- δ/β . Computational modeling also suggests that
- 15 (R)-tianeptine binds more weakly than (S)-tianeptine to PPAR- δ/β , which would further decrease the relative likelihood of C-S bond formation between (R)-tianeptine and cys285.

- [00238] Without wishing to be bound by theory, it is therefore hypothesized that oxidation of (S)-tianeptine by ROS may result in the formation of a covalent bond between any of the aromatic carbons, carbon-11 or the adjacent nitrogen atom of (S)-tianeptine and
- 20 the cys285 sulfur atom of PPAR- β/δ (Scheme 6, dashed lines), leading to irreversible activation of PPAR- β/δ without the toxicity of 4-hydroxyalkenols.

Scheme 5: Possible Delocalized forms of a Tianeptide C11 Radical

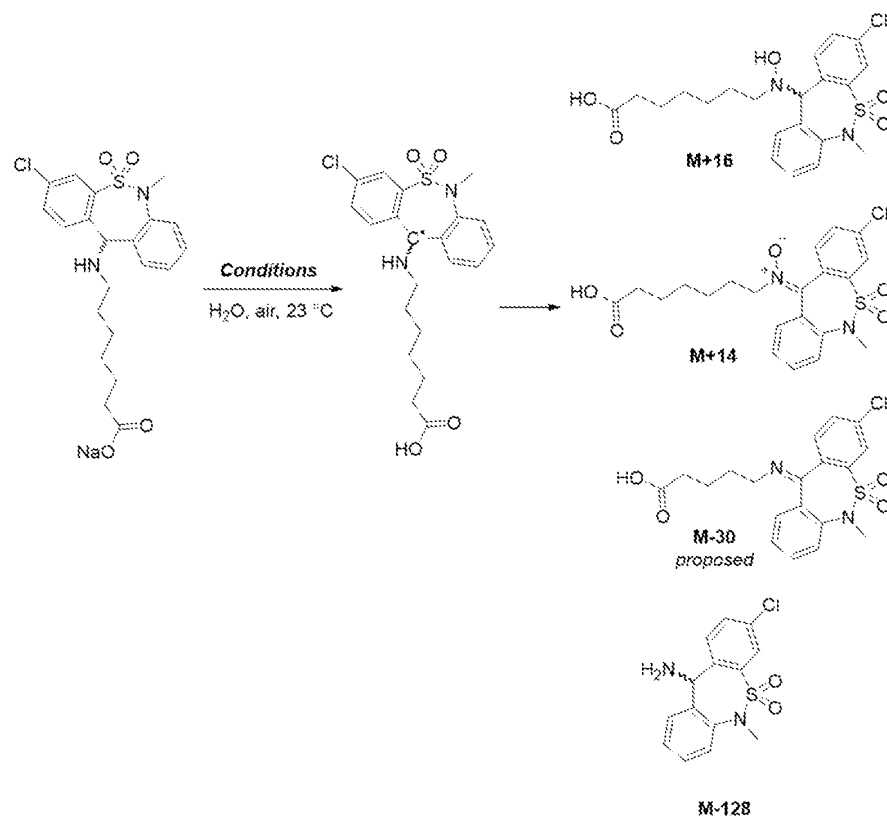
Scheme 6: Proposed mechanism for Bond Formation between (S)-Tianeptine and PPAR- β/δ



Mechanistic Studies of Reaction of Racemic Tianeptine with Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS)

(1) Reaction of Racemic Tianeptine with Reactive Oxygen Species (ROS)

Scheme 7: Reaction of Racemic Tianeptine with H₂O₂ and FeSO₄ (Fenton reagent)



5

Table 11. Results of Reaction of Racemic Tianeptine Sodium with H₂O₂ and FeSO₄ (Fenton reagent)

Conditions				Results
[Tianeptine Sodium] (mM)	[H ₂ O ₂] (mM)	FeSO ₄ (mM)	Temperature (°C)	Conversion (%)
0.001	0.1	0.1	23	81
0.01	0.1	0.1	23	~60
0.05	0.1	0.1	23	43

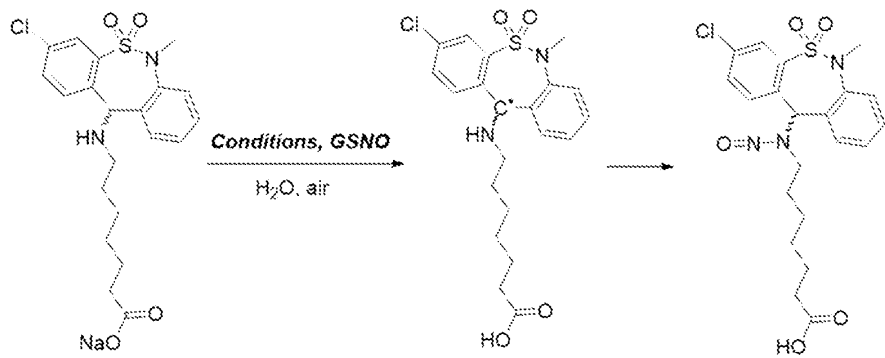
- 10 [00239] Racemic tianeptine sodium reacted with the ROS hydrogen peroxide (1 mM) in water at 23 °C for 24 hours under oxygen in the presence of FeSO₄ to form racemic N-hydroxy-tianeptine (M+16) and other oxidized products analyzed by NMR spectroscopy (*see*,

Scheme 7 and Table 11). In the presence of radical quenchers thiophenol (PhSH) and hydroquinone, the production of the oxidative species was significantly inhibited (data not shown) indicating that the formation of the oxidative species requires the formation of a tianeptine free radical.

5

(2) Reaction of Racemic Tianeptine with Reactive Nitrogen Species (RNS)

Scheme 8: Reaction of Racemic Tianeptine Sodium with S-Glutathione



10 Table 12. Results of Reaction of Racemic Tianeptine Sodium with S-Glutathione

Conditions				Results
Tianeptine Sodium (mg)	Additive (eq.)	Time (hours)	Temperature (°C)	Conversion (%)
10	GSNO (1.0)	24	23	17
10	GSNO (1.0) EBN (1.0)	24	23	2
10	GSNO (1.0)	24	50	35
10	GSNO (1.0)	24	80	50

[00240] Racemic tianeptine sodium reacts with the RNS S-Glutathione in water at varying temperatures for 24 hours under oxygen to form racemic N-nitroso-tianeptine (Scheme 8 and Table 12). EBN (N-tert-butylmethanimine N-oxide) is a potent radical scavenger that traps and inactivates glutathione thiyl radicals. In the presence of EBN, the production of N-nitroso-tianeptine was significantly inhibited (Table 12) indicating that radical formation is required for N-nitroso-tianeptine formation.

15

[00241] Altogether, these data indicate that tianeptine is easily oxidizable by a number of species and that the formation of the tianeptine C11-free radical intermediate is essential in the conversion of tianeptine to an oxidized species.

[00242] In certain proteins, ROS or O₂-mediated oxidation can form a 3-atom nitrogen–oxygen–sulfur covalent bridge (NOS bridge) between free thiol (protein-cysteine-SH) and free amine (protein lysine-NH₂). Examples of this NOS bridge as an intramolecular link within a protein or an intermolecular link between 2 proteins have been established by protein crystal structures. NOS bridge formation is redox-reversible and can act as an important switch for enzyme activity, ligand binding, and gene expression (Rabe von Pappenheim F, et al. *Nat Chem Biol.* 2022). Without wishing to be bound to theory, it is therefore hypothesized that oxidation of tianeptine by ROS or RNS may result in NOS bridge formation at PPAR-β/δ and/or PPAR-γ, allowing potent agonism in conditions of high oxidative stress. This covalent attachment is reversed by the reduction of the NOS bridge.

15 **Example 8: Evaluation of Tianeptine (R)- and (S)- Enantiomers in Neurite Outgrowth**

[00243] The effects of (S)- and (R)-tianeptine on neuronal dynamics were assessed using the Ready-2-Go Neurite Outgrowth Assay Service (PhenoVista). iCell Glutaneurons (Fujifilm Cellular Dynamics) were thawed and cultured according to manufacturer's protocol and allowed to grow for 7 days to allow synapse network formation. Cells were incubated in the presence of either (S)- or (R)-tianeptine zwitterion (99.9% chiral purity) dissolved in PBS at various concentrations (e.g., 0.03 μM, 0.1 μM, 0.32 μM, 1.0 μM, 3.2 μM and 10 μM), staurosporine (positive control, 0.063 μM and 0.2 μM), vincristine (negative control, 2 μM and 20 μM), PBS and DMSO for 24 hours and 72 hours. The cells were then fixed at 24 or 72 hours and stained for imaging and analysis. Nuclei were stained with Hoechst and cell bodies and neurites with CellMask.

[00244] At 24 and 72 hours, the positive and negative controls (staurosporine and vincristine, respectively) had the expected effects on average neurite length, with staurosporine treatment increasing average neurite length and vincristine treatment decreasing average neurite length (Figures 14A and 14B). At 24 hours, (R)-tianeptine and (S)-tianeptine did not differ with respect to neurite outgrowth (Figure 14A). However, by 72 hours, (S)-tianeptine significantly increased neurite outgrowth relative to the Phosphate Buffered Saline (PBS) control with a maximum effect at 0.1 μM (Figure 14B). In contrast, (R)-tianeptine (1.0 μM) did not significantly increase neurite outgrowth relative to the PBS control, and actually decreased neurite outgrowth at 1.0 μM (Figure 14B). These data

indicate that (S)-tianeptine induces neurite outgrowth while (R)-tianeptine inhibits neurite outgrowth, suggesting that, without wishing to be bound by theory, (S)-tianeptine may induce anti-depressive effects by restoring neuroplasticity while minimizing or eliminating the potential for opioid abuse.

5 [00245] The experiment above was repeated by incubating cells in the presence of either (S)- or (R)-tianeptine zwitterion (99.9% chiral purity) dissolved in PBS at various concentrations (*e.g.*, 0.1 μ M, 1.0 μ M, and 10 μ M) – alone or in combination with dexamethasone, dexamethasone being at various concentrations (*e.g.*, 0.001 μ M, 0.01 μ M, 0.1 μ M, 1.0 μ M, 10 μ M and 100 μ M) PBS or DMSO for 5 days. For the control compounds
10 (*i.e.*, staurosporine (0.063 μ M and 0.2 μ M), vincristine (2 μ M and 20 μ M) and carbonyl cyanide-4 (trifluoromethoxy) phenylhydrazone (FCCP, 6.2 μ M and 62.0 μ M)), the cells were incubated for 24 hours, 24 hours, and 2 hours, respectively due to known toxicity in response to prolonged treatment. The cells were then fixed and stained for imaging and analysis. Nuclei were stained with Hoechst, cell body morphology and neurite network were assessed
15 using CellMask Green and mitochondrial function was assessed using MitoTracker CMXRos. Data was normalized to the 1% PBS control.

[00246] As described above, staurosporine and vincristine had the expected effects on average neurite outgrowth, with staurosporine treatment increasing total neurite length and average neurite width and vincristine treatment decreasing both metrics (Figures 14C-14F).
20 Likewise, (S)- performed as previously described significantly increasing neurite outgrowth relative to the 1% PBS control particularly at 1.0 μ M, and 10 μ M (Figures 14C and 14D). However, treatment with (R)-tianeptine showed no significant effect on neurite outgrowth (Figures 14E and 14F). (S)-tianeptine also increased the mitochondrial staining in neurites, indicating an increase in the localization and activity of mitochondria in neurites (Figure
25 15B), although mitochondrial staining in the cell body remained unchanged (Figure 15A). On the other hand, (R)-tianeptine was found to decrease mitochondrial staining in cell bodies (Figure 15C), indicating a decrease in the localization and activity of mitochondria in cell bodies, while no change was observed in the mitochondrial staining in neurites (Figure 15D).

[00247] Dexamethasone was used as an *in vitro* proxy for stress as it inhibits growth or
30 causes cell shrinkage in many systems. However, in this cell line, dexamethasone was found to have pro-growth effects, increasing neurite outgrowth except at the highest doses (*i.e.*, 10 μ M and 100 μ M, Figures 14C-14F), and increasing mitochondrial staining in neurites (Figures 15B and 15C). Dexamethasone did not have a significant effect on the mitochondrial staining in cell bodies (Figures 15A and 15C). (S)-tianeptine acted

synergistically with dexamethasone to enhance its trophic effects (Figures 14C, 14D, 15A and 15D), while (R)-tianeptine antagonized the trophic effects of dexamethasone (Figures 14E, 14F, 15B and 15C). The increase in mitochondrial staining in neurites observed with (S)-tianeptine may play a major role in the observed neuroplastic remodeling. Further, the synergy observed with (S)-tianeptine and dexamethasone suggests that (S)-tianeptine will have its maximal effects under stress conditions. The inhibitory effects of R-tianeptine on mitochondria may be mediated by its μ -opioid agonism.

Example 9: Evaluation of Tianeptine in Novel Object Recognition Test

[00248] The memory enhancing capabilities of racemic tianeptine sodium were assessed using the novel object recognition (NOR) test in rats. The study was conducted at PsychoGenics, Inc and performed using adult male Long-Evans rats (275-299 g) from Charles River Laboratory. Rats were housed 2 per cage and acclimated for at least 7 days prior to testing. During the course of the study, 12h/12h light/dark cycles were maintained. The room temperature was maintained between 20 and 23°C with a relative humidity maintained around 50%. Chow and water were provided ad libitum for the duration of the study. Each rat was randomly assigned across the treatment groups. Testing was performed during the animals' light cycle phase. Rats were assessed for cognitive ability in a test apparatus comprising an open-field arena (40 x 40 cm) under dimmed lighting. All training and testing trials were video-taped and scored by an observer blind to treatments.

[00249] Rats were treated by intraperitoneal (i.p.) injection with galantamine dissolved in saline at a dose volume of 1 mg/kg 30 minutes prior to training and prior to testing, or with racemic tianeptine sodium dissolved in saline at a dose volume of 1 ml/kg prior to training or at a dose volume of 3, 10 or 30 mg/kg 60 minutes prior to testing. On Days 1 and 2, rats were allowed to freely explore the arena (no objects inside) for a 10-minute habituation period. On Day 3, rats were administered saline, galantamine or racemic tianeptine sodium, and following the appropriate pretreatment time (30 min for saline and galantamine; 60 min for racemic tianeptine sodium, rats were placed into the test arena in the presence of two identical objects. Each rat was placed in the arena facing the same direction at the same position, and the time spent actively exploring the objects during a 3-minute T1 was recorded. The rat was returned to its home cage following training. After 48 hours, the rats were administered saline, galantamine or racemic tianeptine sodium again, and following the appropriate pretreatment time, they were placed into the test arena in the presence of one familiar object and one novel object, and the time spent exploring each object were recorded

for 5 minutes in the testing session (T2). The presentation order and position of the objects (left/right) in T2 is randomized between rats to prevent bias from order or place preference. Data were expressed as Recognition Index, which is defined as the ratio of the time spent exploring the novel object over the total time spent exploring both objects (Novel / (Familiar + Novel) $\times$ 100%) during the 5 min test session. A value of 50% in recognition index means entire forgetting. Data were analyzed by one-way ANOVA followed by Dunnett's post hoc analysis. Statistical outliers that exceeded two standard deviations from the mean were removed from the final analysis. Once one data point was identified as outlier, the whole animal was removed. Animals with recognition index above 90% or below 30% were also eliminated because they suggest strong (non-memory) bias between two objects.

[00250] Racemic tianeptine sodium (10 and 30 mg/kg) and galantamine significantly increased the Recognition Index during the 5-minute test as well as during the first 3 minutes of the test. Racemic tianeptine sodium (3 mg/kg) showed a non-significant trend to increasing recognition index during these two timepoints. During the first minute of the test, racemic tianeptine sodium (3 and 10 mg/kg) significantly increased the Recognition Index (Figure 16A). These results suggest that racemic tianeptine sodium is capable of memory enhancement.

[00251] The memory enhancing capabilities of (S)- and (R)-tianeptine sodium was also assessed in the NOR test using substantially pure enantiomers (*i.e.*, 99.9% chiral purity). Rats were treated by i.p. injection with (S)- or (R)-tianeptine sodium dissolved in saline at a dose volume of 1 ml/kg prior to training or at a dose volume of 3, 10 or 30 mg/kg 60 minutes prior to testing or with galantamine or racemic tianeptine sodium, and the experiments and analysis were conducted as described above.

[00252] As predicted, (S)-tianeptine sodium showed a significant increase in the Recognition Index during the NOR test with similar activity to racemic tianeptine sodium (Figure 16B), suggesting that (S)-tianeptine sodium is efficacious in improving recognition memory. (R)-tianeptine, on the other hand, showed no efficacy in the NOR test at 3 and 10 mg/kg (Figure 16C). 30 mg/kg (R)-tianeptine was not evaluated in the NOR test due to overt sedation and catalepsy-like behavior in rats, perhaps due to MOR agonism.

30

Example 10: Evaluation of Tianeptine (R)- and (S)- Enantiomers in Forced Swim Test

[00253] The antidepressant efficacy of (S)- and (R)-tianeptine sodium (99.9% chiral purity) and racemic tianeptine sodium was assessed using the forced swim test in mice. The study was conducted at PsychoGenics, Inc and performed using male BalbC/J mice (8 weeks

of age) purchased from Jackson Laboratories (Bar Harbor, ME). Mice were group housed in OPTIMice ventilated cages and allowed to acclimate for 1 week prior to testing. During the course of the study, 12h/12h light/dark cycles were maintained. The room temperature was maintained between 20 and 23°C with a relative humidity maintained around 50%. Chow and water were provided ad libitum for the duration of the study. Each mouse was randomly assigned across the treatment groups. Testing was performed during the animals' light cycle phase.

[00254] Mice were treated by i.p. injection with sertraline dissolved in saline at a dose volume of 20 mg/kg prior to testing and at a dose volume of 10 mg/kg prior to training, or with racemic tianeptine sodium, (S)-tianeptine sodium or (R)-tianeptine sodium at a dose volume of 3, 10 or 30 mg/kg dissolved in saline 60 minutes prior to testing and at a dose volume of 10 ml/kg 60 minutes prior to training. The forced swim test consisted of one 6 min-session of forced swimming in individual opaque cylinders (*i.e.*, 15 cm tall x 10 cm wide, 1000 ml beakers) containing fresh 23°C ± 2°C tap water 12 cm deep (approximately 800 ml) for each test animal. Immobility was described as the postural position of floating in the water. The animal was observed with the back slightly hunched and the head above water with no movements or with small stabilizing movements of the limbs. Sometimes the back was arched with the animal stretched across the sides of the beaker and in this posture, immobility was recorded only if the animal was not struggling. Mice were administered either vehicle, sertraline or racemic tianeptine sodium, (S)-tianeptine sodium or (R)-tianeptine sodium and placed in holding cages for the appropriate pretreatment time prior to test. The time the mice spent immobile was assessed every minute. The total time spent immobile was summed over the 6-minute test period. Data were analyzed by analysis of variance (ANOVA) followed by Dunnett's post-hoc comparisons, where appropriate. An effect was considered significant if $p < 0.05$. Data were represented as mean and standard error to the mean (s.e.m).

[00255] Racemic tianeptine sodium (10 mg/kg and 30 mg/kg) and (R)-tianeptine sodium (30 mg/kg) significantly reduced time immobile compared to vehicle (Figures 17A-17D), however (S)-tianeptine sodium did not show efficacy on this measure at any concentration (Figures 17E and 17F). These results were surprising: racemic and (R)-tianeptine effective; (S)-tianeptine not effective. While there are some questions as to what anti-depressive mechanism the FST assesses (see, *e.g.*, Reardon S. Nature 2019, 571 (7766) 456-57), without wishing to be bound by theory, it may be that the rapid metabolism in mice of (S)-tianeptine, but not R-tianeptine, to (S)-MC5 or (R)-MC5, respectively, may explain the

results. (S)-MC5 has no activity as a MOR or PPAR agonist. By contrast, (R)-MC5 retains MOR agonist activity. Such rapid metabolism is believed to be specific to mice. For example, it is not observed in rat models.

5 **Example 11: Evaluation of Tianeptine (R)- and (S)- Enantiomers for Genotoxicity**

[00256] Racemic tianeptine and (R)-tianeptine (99.9% chiral purity) and (S)-tianeptine (99.9% chiral purity) were evaluated for the potential to induce micronuclei in TK6 cells during short (4-hour) and long (72-hour) incubations with or without an exogenous metabolic activation system using an *in vitro* micronuclease assay. The micronuclease assay evaluates
10 the ability of a test article to interfere with normal mitotic cell division

[00257] The test compounds (racemic tianeptine, (R)- tianeptine and (S)-tianeptine) were prepared in DMSO using serial dilutions to achieve the test concentrations. Target concentrations of the test compounds were determined by range finding-assay. DMSO (1%) was used as a vehicle control and positive controls used included mitomycin C (MMC, Sigma-Aldrich Inc.) for the 4-hour treatments without metabolic activation, vinblastine sulfate (VIN, Sigma-Aldrich Inc.) for the 27-hour treatments without metabolic activation and cyclophosphamide monohydrate (CP, Sigma-Aldrich Inc.) for the 4-hour treatments with
15 metabolic activation. TK6 cell cultures, a human lymphoblast cell line, were treated with the test compounds, positive control or vehicle control in the presence or absence of phenobarbital/5,6-benzoflavone-induced rat liver S9 microsomal fraction, the metabolic activation system. Cytotoxicity was assessed using cell count data obtained from Coulter counts and micronucleus evaluation was performed by flow cytometry using a FACSCanto II (or equivalent) with FACSDiva Software.

[00258] Racemic tianeptine was positive for inducing micronuclei in TK6 cells in the
25 27-hour treatment without metabolic activation and negative for inducing micronuclei in TK6 cells in the 4-hour treatments with and without metabolic activation. (R)-tianeptine was positive for inducing micronuclei in TK6 cells in the 4-hour and the 27-hour treatments without metabolic activation and negative for inducing micronuclei in TK6 cells in the 4-hour treatments with metabolic activation. By comparison, (S)-tianeptine was found to be negative
30 for inducing micronuclei in TK6 cells at all test conditions. See Tables 13-15. These data suggest that (S)-tianeptine is non-genotoxic as compared to racemic tianeptine and (R)-tianeptine.

Table 13. 4-hour Treatment without Metabolic Activation

Racemic Tianeptine			(R)-Tianeptine			(S)-Tianeptine		
Treatment (µg/mL)	Cytotox. (%)	Mean MN (%)	Treatment (µg/mL)	Cytotox. (%)	Mean MN (%)	Treatment (µg/mL)	Cytotox. (%)	Mean MN (%)
DMSO (1%)	0	0.82	DMSO (1%)	0	0.53	DMSO (1%)	0	0.59
MMC 0.0625	20	2.96*	MMC 0.0625	45	4.62*	MMC 0.0625	51	5.62*
MMC 0.125	37	6.82*	MMC 0.125	71	12.81*	MMC 0.125	73	14.21*
31.3	7	0.63	27	1	0.28	27	-7	0.5
62.5	6	0.70	55	2	0.44	55	-1	0.37
125	8	0.63	109	8	0.47	109	6	0.46
250	12	0.73	219	18	0.80	219	16	0.55
500	20	1.09	437	45	2.45*	437	42	0.87

DMSO = Dimethyl sulfoxide, MN = Micronucleated Cells, Cytotox. = Cytotoxicity, MMC = Mitomycin C, *= $z' \geq 0.6$

5 **Table 14. 27-hour Treatment without Metabolic Activation**

Racemic Tianeptine			(R)-Tianeptine			(S)-Tianeptine		
Treatment (µg/mL)	Cytotox. (%)	Mean MN (%)	Treatment (µg/mL)	Cytotox. (%)	Mean MN (%)	Treatment (µg/mL)	Cytotox. (%)	Mean MN (%)
DMSO (1%)	0	0.41	DMSO (1%)	0	0.18	DMSO (1%)	0	0.23
VIN 0.0025	31	4.97*	VIN 0.0025	54	0.75*	VIN 0.0025	55	3.81*
VIN 0.003	38	4.54*	VIN 0.003	52	0.83*	VIN 0.003	55	4.16*
31.3	6	0.45	13.7	0	0.29	175	-7	49
125	28	0.57	109	25	0.41	219	-1	59
160	37	0.80	140	33	0.61	262	6	64
250	46	1.48*	219	45	1.61*	312	16	69
300	53	2.42*	312	61	2.56*	376	42	76

DMSO = Dimethyl sulfoxide, MN = Micronucleated Cells, Cytotox. = Cytotoxicity, VIN = Vinblastine Sulfate, *= $z' \geq 0.6$

Table 15. 4-hour Treatment with Metabolic Activation

Racemic Tianeptine			(R)-Tianeptine			(S)-Tianeptine		
Treatment ($\mu\text{g/mL}$)	Cytotox. (%)	Mean MN (%)	Treatment ($\mu\text{g/mL}$)	Cytotox. (%)	Mean MN (%)	Treatment ($\mu\text{g/mL}$)	Cytotox. (%)	Mean MN (%)
DMSO (1%)	0	0.72	DMSO (1%)	0	0.70	DMSO (1%)	0	0.23
CP 4.7	28	6.09*	CP 4.7	44	2.86*	CP 4.7	55	3.81*
CP 11.9	45	12.02*	CP 11.9	77	41.95*	CP 11.9	55	4.16*
31.3	3	0.67	27	-3	0.30	27	-9	0.49
62.5	1	0.78	55	0	0.38	55	-4	0.69
125	4	0.84	109	9	0.74	109	-3	0.65
250	8	0.81	219	15	0.57	219	11	0.60
500	12	1.31	437	39	1.80	437	37	0.89

DMSO = Dimethyl sulfoxide, MN = Micronucleated Cells, Cytotox. = Cytotoxicity, CP = Cyclophosphamide Monohydrate, *= $z' \geq 0.6$

5 Example 12: Synthesis of Racemic N-nitroso-tianeptine

General Methods

[00259] Reagent grade chemicals and anhydrous solvents were purchased from commercial sources and, unless otherwise mentioned, were used without further purification. Silica gel chromatography was performed on Teledyne Isco instruments using pre-packaged disposable SiO₂ stationary phase columns with eluent flow-rate ranges of 15 to 200 mL/min, UV detection (254 and 280 nm). Reverse phase purification was carried out using C18 columns, UV detection (214 and 254 nm).

[00260] The analytical QA/QC chromatograms were performed using a Waters Acquity UPLC instrument with DAD detector (200 nm to 320 nm) and a thermostatted column compartment. The mass spectra were recorded with a Waters SQD detector with the desolvation temperature set to 450 °C, the source temperature set to 150 °C, and the desolvation gas flow set to 1000 L/h. The mass spectrometer was equipped with an electrospray ion source (ESI) operated in a positive, or negative, ion mode and was set to scan between m/z 100-2000 with a scan time of 0.2 s.

[00261] Products were analyzed by ultra-performance liquid chromatography-mass spectrometry (UPLC/MS) using an Acquity UPLC Premier BEH C18 VanGuard FIT (1.7 μM , 2.1 x 50 mm) column heated to 35 °C, a flow rate of 0.700 mL/min, consisting of

MeCN, H₂O, and 10 mM aq. NH₄HCO₂ adjusted to pH 7.4 (80:18:2) for 10 min ((XCB/XCM/XCW)_ACN_AmForm_QC_10min_V2). The percentage of MeCN increased from 5% to 100% from 0.00-9.00 min and was maintained at 100% from 9.00-10.00 min.

[00262] The ¹H NMR spectra were recorded on a Varian Mercury 300 MHz/54 mm instrument, a Varian AS 400 MHz/54 mm instrument, and a Bruker UltraShield 500 MHz/54 mm instrument (BZH 43/500/70B, D221/54-3209). The chemical shifts were reported in parts-per-million and were referenced to solvent peaks, which in ¹H NMR appeared at 7.26 ppm for CDCl₃, 2.50 for DMSO-*d*₆, and 3.31 ppm for CD₃OD.

10 **Scheme 9: Exemplary Synthetic Scheme for Racemic N-nitroso-tianeptine**

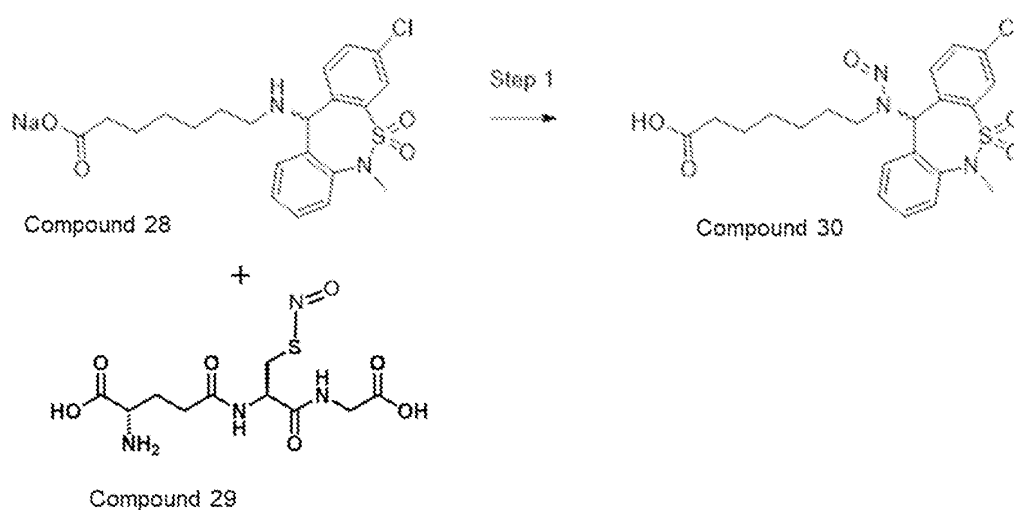
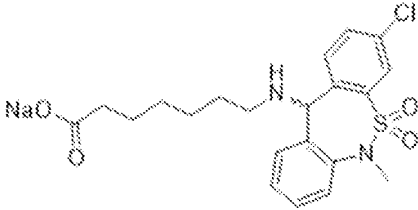
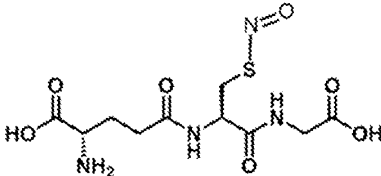
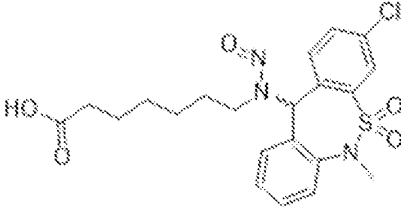


Table 16. Compounds of Scheme 9

Compound Number	Compound Structure and Name
28	 Racemic sodium;7-[[[(11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepine-11-yl]amino]heptanoate
29	 S-Nitrosoglutathione
30	 Racemic 7-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)(nitroso)amino)heptanoic acid

[00263] S-Nitrosoglutathione (compound 29, 116 mg, 0.345 mmol) was added to a mixture of racemic sodium 7-[[[(11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepine-11-yl]amino]heptanoate (compound 28, 158 mg, 0.345 mmol) in water (15.8 mL) at 23 °C. The mixture was stirred at 80 °C for 23 hours and concentrated. The residue was purified by preparative HPLC (Phenomenex Gemini NX Prep C18, 50x50mm AXIA) with water (0.1% HCOOH) and MeCN (5-100%) to provide racemic 7-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)(nitroso)amino)heptanoic acid (compound 30) as a solid (15.2 mg, 10%). ¹H NMR (400

MHz, DMSO- d_6) δ 11.82 (s, 1H), 7.95 – 7.85 (m, 1H), 7.80 (*dd*, $J = 8.4, 2.0$ Hz, 1H), 7.79 – 7.74 (m, 2H), 7.67 (*dd*, $J = 7.9, 1.3$ Hz, 1H), 7.60 (td, $J = 7.7, 1.6$ Hz, 1H), 7.50 (td, $J = 7.5, 1.4$ Hz, 1H), 6.71 (s, 1H), 3.63 (*ddd*, $J = 13.2, 9.9, 5.6$ Hz, 1H), 3.05 (s, 4H), 2.13 (t, $J = 7.3$ Hz, 2H), 1.37 (*q*, $J = 7.4$ Hz, 3H), 1.14 – 0.87 (*m*, 5H). m/z (ES+) $[M+Na]^+ = 488.1$ and 490.1; UPLC (XCB_AcN_AmForm_QC_10min_V2) $t_R = 4.33$ min.

Example 13: Crystalline Forms of Pharmaceutically Acceptable Salts of (S)-Tianeptine.

General Methods

[00264] Crystalline forms of pharmaceutically acceptable salts of (S)-tianeptine of this disclosure can be made by methods known in the art. The crystalline forms may then be characterized by methods known in the art, including but not limited to X-Ray powder diffraction (XRPD), Fourier Transform Infrared (FT-IR) spectra, Differential Scanning calorimetry (DSC), Thermogravimetric Analysis (TGA), and Nuclear Magnetic Resonance (NMR). It should be understood that operator, instrument and other related changes may result in some margin of error with respect to analytical characterization of the salts or crystalline forms.

X-Ray Powder Diffraction (XRPD)

[00265] X-ray powder diffraction patterns were obtained using a Rigaku MiniFlex600 X-ray Diffractometer. Diffractogram was acquired using the Miniflex Guidance application software. The measurement and instrument details are listed in Tables 17 and 18 below.

Table 17. X-Ray Powder Diffraction (XRPD): Measurement Details

Measurement type:	Single scan
Sample mode:	Reflection
<i>Scan</i>	
Scan axis:	Gonio
Scan range:	3.0010 – 40.000 ° (2 θ)
Step size:	0.0167 ° (2 θ)
Speed:	10 °/min (2 θ)
Scan mode:	Continuous
<i>Used wavelength</i>	
Intended wavelength type:	K α 1
K α 1:	1.540598 Å

K α 2:	1.544426 Å
K α 2/K α 1 intensity ratio:	0.50
K α :	1.541874 Å
K β (Å):	1.392250 Å

Table 18. X-Ray Powder Diffraction (XRPD): Instrument Details

<i>X-Ray Generator</i>	
Tube Output Voltage:	40 kV
Current:	15 mA
High-voltage generation method:	High-frequency Cockcroft-Walton method
Stability	Within $\pm 0.05\%$ for both the tube voltage and tube current, with reference to $\pm 10\%$ of input power variation
<i>X-Ray Tube</i>	
Name	Toshiba Analix type A-26L
Anode material:	Cu
Maximus Output:	0.60 kW
Focus Size:	1 x 10 mm
<i>Kβ Filter</i>	
Name	Ni-filter
Thickness	0.015 mm
Material	Ni
<i>Goniometer (Angle Measuring Device)</i>	
Type:	Vertical $\theta/2\theta$
Goniometer radius:	150 mm
Scanning Axis:	$\theta/2\theta$ linked
2 θ Scanning range:	+2° to +140°
$\theta/2\theta$ axis minimum step angle:	0.005 ° (2 θ)
Position Speed:	500 °/min (2 θ)
Scanning Speed:	0.01 to 100 °/min (2 θ)
Datum angle:	2 θ = 10 °
X-ray take-off angle	6 ° (fixed)
<i>Slit</i>	

DS:	1.25 °
IHS:	10 mm
SS	none (open)
RS:	none (open)
Incident side Soller Slit:	2.5 °
Receiving side Soller Slit:	2.5 °
Detector	
Name:	D/teX Ultra High-speed 1D Detector
Detection element:	1D semiconductor element
Window material:	Be
Effective window size:	13 mm (H) x 20 mm (W)
Dimensions:	80 mm(L)

[00266] The XRPD pattern of crystalline (S)-tianeptine are illustrated in Figure 18A and in Table 19.

Table 19. XRPD peaks list of (S)-Tianeptine hemi-oxalate

Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]	Backgr. [cts]
8.69	813.66	10.18	25.55	117.00
9.05	623.72	9.77	19.58	120.00
10.57	1140.71	8.37	35.82	137.00
11.37	171.06	7.78	5.37	147.00
12.62	981.45	7.02	30.82	157.00
13.01	3184.95	6.81	100.00	159.00
13.80	256.80	6.42	8.06	160.00
14.77	402.68	6.00	12.64	157.00
16.28	42.00	5.44	1.32	157.00
16.51	69.68	5.37	2.19	160.00
17.00	134.27	5.22	4.22	165.00
17.31	183.37	5.12	5.76	167.95
17.67	96.80	5.02	3.04	171.00
18.11	837.93	4.90	26.31	174.00
19.00	91.73	4.67	2.88	182.00
19.50	685.14	4.55	21.51	188.00
20.22	330.90	4.39	10.39	195.00
20.43	828.49	4.35	26.01	196.00
21.09	1213.12	4.21	38.09	199.00
22.11	219.15	4.02	6.88	211.00
22.30	203.29	3.99	6.38	217.00
22.92	795.35	3.88	24.97	231.00
23.71	1672.33	3.75	52.51	241.00
24.23	451.40	3.67	14.17	242.00
24.56	414.20	3.62	13.00	241.84
25.07	323.03	3.55	10.14	238.00

26.14	769.97	3.41	24.18	228.00
26.54	115.90	3.36	3.64	224.00
27.12	505.55	3.29	15.87	217.00
27.75	209.18	3.22	6.57	208.00
29.21	141.26	3.06	4.44	183.00
29.51	158.33	3.03	4.97	177.00
29.73	297.46	3.01	9.34	172.39
30.47	69.36	2.93	2.18	163.00
30.81	72.80	2.90	2.29	163.00
31.44	56.46	2.85	1.77	163.00
31.98	147.63	2.80	4.64	162.00
32.36	99.54	2.77	3.13	160.00
32.95	108.51	2.72	3.41	157.00
33.35	71.74	2.69	2.25	155.00
34.02	56.69	2.64	1.78	150.00
34.38	56.51	2.61	1.77	147.00
35.13	140.35	2.55	4.41	146.00
35.60	72.46	2.52	2.28	147.00
36.12	69.00	2.49	2.17	148.00
36.63	197.79	2.45	6.21	147.00
37.04	92.00	2.43	2.89	147.00
38.15	49.00	2.36	1.54	145.00
38.63	87.65	2.33	2.75	147.00
39.76	76.00	2.27	2.39	164.00

[00267] The XRPD pattern of crystalline (S)-tianeptine hemi-oxalate salt are illustrated in Figure 18B and in Table 20.

Table 20. XRPD peaks list of (S)-Tianeptine sodium

Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]	Backgr. [cts]
5.17	20.00	17.09	1.72	109.00
7.29	159.80	12.12	13.75	111.00
8.53	1082.35	10.36	93.16	121.00
9.97	89.20	8.87	7.68	132.00
10.25	352.08	8.63	30.30	134.00
10.92	101.38	8.10	8.73	138.00
11.21	118.82	7.89	10.23	140.00
11.48	170.20	7.71	14.65	142.00
12.05	684.19	7.34	58.89	146.00
13.33	606.66	6.64	52.21	155.00
13.65	257.52	6.49	22.17	158.00
13.90	149.16	6.37	12.84	160.00
14.55	96.00	6.09	8.26	166.00
15.38	105.70	5.76	9.10	173.00
16.10	453.23	5.51	39.01	180.00
16.85	92.02	5.26	7.92	190.00
17.05	68.00	5.20	5.85	192.00
17.82	111.18	4.98	9.57	202.00
18.56	233.98	4.78	20.14	213.00
18.87	457.32	4.70	39.36	218.00

19.09	691.76	4.65	59.54	221.00
19.93	485.71	4.46	41.81	232.00
20.56	834.71	4.32	71.84	239.00
21.04	997.37	4.22	85.84	242.00
21.63	256.15	4.11	22.05	244.00
21.89	491.09	4.06	42.27	245.00
22.36	659.81	3.98	56.79	244.00
22.99	203.40	3.87	17.51	242.00
23.27	156.40	3.82	13.46	241.00
23.59	109.50	3.77	9.42	238.00
24.20	1161.85	3.68	100.00	233.00
25.68	200.98	3.47	17.30	218.00
26.84	120.32	3.32	10.36	208.00
27.30	118.80	3.27	10.23	205.00
27.47	127.60	3.25	10.98	204.00
27.67	126.00	3.22	10.84	203.00
27.94	85.11	3.19	7.33	201.00
28.40	50.00	3.14	4.30	198.00
28.78	237.18	3.10	20.41	195.00
29.29	100.30	3.05	8.63	191.00
29.66	101.07	3.01	8.70	188.00
30.47	118.89	2.93	10.23	181.70
31.01	101.26	2.88	8.72	177.00
31.67	64.82	2.83	5.58	174.00
31.97	61.00	2.80	5.25	174.00
32.30	89.38	2.77	7.69	173.00
33.09	57.02	2.71	4.91	172.00
34.08	97.16	2.63	8.36	171.00
35.57	73.47	2.52	6.32	166.00
36.11	45.68	2.49	3.93	165.00
38.61	75.44	2.33	6.49	162.00

[00268] (S)-tianeptine sodium salt also forms an amorphous salt (Form B) depicted in Figure 18C. A comparison of the XRPDs of crystalline (S)-tianeptine, crystalline (S)-tianeptine hemi-oxalate, (S)-tianeptine sodium and crystalline racemic tianeptine hemi-oxalate is depicted in Figure 18D.

Example 14: Synthesis of Aryl Substituted Tianeptine Derivatives

General Methods

[00269] Reagent grade chemicals and anhydrous solvents were purchased from commercial sources and, unless otherwise mentioned, were used without further purification. The names of the products were determined using the naming software included in Biovia Draw version 18.1 or ChemDraw Professional version 20.1.1.125. Silica gel chromatography was performed on Teledyne Isco instruments using pre-packaged disposable SiO₂ stationary phase columns with eluent flow-rate ranges of 15 to 200 mL/min, UV detection (254 and 280

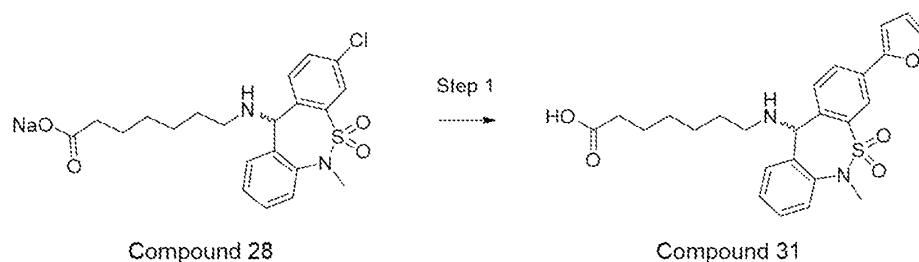
nm). Reverse phase purification was carried out using C18 columns, UV detection (214 and 254 nm).

[00270] The analytical QA/QC chromatograms were performed using a Waters Acquity UPLC instrument with DAD detector (200 nm to 320 nm) and a thermostatted column compartment. The mass spectra were recorded with a Waters SQD detector with the desolvation temperature set to 450 °C, the source temperature set to 150 °C, and the desolvation gas flow set to 1000 L/h. The mass spectrometer was equipped with an electrospray ion source (ESI) operated in a positive, or negative, ion mode and was set to scan between m/z 100-2000 with a scan time of 0.2 s. Products were analyzed by UPLC/MS using one of the following methods:

1. **XCB_4min_normal_A1B1_ELS_EVO**: a 4.00 min method which used a Kinetex EVO C18 100 A (2.6 µM, 3.0 x 50mm) column heated to 40°C, a flow rate of 1.200 mL/min, a buffer consisting of 0.1% TFA in H₂O, and 0.1% TFA in MeCN as the organic solvent. The percentage MeCN increases from 5% to 35% from 0.00-1.00 min and from 35% to 95% from 1.00-2.70 min and then kept stable at 95% from 2.70-3.55 min;
2. **XCB_4min_medium_A2B2_EVO**: a 4.00 min method which used a Kinetex EVO C18 100 A (2.6 µM, 3.0 x 50mm) column heated to 40°C, a flow rate of 1.200 mL/min, a buffer consisting of 10 mM NH₄HCO₂ in H₂O adjusted to pH 7.4 with NH₄OH, and 180 mL H₂O 800 mL MeCN and 20 mL NH₄HCO₂ buffer pH 7.4 as the organic solvent. The percentage of organic solvent increases from 30% to 70% from 0.00-1.00 min and from 70% to 90% from 1.00-3.00 min and then kept stable at 90% from 3.00-3.55 min; or
3. **(XCB/XCM/XCW)_ACN_TFA_QC_10min_V1**: a 10.00 min method which used an Acquity UPLC BEH C18 (1.7 µM, 2.1 x 50 mm) column heated to 35 °C, a flow rate of 0.700 mL/min, a buffer consisting of 0.1% aq TFA and MeCN. The percentage of MeCN increases from 5% to 100% from 0.00-9.00 min and is maintained at 100% from 9.00-10.00 min.

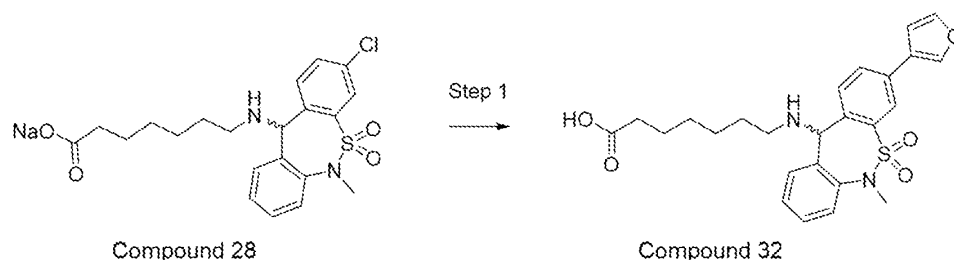
[00271] The ¹H NMR spectra were recorded on a Varian Mercury 300 MHz/54 mm instrument, a Varian AS 400 MHz/54 mm instrument, and a Bruker UltraShield 500 MHz/54 mm instrument (BZH 43/500/70B, D221/54-3209). The chemical shifts were reported in parts-per-million and were referenced to solvent peaks, which in ¹H NMR appeared at 7.26 ppm for CDCl₃, 2.50 for DMSO-*d*₆, and 3.31 ppm for CD₃OD.

Scheme 10: Exemplary Synthetic Scheme for 7-((3-(furan-2-yl)-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid



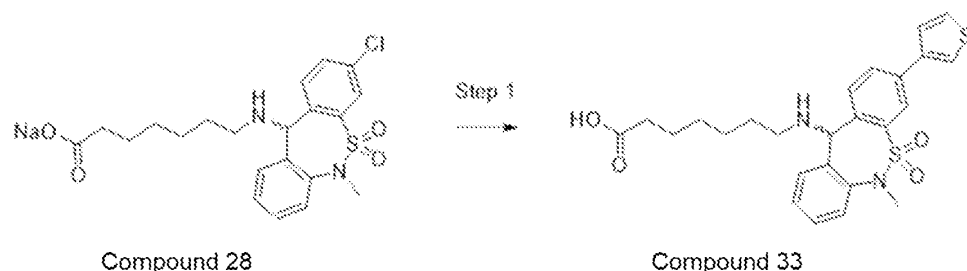
- 5 [00272] Racemic sodium;7-[[[(11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2] benzothiazepine-11-yl]amino]heptanoate (compound 28, 500 mg, 1.09 mmol) was added to a mixture of 2-furanboronic acid (183 mg, 1.63 mmol), PEPPSI™-IPr (74.0 mg, 0.109 mmol) and Cs₂CO₃ (710 mg, 2.18 mmol) in a 10:1 mixture of 1,4-dioxane and water (20.0 mL) at rt under argon. The mixture was stirred at 90 °C for 16 h, and concentrated. The residue was
- 10 diluted with THF (10.0 mL) and filtered through Celite, washing with THF (4.00 mL), and the filtrate was concentrated. The residue was purified by reverse phase chromatography (C18, 50 g cartridge) with water [10 mM (NH₄)(HCO₃)] and MeCN (5-100%) and by preparative HPLC (Phenomenex Gemini 5um NX-Prep C18 50x50mm AXIA) with water [10 mM (NH₄)(HCO₃)] and MeCN (20-100%) to provide 7-((3-(furan-2-yl)-6-methyl-5,5-
- 15 dioxido-6,11-dihydrodibenzo[c,f][1,2] thiazepin-11-yl)amino)heptanoic acid (compound 31) as a solid (116 mg, 23%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.04 (d, *J* = 1.9 Hz, 1H), 7.93 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.81 (d, *J* = 1.8 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.50 (dt, *J* = 7.5, 2.1 Hz, 2H), 7.37 (dtd, *J* = 19.5, 7.4, 1.6 Hz, 2H), 7.14 (d, *J* = 3.4 Hz, 1H), 6.63 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.18 (s, 1H), 3.37 (s, 3H), 2.41 (t, *J* = 7.1 Hz, 2H), 2.15 (t, *J* = 7.3 Hz, 2H), 1.45
- 20 (h, *J* = 7.1 Hz, 4H), 1.23 (dd, *J* = 8.3, 4.5 Hz, 4H), two protons not observed; *m/z* (ES⁺) [M+H]⁺ = 469.2; UPLC (XCB_AcN_TFA_QC_10min_V1) *t*_R = 3.71 min.)

Scheme 11: Exemplary Synthetic Scheme for 7-((3-(furan-3-yl)-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid



- [00273] Racemic sodium;7-[[[(11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepine-11-yl]amino]heptanoate (compound 28, 500 mg, 1.09 mmol) was added to a mixture of 3-furanboronic acid (122 mg, 1.09 mmol), PEPPSI™-IPr (74.0 mg, 0.109 mmol) and Cs₂CO₃ (710 mg, 2.18 mmol) in a 10:1 mixture of 1,4-dioxane and water (20.0 mL) at rt under argon. The mixture was stirred at 90 °C for 16 h, and concentrated. The residue was diluted with THF (10.0 mL) and filtered through Celite, washing with THF (10.0 mL), and the filtrate was concentrated. The residue was purified by reverse phase chromatography (C18, 50 g cartridge) with water [10 mM (NH₄)(HCO₃)] and MeCN (5-100%), by preparative HPLC (Phenomenex Gemini 5um NX-Prep C18 50x50mm AXIA) with water [0.1% TFA] and MeCN (0-95%), and by reverse phase chromatography (C18, 50 g cartridge) with water [10 mM (NH₄)(HCO₃)] and MeCN (5-100%) to provide 7-((3-(furan-3-yl)-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid (compound 32) as a solid (61.0 mg, 12%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.35 (t, *J* = 1.2 Hz, 1H), 7.96 (d, *J* = 1.9 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.77 (t, *J* = 1.7 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.49 (ddd, *J* = 7.5, 3.2, 1.6 Hz, 2H), 7.37 (dtd, *J* = 19.6, 7.4, 1.6 Hz, 2H), 7.04 (dd, *J* = 1.9, 0.9 Hz, 1H), 5.17 (s, 1H), 3.36 (s, 3H), 2.41 (t, *J* = 7.1 Hz, 2H), 2.16 (t, *J* = 7.4 Hz, 2H), 1.45 (h, *J* = 7.2 Hz, 4H), 1.23 (dd, *J* = 7.9, 4.3 Hz, 4H), two protons not observed; *m/z* (ES⁺) [M+H]⁺ = 469.2; UPLC (XCB_AcN_TFA_QC_10min_V1) *t*_R = 3.62 min.

Scheme 12: Exemplary Synthetic Scheme for 7-((6-methyl-5,5-dioxido-3-(thiophen-3-yl)-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid



5 [00274] Racemic sodium;7-[[[(11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepine-11-yl]amino]heptanoate (compound 28, 500 mg, 1.09 mmol) was added to a mixture of thiophene-3-boronic acid (139 mg, 1.09 mmol), PEPPSI™-IPr (74.0 mg, 0.109 mmol) and Cs₂CO₃ (710 mg, 2.18 mmol) in a 10:1 mixture of 1,4-dioxane and water (20.0 mL) at rt under argon. The mixture was stirred at 90 °C for 16 h, and concentrated. The residue was diluted with THF (10.0 mL) and filtered through Celite, washing with THF (4.00 mL), and the filtrate was concentrated. The residue was purified by reverse phase chromatography (C18, 50 g cartridge) with water [10 mM (NH₄)(HCO₃)] and MeCN (5-100%) to provide 7-((6-methyl-5,5-dioxido-3-(thiophen-3-yl)-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid (compound 33) as a solid (187 mg, 35%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.04 (dd, *J* = 2.9, 1.5 Hz, 2H), 7.96 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.73 – 7.64 (m, 2H), 7.60 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.50 (dd, *J* = 7.7, 1.6 Hz, 2H), 7.37 (dtd, *J* = 19.3, 7.4, 1.6 Hz, 2H), 5.19 (s, 1H), 3.36 (s, 3H), 2.54 (s, 1H), 2.42 (t, *J* = 7.1 Hz, 2H), 2.14 (t, *J* = 7.4 Hz, 2H), 1.51 – 1.38 (m, 4H), 1.23 (dq, *J* = 10.8, 5.7 Hz, 4H), one proton not observed; *m/z* (ES⁺) [M+H]⁺ = 485.2; UPLC (XCB_AcN_TFA_QC_10min_V1) *t*_R = 3.91 min.

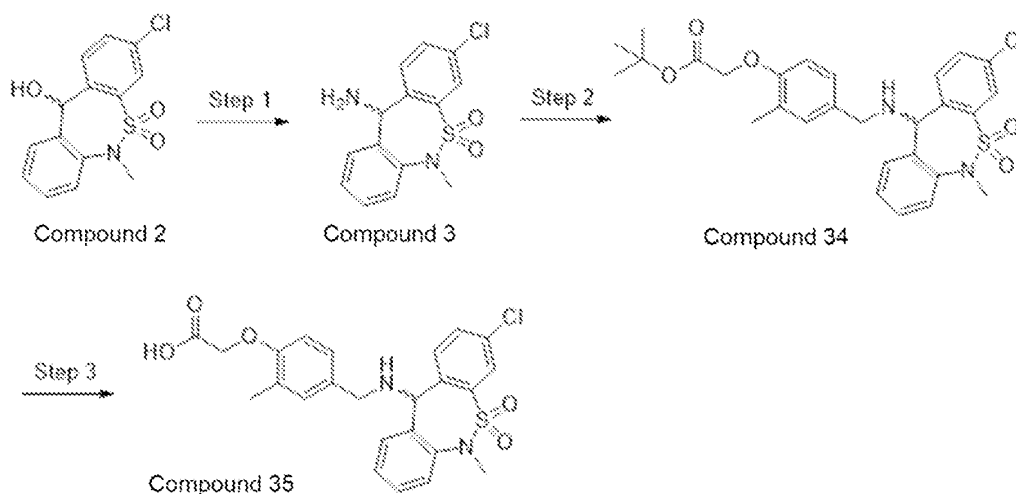
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Scheme 13: Exemplary Synthetic Scheme for 2-(4-(((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)methyl)-2-methylphenoxy)acetic acid

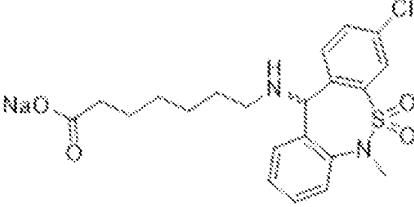
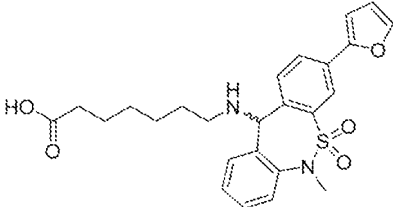
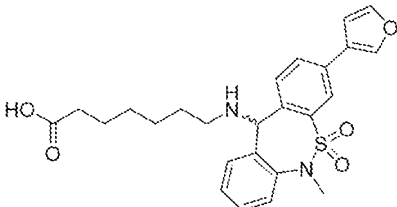
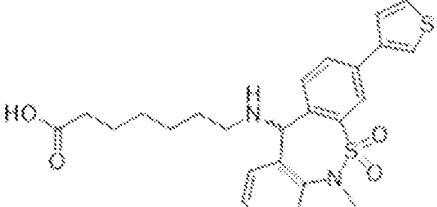


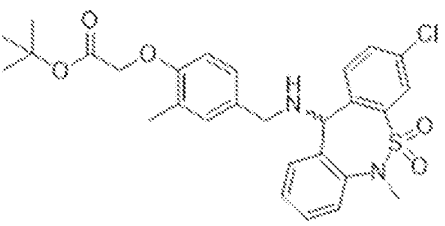
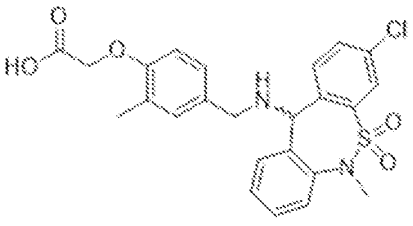
- 5 [00275] In step 1, 3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-ol (compound 2) was added to a mixture of oxalyl chloride (1.40 mL, 16.1 mmol) and DMF (12.5 μ L, 0.161 mmol) in DCM (10.0 mL) at rt. The mixture was stirred at 23 $^{\circ}$ C for 1 h, and concentrated. The residue was diluted with toluene (20.0 mL) and concentrated twice. The residue was diluted with THF (20.0 mL) and stirred at 60 $^{\circ}$ C in an autoclave under ammonia
- 10 (2 bars) for 16 h. The mixture was concentrated, and diluted with DCM (50.0 mL), water (50.0 mL) and sat. aq. NaHCO_3 (20.0 mL). The mixture was filtered through Celite, washing with DCM (20.0 mL). The aqueous phase of the filtrate was extracted with DCM (2 x 30.0 mL) and the combined organic extracts were concentrated. The residue was purified by silica gel chromatography (120 g cartridge) using a gradient of MeOH in DCM (0-20%) to provide
- 15 3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-amine (compound 3) as a solid (401 mg, 40%). m/z (ES^+) $[\text{M}-\text{NH}_2]^+ = 292.0$; UPLC (4min_normal_A1B1_ELS_EVO) $t_R = 1.41$ min.

- [00276] Synthesis of tert-butyl 2-(4-formyl-2-methylphenoxy)acetate: 4-Hydroxy-3-methylbenzaldehyde (300 mg, 2.20 mmol) was added to tert-butyl bromoacetate (390 μ L, 2.64 mmol) in MeCN (17.2 mL) at rt under argon. The mixture was stirred at 80 $^{\circ}$ C for 3 h. The mixture was filtered through Celite, washing with MeCN (50.0 mL), and the filtrate was concentrated to provide tert-butyl 2-(4-formyl-2-methylphenoxy)acetate as a solid (542 mg, 98%). m/z (ES^+) $[\text{M}]^+ = 250.0$; GCMS (23min_normal_HP5MS.amx) $t_R = 13.42$ min.
- 20

- [00277] In step 2, 3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-amine (compound 3) was added to tert-butyl 2-(4-formyl-2-methylphenoxy)acetate (324 mg, 1.30 mmol), NaBH₃CN (40.7 mg, 0.648 mmol) and AcOH (37.0 μ L, 0.648 mmol) in MeOH (2.57 mL) at rt. The mixture was stirred at 65 °C for 16 h, and cooled to 23 °C. The pH of the mixture was adjusted to 2 with 12 M aq. HCl, then to 12 with 50% aq. NaOH. The mixture was concentrated, and the residue was diluted with water (10.0 mL) and DCM (10.0 mL). The aqueous phase was extracted with DCM (2 x 10.0 mL), and the combined organic extracts were washed with brine (20.0 mL) and concentrated. The residue was purified by silica gel chromatography (12 g cartridge) using a gradient of EtOAc in hexanes (0-100%) to provide racemic tert-butyl 2-[4-[[[(3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl)amino]methyl]-2-methyl-phenoxy] acetate (compound 34) as a solid (326 mg, 93%). m/z (ES+) [M+H]⁺ = 543.2; UPLC (4min_medium_A2B2_EVO) tR = 3.04 min.
- [00278] In step 3, TFA (2.20 mL, 29.1 mmol) was added to tert-butyl 2-[4-[[[(3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepin-11-yl)amino]methyl]-2-methyl-phenoxy] acetate (compound 34, 316 mg, 582 μ mol) in DCM (5.57 mL) at rt. The mixture was stirred at rt for 16 h and concentrated. The residue was purified by reverse phase chromatography (C18, 13 g cartridge) with water [10 mM (NH₄)(HCO₃)] and MeCN (0-50%), and by reverse phase chromatography (C18, 13 g cartridge) with water [10 mM (NH₄)(HCO₃)] and MeCN (0-20%) to provide 2-(4-(((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)methyl)-2-methylphenoxy)acetic acid (compound 35) as a solid (70.0 mg, 25%). ¹H NMR (400 MHz, DMSO-d₆) δ 7.77 (d, J = 2.1 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.54 – 7.47 (m, 2H), 7.45 – 7.35 (m, 2H), 7.03 (s, 1H), 6.98 (d, J = 9.0 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.19 (s, 1H), 4.47 (s, 2H), 3.59 – 3.49 (m, 2H), 3.31 (s, 3H), 2.14 (s, 3H), two protons not observed; m/z (ES+) [M+H]⁺ = 487.1; HPLC (XCB_AcN_TFA_QC_10min_V1) tR = 3.55 min.

Table 16. Compounds of Schemes 10-13

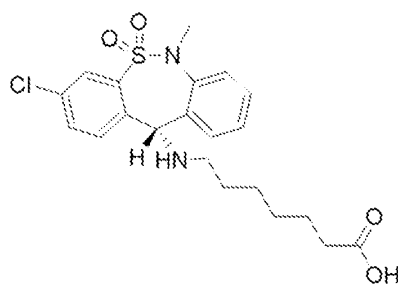
Compound Number	Compound Structure and Name
28	 Racemic sodium;7-[[[(11R)-3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][1,2]benzothiazepine-11-yl]amino]heptanoate
31	 7-((3-(furan-2-yl)-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid
32	 7-((3-(furan-3-yl)-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid
33	 7-((6-methyl-5,5-dioxido-3-(thiophen-3-yl)-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid

34	 tert-butyl 2-[4-[[[(3-chloro-6-methyl-5,5-dioxo-1H-benzo[c][1,2]benzothiazepin-11-yl)amino]methyl]-2-methyl-phenoxy] acetate
35	 2-(4-(((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)methyl)-2-methylphenoxy)acetic acid

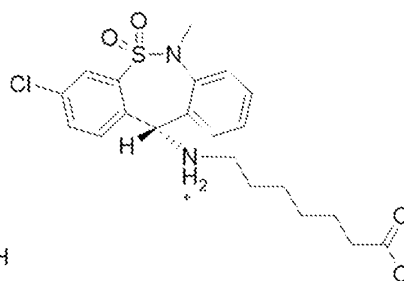
CLAIMS

What is claimed is:

1. The (S)-enantiomer of 7-(3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-ylamino)heptanoic acid ((S)-enantiomer of tianeptine) of the general Formula (Ia), the zwitterion thereof of Formula (Ib) or a pharmaceutically acceptable salt of the (S)-enantiomer, or a mixture of two or more of these species, wherein the (S)-enantiomer, zwitterion or pharmaceutically acceptable salt are characterized by comprising $\leq$ about 2% of the (R)-enantiomer of tianeptine, the zwitterion thereof or a pharmaceutically acceptable salt of the (R)-enantiomer:



Formula (Ia)

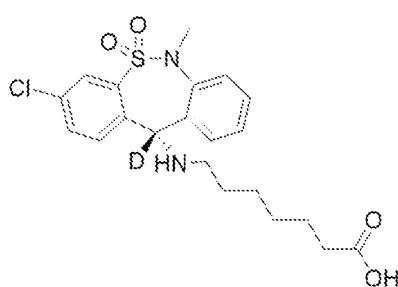


Formula (Ib).

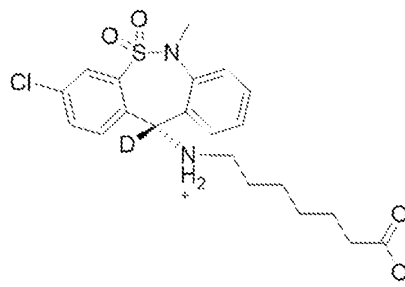
2. The (S)-enantiomer according to claim 1, wherein the (S)-enantiomer, the zwitterion or pharmaceutically acceptable salt of the (S)-enantiomer are characterized by comprising $\leq$ about 0.1% of the (R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer.
3. A pharmaceutically acceptable salt of the (S)-enantiomer according to claim 1 or 2, wherein the pharmaceutically acceptable salt is (S)-tianeptine benzenesulfonate (1:1), (S)-tianeptine fumarate (1:1), (S)-tianeptine fumarate (2:1), (S)-tianeptine hippurate (1:1), (S)-tianeptine maleate (1:1), (S)-tianeptine maleate (2:1), (S)-tianeptine p-toluenesulfonate (1:1), (S)-tianeptine orotate (1:1), (S)-tianeptine camphorsulfonate (1:1), (S)-tianeptine N-acetyl-L-tyrosinate (1:1), (S)-tianeptine polisterix, (S)-tianeptine: L-DBTA (2:1), (S)-tianeptine sodium, (S)-tianeptine oxalate or (S)-tianeptine hemi-oxalate (2:1).

4. The pharmaceutically acceptable salt of the (S)-enantiomer according to claim 3, wherein the pharmaceutically acceptable salt is (S)-tianeptine hemi-oxalate (2:1).
5. A zwitterion comprising the zwitterion of the (S)-enantiomer according to claim 1 or 2.
6. A co-crystal of the (S)-enantiomer according to claim 1 or 2, wherein the (S)-enantiomer or the zwitterion thereof forms a complex with L-tyrosine, L-tryptophan, L-phenylalanine, or another L-amino acid.
7. An ester of the (S)-enantiomer according to claim 1 or 2, wherein the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof.
8. The ester of the (S)-enantiomer according to claim 7, wherein the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof.
9. An amide of the (S)-enantiomer according to claim 1 or 2, wherein the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof.
10. The amide of the (S)-enantiomer according to claim 9, wherein the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof.
11. The (S)-enantiomer of deuterated 7-((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl-11-d)amino)heptanoic acid (11-D-(S)-enantiomer of tianeptine) of the general Formula (IIa) or the zwitterion thereof of

Formula (IIb) or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, or a mixture of two or more of these species, wherein deuterium replaces hydrogen at the 11- position, and wherein the 11-D-(S)-enantiomer or zwitterion or pharmaceutically acceptable salt thereof are characterized by comprising $\leq$ about 2% of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of the 11-D-(R)-enantiomer:



Formula (IIa)



Formula (IIb).

12. The (S)-enantiomer according to claim 11, wherein the 11-D-(S)-enantiomer, the zwitterion or pharmaceutically acceptable salt of the 11-D-(S)-enantiomer are characterized by comprising $\leq$ about 0.1% of the 11-D-(R)-enantiomer of tianeptine or the zwitterion thereof or a pharmaceutically acceptable salt of that enantiomer.
13. The (S)-enantiomer according to claim 11 or 12, wherein the 11-D-(S)-enantiomer or the zwitterion or pharmaceutically acceptable salt of the 11-D-(S)-enantiomer is characterized by reduced racemization at position 11 as compared to the (S)-enantiomer of tianeptine or the zwitterion or a pharmaceutically acceptable salt of that enantiomer.
14. A pharmaceutically acceptable salt of the 11-D-(S)-enantiomer according to any one of claims 11-13, wherein the pharmaceutically acceptable salt is 11-D-(S)-tianeptine benzenesulfonate (1:1), 11-D-(S)-tianeptine fumarate (1:1), 11-D-(S)-tianeptine fumarate (2:1), 11-D-(S)-tianeptine hippurate (1:1), 11-D-(S)-tianeptine maleate (1:1), 11-D-(S)-tianeptine maleate (2:1), 11-D-(S)-tianeptine p-toluenesulfonate (1:1), 11-D-(S)-tianeptine orotate (1:1), 11-D-(S)-tianeptine camphorsulfonate (1:1), 11-D-(S)-tianeptine N-acetyl-L-tyrosinate (1:1), 11-D-(S)-tianeptine polisterix, 11-D-

- (S)-tianeptine: L-DBTA (2:1), 11-D-(S)-tianeptine sodium, 11-D-(S)-tianeptine oxalate or 11-D-(S)-tianeptine hemi-oxalate (2:1).
15. The pharmaceutically acceptable salt of the 11-D-(S)-enantiomer according to claim 14, wherein the pharmaceutically acceptable salt is 11-D-(S)-tianeptine hemi-oxalate (2:1).
 16. A zwitterion comprising the zwitterion of the 11-D-(S)-enantiomer according to any one of claims 11-13.
 17. A co-crystal of the 11-D-(S)-enantiomer according to any one of claims 11-13, wherein the 11-D-(S)-enantiomer or the zwitterion thereof forms a complex with L-tyrosine, L-tryptophan, L-phenylalanine, or another L-amino acid.
 18. An ester of the (S)-enantiomer according to any one of claims 11-13, wherein the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.
 19. The ester of the (S)-enantiomer according to claim 18, wherein the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the ester of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.
 20. An amide of the (S)-enantiomer according to any one of claims 11-13, wherein the amide of the 11-D-(S)-enantiomer or the pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 2% of the amide of the 11-D-(R)-enantiomer or the pharmaceutically acceptable salt thereof.
 21. The amide of the (S)-enantiomer according to claim 20, wherein the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof is characterized by comprising $\leq$ about 0.1% of the amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.

22. A pharmaceutically acceptable acid salt of the (S)-enantiomer or the 11-D-(S)-enantiomer according to any one of claims 1, 2 or 11-13, wherein the nitrogen atom in the sidechain attached to Carbon-11 (C-11) is 100% protonated, the 100% protonated salt being less sensitive to air oxidation in solid or solution forms when compared to the (S)-enantiomer, 11-D-(S)-enantiomer, the zwitterion of either or the sodium salts of either.
23. A pharmaceutical composition comprising the (S)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or zwitterion thereof according to any one of claims 1-6, or an ester of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to claim 7 or 8, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to claim 9 or 10 and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises $\leq$ about 2% of the (R)-enantiomer of tianeptine, the zwitterion thereof or a pharmaceutically acceptable salt of the (R)-enantiomer, or a co-crystal of the (R)-enantiomer or zwitterion thereof, or the ester of the (R)-enantiomer or a pharmaceutically acceptable salt thereof, or the amide of the (R)-enantiomer or a pharmaceutically acceptable salt thereof.
24. The pharmaceutical composition of claim 23, wherein the pharmaceutical composition comprises $\leq$ about 0.1% of the (R)-enantiomer of tianeptine, the zwitterion thereof or pharmaceutically acceptable salt of the (R)-enantiomer, or co-crystal of the (R)-enantiomer or zwitterion thereof, or the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (R)-enantiomer or pharmaceutically acceptable salt thereof.
25. A pharmaceutical composition comprising the 11-D-(S)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, or a co-crystal of the 11-D-(S)-enantiomer or zwitterion thereof according to any one of claims 11-17, or an ester of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt thereof according to claim 18 or 19, or an amide of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt thereof according to claim 20 or 21 and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises $\leq$ about 2% of the 11-D-(R)-enantiomer of tianeptine, the

- zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(R)-enantiomer, or a co-crystal of the 11-D-(R)-enantiomer or zwitterion thereof, or an ester of the 11-D-(R)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the 11-D-(R)-enantiomer or a pharmaceutically acceptable salt thereof.
26. The pharmaceutical composition according to claim 25, wherein the pharmaceutical composition comprises $\leq$ about 0.1% of the 11-D-(R)-enantiomer of tianeptine, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(R)-enantiomer, or co-crystal of the 11-D-(R)-enantiomer or zwitterion thereof, or the ester of the (R)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the 11-D-(R)-enantiomer or pharmaceutically acceptable salt thereof.
27. The pharmaceutical composition according to any one of claims 23-26, wherein the composition is in the form of a tablet, a thin film, a powder, a caplet, a capsule, a soft gel, a suppository, a nasal spray, an oral spray or a lung spray.
28. The pharmaceutical composition according to any one of claims 23-26, wherein the composition is formulated for immediate release, controlled release, sustained release, extended release, or slow release of the (S)-enantiomer or the 11-D-(S)-enantiomer, or the zwitterion or an ester or an amide of either, or a pharmaceutically acceptable salt of either, or a co-crystal of the (S)-enantiomer or the 11-D-(S)-enantiomer or the zwitterion of either.
29. A pharmaceutical composition comprising a mixture of two or more pharmaceutically acceptable salts or co-crystals of the (S)-enantiomer or the 11-D-(S)-enantiomer according to any one of claims 23-26, wherein the mixture is characterized by an enhanced extended release when administered orally as compared to administering a composition comprising a single pharmaceutically acceptable salt or co-crystal of the (S)-enantiomer or the 11-D-(S)-enantiomer according to any one of claims 23-26.
30. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, comprising administering to a subject in need or at risk thereof a therapeutically

effective amount of the (S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of claims 1-10 and 22, or a pharmaceutical composition according to any one of claims 23, 24 and 27-29.

31. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 11-22, or a pharmaceutical composition according to any one of claims 25-29.
32. The method according to claim 30 or 31, wherein the disease, disorder or condition is selected from the group consisting of a central nervous system (CNS) disorder, inflammatory disease, autoimmune disease, infectious illness, a hearing loss condition, ocular disease, musculoskeletal disease, metabolic disease, mitochondrial disease, hypertriglyceridemia, cancer, menopause and chronic overlapping pain conditions (COPCs), and psychological, physical, metabolic or hormonal stress and COPCs.
33. The method according to claim 32, wherein the CNS disorder is selected from the group consisting of a mood disorder, a trauma and stress-related disorder, an anxiety disorder, obsessive-compulsive disorder, a neurodegenerative or neuroinflammatory disorder, a neurodevelopmental disorder, a leukodystrophy and CNS oxidative stress.
34. The method according to claim 33, wherein the mood disorder is a depressive disorder, a bipolar disorder, or a substance-induced disorder.

35. The method according to claim 34, wherein the depressive disorder is major depressive disorder (MDD).
36. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, in a subject who has experienced high stress, comprising administering to the subject a therapeutically effective amount of the (S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of claims 1-10 and 22, or a pharmaceutical composition according to any one of claims 23, 24 or 27-29.
37. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, in a subject who has experienced high stress, comprising administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of claims 11-22, or a pharmaceutical composition according to any one of claims 25-29.
38. The method according to claim 36 or 37, wherein the stress is caused by adversity early in life or by childhood trauma.
39. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, while reducing μ -opioid receptor agonism associated with treatment with racemic tianeptine, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, the zwitterion thereof, or a

pharmaceutically acceptable salt of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of claims 1-10 and 22, or a pharmaceutical composition according to any one of claims 23, 24 and 27-29.

40. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, while reducing μ -opioid receptor agonism associated with treatment with racemic tianeptine, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or a pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or a pharmaceutically acceptable salt thereof according to any one of claims 11-22, or a pharmaceutical composition according to any one of claims 25-29.
41. The method according to any one of claims 30-40 or 59, wherein the (S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof or the 11-D-(S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, the co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof or the pharmaceutical composition is administered one or more times daily.
42. The method according to any one of claims 30-40 or 59, wherein the (S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof or the 11-D-(S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the

11-D-(S)-enantiomer, the co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition is administered parenterally, orally, sublingually, buccally, inhalationally, palatally, transdermally, rectally, or vaginally.

43. The method according to any one of claims 30-42 or 59, wherein the (S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof or the 11-D-(S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, the co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof or the pharmaceutical composition is administered sequentially or concurrently with one or more additional therapeutic agents selected from the group consisting of an antidepressant, an anticonvulsant, an anti-anxiety agent, an antipsychotic agent, a cholinesterase inhibitor, an N-methyl-D-aspartate (NMDA) receptor antagonist, a 5HT2 modulator, a corticosteroid, an anti-amyloid agent, an anti-tau agent and a chemotherapeutic agent.
44. The method according to any one of claims 30-42 or 59, wherein the (S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof or the 11-D-(S)-enantiomer, the zwitterion or ester thereof, the pharmaceutically acceptable salt of the 11-D-(S)-enantiomer, the co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or the ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof or the pharmaceutical composition is administered as part of a treatment regime also including psychotherapeutic intervention.

45. A method of reducing the potential racemization of the (S)-enantiomer, the zwitterion thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 1-10 and 22, comprising the step of deuterating the (S)-enantiomer, the zwitterion thereof, the pharmaceutically acceptable salt of the (S)-enantiomer, the co-crystal of the (S)-enantiomer or the zwitterion thereof, or the ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or the amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof at position C-11.
46. A method of producing the (S)-enantiomer of tianeptine according to claim 1 or 2, said method comprising the steps of:
- (i) resolving a racemic or other mixture of the (S)- and (R)-enantiomers of a chiral amine tianeptine intermediate, which mixtures are characterized by $\geq 0.1\%$ of the (R)-enantiomer of the chiral amine tianeptine intermediate by enantioselective crystallization using a conformer selective for the (S)-enantiomer in a solvent mixture to produce an (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer, the (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer being crystallized from the solvent mixture, and being characterized in that it comprises $\leq 2\%$ of the (R)-amine tianeptine intermediate: (R)-enantiomer-selective-conformer;
 - (ii) reacting the (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer with a 7-bromoheptanoate alkyl ester to produce an (S)-tianeptine alkyl ester intermediate:(S)-enantiomer-selective-conformer;
 - (iii) reacting the (S)-tianeptine alkyl ester intermediate:(S)-enantiomer-selective-conformer with a base to produce the (S)-tianeptine alkyl ester intermediate and
 - (iv) saponifying the (S)-tianeptine alkyl ester intermediate to produce the (S)-enantiomer of tianeptine, which tianeptine comprises $\leq 2\%$ of the (R)-enantiomer of tianeptine.
47. The method according to embodiment 46, wherein the (S)-enantiomer of tianeptine is characterized by $\leq 0.1\%$ of the (R)-enantiomer of tianeptine.

48. A method of producing the 11-D-(S)-tianeptine according to claim 11 or 12, said method comprising the steps of:
- (i) resolving a racemic or other mixture of the (S)- and (R)-enantiomers of a chiral amine 11-D-tianeptine intermediate, which mixtures are characterized by $\geq 0.1\%$ of the (R)-enantiomer of the chiral amine 11-D-tianeptine intermediate by enantioselective crystallization using a conformer selective for the (S)-enantiomer in a solvent mixture to produce an (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer, the (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer being crystallized from the solvent mixture, and being characterized in that it comprises $\leq 2\%$ of the (R)-amine 11-D-tianeptine intermediate:(R)-enantiomer-selective-conformer -conformer;
 - (ii) reacting the (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer with a 7-bromoheptanoate alkyl ester to produce an 11-D-(S)-tianeptine alkyl ester intermediate:(S)-enantiomer-selective-conformer;
 - (iii) reacting the 11-D-(S)-tianeptine alkyl ester intermediate:(S)-enantiomer-selective-conformer with a base to produce the 11-D-(S)-tianeptine alkyl ester intermediate and
 - (iv) saponifying the 11-D-(S)-tianeptine alkyl ester intermediate to produce the 11-D-(S)-enantiomer of tianeptine, which 11-D-(S)-tianeptine comprises $\leq 2\%$ of the (R) enantiomer of 11-D-tianeptine.
49. The method according to claim 48, wherein the (S)-enantiomer of 11-D-tianeptine is characterized by $\leq 0.1\%$ of the (R)-enantiomer of 11-D-tianeptine.
50. A method of producing the (S)-enantiomer of tianeptine or zwitterion thereof according to claim 1 or 2, said method comprising the steps of:
- (i) resolving a racemic or other mixture of the (S)- and (R)-enantiomers of a tianeptine alkyl ester, which mixtures are characterized by $\geq 0.1\%$ of the (R)-enantiomer of a tianeptine alkyl ester by enantioselective crystallization using conformer selective for the (R)-enantiomer in a solvent mixture to produce an (R)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer and an (S)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer, crystallizing and

- separating the (R)-tianeptine alkyl ester from the solvent mixture, the (S)-tianeptine alkyl ester remaining in the solvent mixture and being characterized in that it comprises $\leq 2\%$ of the (R)-tianeptine alkyl ester;
- (ii) hydrolyzing the (S)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer with a strong acid to produce the (S)-tianeptine acid salt, which tianeptine acid salt comprises $\leq 2\%$ of the (R)-tianeptine acid salt; and
- (iii) neutralizing the (S)-tianeptine acid salt with a base to produce the zwitterion of the (S)-enantiomer of tianeptine.
51. A method of producing the 11-D-(S)-enantiomer or zwitterion thereof according to claim 11 or 12, said method comprising the steps of:
- (i) resolving a racemic or other mixture of the (S)- and (R)-enantiomers of an 11-D-tianeptine alkyl ester, which mixtures are characterized by $\geq 0.1\%$ of the (R)-enantiomer of an 11-D-tianeptine alkyl ester by enantioselective crystallization using a conformer selective for the (R)-enantiomer in a solvent mixture to produce an 11-D-(R)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer and an 11-D-(S)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer, crystallizing and separating the 11-D-(R)-tianeptine alkyl ester from the solvent mixture, the 11-D-(S)-tianeptine alkyl ester remaining in the solvent mixture and being characterized in that it comprises $\leq 2\%$ of the 11-D-(R)-tianeptine alkyl ester;
- (ii) hydrolyzing the 11-D-(S)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer with a strong acid to produce the 11-D-(S)-tianeptine acid salt, which 11-D-tianeptine acid salt comprises $\leq 2\%$ of the 11-D-(R)-tianeptine acid salt; and
- (iii) neutralizing the 11-D-(S)-tianeptine acid salt with a base to produce the zwitterion of the 11-D-(S)-enantiomer of tianeptine.
52. The method according to any one of claims 46-51, wherein the tianeptine alkyl ester is a methyl ester, an ethyl ester or any other C_1 - C_6 alkyl ester.
53. The method according to any one of claims 46-51, wherein the enantioselective crystallization comprises using a conformer selected from the group consisting of L-dibenzoyl tartaric acid (DBTA), D-DBTA, Di-o-toluoyl-L-tartaric acid (L-D(2-

Me)BTA), D-D(2-Me)BTA, other DBTA derivatives, (S)-1,1'-Bi-2-naphthol-2,2'-diyl hydrogen phosphate, (R)-1,1'-Bi-2-naphthol-2,2'-diyl hydrogen phosphate, (S)-(R)-mandelic acid, (R)-(S)-mandelic acid, (S)-(S)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid, (R)-(S)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid, (1S)-(R)-10-camphorsulfonic acid and (1R)-(R)-10-camphorsulfonic acid.

54. The method according to any one of claims 46-51, wherein the solvent comprises a mixture of benzene, acetone and trichloromethane.
55. The method according to any one of claims 46-51, wherein the enantioselective crystallization of the (S)-amine tianeptine intermediate:(S)-enantiomer-selective-conformer, the (S)-amine 11-D-tianeptine intermediate:(S)-enantiomer-selective-conformer, (R)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer or the 11-D-(R)-tianeptine alkyl ester:(R)-enantiomer-selective-conformer comprises the step of slow evaporation of the solvent mixture.
56. The method according to any one of claims 46-55, wherein the enantioselective crystallization is repeated to increase the enantiomeric purity or chiral purity of the resolved (S)-amine tianeptine intermediate, the (S)-amine 11-D-tianeptine intermediate, the (S)-tianeptine methyl ester or 11-D-(S)-tianeptine methyl ester.
57. The method according to any one of claims 46-51, wherein resolving the racemic or other mixture is performed using high performance liquid chromatography (HPLC).
58. The method according to any one of claims 46-51, wherein resolving the racemic or other mixture is performed using supercritical fluid chromatography with a chiral column.
59. A method of treating a disease, disorder or condition selected from the group consisting of a central nervous system (CNS) disorder, inflammatory disease, autoimmune disease, infectious illness, a hearing loss condition, ocular disease, musculoskeletal disease, metabolic disease, mitochondrial disease, hypertriglyceridemia, cancer, menopause and chronic overlapping pain conditions

(COPCs), and psychological, physical, metabolic or hormonal stress and COPCs, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 1-10 and 22, or a pharmaceutical composition according to any one of claims 23, 24 or 27-29 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 11-22, or a pharmaceutical composition according to any one of claims 25-29.

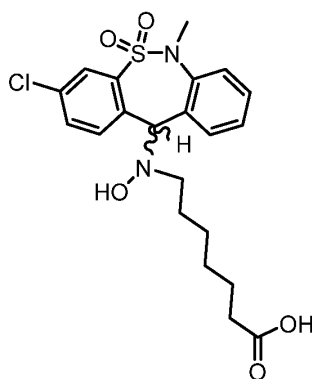
60. A method of enhancing neurite outgrowth comprising administering to a subject in need thereof the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 1-10 and 22, or a pharmaceutical composition according to any one of claims 23, 24 or 27-29 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 11-22, or a pharmaceutical composition according to any one of claims 25-29.
61. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with excessive levels of metal ions in circulation, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 1-10 and 22, or a pharmaceutical composition according to any one

of claims 23, 24 or 27-29 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 11-22, or a pharmaceutical composition according to any one of claims 25-29.

62. A method of reducing violent or aggressive behavior associated with a CNS disorder, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 1-10 and 22, or a pharmaceutical composition according to any one of claims 23, 24 or 27-29 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 11-22, or a pharmaceutical composition according to any one of claims 25-29.
63. A method of reducing the potential of being committed to a psychiatric hospital or being incarcerated due to behavior or actions associated with a CNS disorder, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 1-10 and 22, or a pharmaceutical composition according to any one of claims 23, 24 or 27-29 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or

pharmaceutically acceptable salt thereof according to any one of claims 11-22, or a pharmaceutical composition according to any one of claims 25-29.

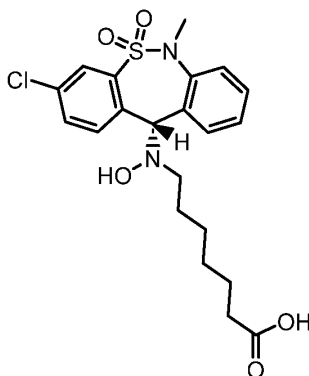
64. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with high levels of S-nitrosylation of PPAR- β/δ and/or PPAR- γ , comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the (S)-enantiomer, or a co-crystal of the (S)-enantiomer or the zwitterion thereof, or an ester of the (S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 1-10 and 22, or a pharmaceutical composition according to any one of claims 23, 24 or 27-29 or administering to the subject a therapeutically effective amount of the 11-D-(S)-enantiomer, the zwitterion thereof, or a pharmaceutically acceptable salt of the 11-D-(S)-enantiomer or a co-crystal of the 11-D-(S)-enantiomer or the zwitterion thereof, or an ester of the 11-D-(S)-enantiomer or pharmaceutically acceptable salt thereof, or an amide of the (S)-enantiomer or pharmaceutically acceptable salt thereof according to any one of claims 11-22, or a pharmaceutical composition according to any one of claims 25-29.
65. N-hydroxy-tianeptine of the Formula (XV) or a pharmaceutically acceptable salt thereof:



Formula (XV).

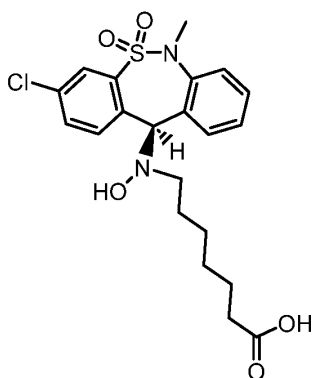
66. The (S)-enantiomer of N-hydroxy-tianeptine (N-hydroxy-(S)-tianeptine) of the Formula (XVI) or a pharmaceutically acceptable salt thereof, wherein the (S)-enantiomer of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are

characterized by comprising $\leq$ about 2% of the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of the (R)-enantiomer of N-hydroxy-tianeptine:



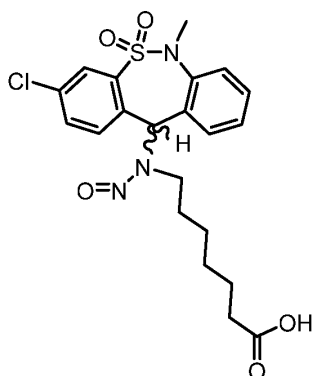
Formula (XVI).

67. The (R)-enantiomer of N-hydroxy-tianeptine (N-hydroxy-(R)-tianeptine) of the Formula (XVII) or a pharmaceutically acceptable salt thereof, wherein the (R)-enantiomer, of N-hydroxy-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising $\leq$ about 2% of the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt of the (S)-enantiomer of N-hydroxy-tianeptine:



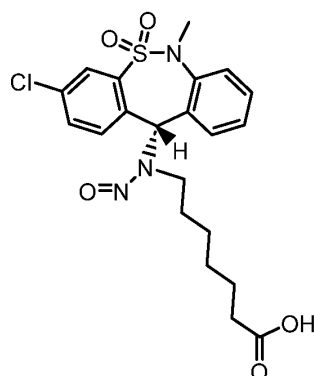
Formula (XVII).

68. N-nitroso-tianeptine of the Formula (XVIII) or a pharmaceutically acceptable salt thereof:



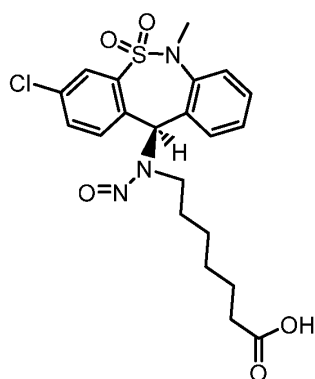
Formula (XVIII).

69. The (S)-enantiomer of N-nitroso-tianeptine (N-nitroso-(S)-tianeptine) of the Formula (XIX) or a pharmaceutically acceptable salt thereof, wherein the (S)-enantiomer, of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising $\leq$ about 2% of the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of the (R)-enantiomer of N-nitroso-tianeptine:



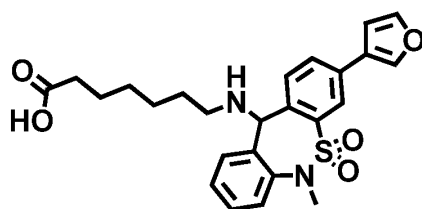
Formula (XIX).

70. The (R)-enantiomer of N-nitroso-tianeptine (N-nitroso-(R)-tianeptine) of the Formula (XX) or a pharmaceutically acceptable salt thereof, wherein the (R)-enantiomer, of N-nitroso-tianeptine or pharmaceutically acceptable salt thereof are characterized by comprising $\leq$ about 2% of the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt of the (S)-enantiomer of N-nitroso-tianeptine:

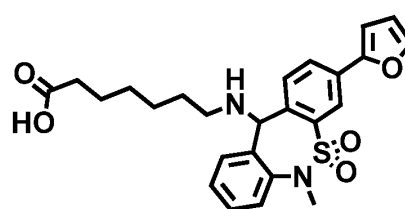


Formula (XX).

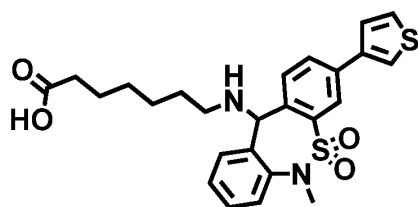
71. An aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof.
72. The aryl substituted tianeptine analog according to claim 71, wherein the aryl substituted tianeptine derivative is 7-((3-(furan-2-yl)-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid of Formula (XXI), 7-((3-(furan-3-yl)-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid of Formula (XXII), 7-((6-methyl-5,5-dioxido-3-(thiophen-3-yl)-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)heptanoic acid of Formula (XXIII) or 2-(4-(((3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl)amino)methyl)-2-methylphenoxy)acetic acid of Formula (XXIV).



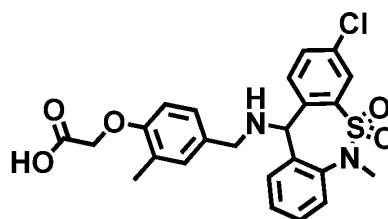
Formula (XXI)



Formula (XXII)



Formula (XXIII)



Formula (XXIV)

73. A pharmaceutical composition comprising the N-hydroxy-tianeptine or a pharmaceutically acceptable salt thereof according to claim 65, or the N-nitroso-tianeptine or a pharmaceutically acceptable salt thereof according to claim 68, or an aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof according to claim 71 or 72 and a pharmaceutically acceptable carrier, diluent, or excipient.
74. A pharmaceutical composition comprising the (S)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt thereof according to claim 66, or the (S)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt thereof according to claim 69 and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises $\leq$ about 2%, or $\leq$ about 0.1%, of the (R)-enantiomer of N-hydroxy-tianeptine or N-nitroso-tianeptine or pharmaceutically acceptable salt of the (R)-enantiomer of N-hydroxy-tianeptine or N-nitroso-tianeptine or pharmaceutically acceptable salt thereof.
75. A pharmaceutical composition comprising the (R)-enantiomer of N-hydroxy-tianeptine or a pharmaceutically acceptable salt thereof according to claim 67, or the (R)-enantiomer of N-nitroso-tianeptine or a pharmaceutically acceptable salt thereof according to claim 70 and a pharmaceutically acceptable carrier, diluent, or excipient, wherein the composition comprises $\leq$ about 2%, or $\leq$ about 0.1%, of the (S)-enantiomer of N-hydroxy-tianeptine or N-nitroso-tianeptine or pharmaceutically acceptable salt of the (S)-enantiomer of N-hydroxy-tianeptine or N-nitroso-tianeptine or pharmaceutically acceptable salt thereof.
76. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of claims 65-67, or the N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, or the (R)-enantiomer of N-

nitroso-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of claims 68-70, or an aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof according to claim 71 or 72 or the pharmaceutical composition according to any one of claims 73-75.

77. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, in a subject who has experienced high stress, comprising administering to the subject a therapeutically effective amount of the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of claims 65-67, or the N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, or the (R)-enantiomer of N-nitroso-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of claims 68-70, or an aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof according to claim 71 or 72 or the pharmaceutical composition according to any one of claims 73-75.
78. A method of treating a disease, disorder or condition modulated by, exacerbated by, or associated with altered activity of peroxisome proliferator-activated receptor (PPAR)- β/δ and/or PPAR- γ and one or more associated symptoms thereof, while reducing μ -opioid receptor agonism associated with treatment with racemic tianeptine, comprising administering to a subject in need or at risk thereof a therapeutically effective amount of the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of claims 65-67, or the N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, or the (R)-enantiomer of N-nitroso-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of claims 68-70, or an aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof according to claim 71 or 72 or the pharmaceutical composition according to any one of claims 73-75.
79. A method of treating a disease, disorder or condition selected from the group consisting of a central nervous system (CNS) disorder, asthma, primary biliary

cholangitis, hypertriglyceridemia, cardiac hypertrophy, fibromyalgia, cancer, infectious illness, COVID-19, long COVID, menopause and chronic overlapping pain conditions (COPCs), psychological, physical, metabolic or hormonal stress and COPCs, and obesity, comprising administering to the subject a therapeutically effective amount of the N-hydroxy-tianeptine, the (S)-enantiomer of N-hydroxy-tianeptine, the (R)-enantiomer of N-hydroxy-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of claims 65-67, or the N-nitroso-tianeptine, the (S)-enantiomer of N-nitroso-tianeptine, or the (R)-enantiomer of N-nitroso-tianeptine, or a pharmaceutically acceptable salt of any of them according to anyone of claims 68-70, or an aryl substituted tianeptine analog or a pharmaceutically acceptable salt thereof according to claim 71 or 72 or the pharmaceutical composition according to any one of claims 73-75.

80. A crystalline hemi-oxalate salt of (S)-7-(3-chloro-6-methyl-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-ylamino)heptanoic acid 5,5-dioxide ((S)-tianeptine), wherein the salt exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak selected from 8.5, 20.6, 21.0 and 24.2 degrees $2\theta \pm 0.3$ degrees 2θ .
81. A crystalline free acid/free base of the (S)-enantiomer of tianeptine according to claim 1, wherein the crystalline (S)-enantiomer of tianeptine exhibits an X-ray diffraction pattern (XRPD) comprising at least one peak selected from 10.6, 13.0, 21.1 and 23.7 degrees $2\theta \pm 0.3$ degrees 2θ .