

LINE-1 INHIBITORS TO TREAT DISEASE

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present disclosure provides methods of treating or preventing a disease, disorder, or condition caused by LINE-1 retrotransposition in a subject in need thereof, the method comprising administering a compound of any one of Formulae **I-III**, or a pharmaceutical composition thereof, or a tautomer thereof, to the subject.

Background

[0002] Long INterspersed Element-1 (LINE-1 or L1) retrotransposons form the only autonomously active family of transposable elements in humans. They are expressed and mobile in the germline, in embryonic stem cells, and in the early embryo, but are silenced in most somatic tissues. LINE-1 plays an important role in individual genome variations through insertional mutagenesis and sequence transduction, which occasionally lead to genetic diseases and disorders. In addition, LINE-1 is reactivated in certain cancers thus contributing to tumor genome dynamics. The LINE-1 element codes for two proteins, ORF1p and ORF2p, which are essential for its mobility. ORF1p is an RNA-binding protein with nucleic acid chaperone activity. ORF2p possesses endonuclease and reverse transcriptase activities. These proteins and the LINE-1 RNA assemble into a ribonucleoprotein particle (LINE-1 RNP) – the core of the retrotransposition machinery. The LINE-1 RNP mediates the synthesis of new LINE-1 copies upon cleavage of the target DNA and reverse transcription of the LINE-1 RNA at the target site. The LINE-1 element takes benefit of cellular host factors to complete its life cycle, however several cellular pathways also limit the cellular accumulation of LINE-1 RNPs and their deleterious activities. See, e.g., Pizarro and Cristofari (2016) *Front. Cell Dev. Biol.* 4:14. doi: 10.3389/fcell.2016.00014. There exists a need for methods to treat or prevent diseases, disorders, or conditions caused by LINE-1 retrotransposition in subjects.

BRIEF SUMMARY OF THE INVENTION

- [0003] In one aspect, the present disclosure provides methods of treating or preventing a disease, disorder, or condition caused by a pathophysiological retrotransposon-associated process in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of Formula **I-III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, collectively referred to as "Compounds of the Disclosure," *see* below. Exemplary diseases, disorders, or conditions include, but are not limited, to neurodegenerative diseases, autoimmune diseases, and age-associated diseases.
- [0004] In another aspect, the present disclosure provides methods of treating or preventing a symptom of a disease, disorder, or condition caused by a pathophysiological retrotransposon-associated process in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a Compound of the Disclosure, or a pharmaceutical composition thereof.
- [0005] In another aspect, the present disclosure provides methods of inhibiting a LINE-1 retrotransposition event, e.g., a somatic LINE-1 insertion, that causes a disease, disorder, or condition, in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a Compound of the Disclosure to the subject, or a pharmaceutical composition thereof.
- [0006] In another aspect, the present disclosure provides methods of treating a disease, condition, or disorder in a subject in need thereof, the method comprising (a) determining whether an overexpression of a biomarker, e.g., retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA, e.g., LINE-1 RNA, ORF1p, or ORF2p, is present or absent in a biological sample taken from the subject; and (b) administering a therapeutically effective amount of a compound of a Compound of the Disclosure, or a pharmaceutical composition thereof, to the subject if an overexpression of the biomarker is present in the biological sample.
- [0007] In another aspect, the present disclosure provides methods of identifying whether a subject having a disease, condition, or disorder is a candidate for treatment with a Compound of the Disclosure, or a pharmaceutical composition thereof, the method

comprising (a) determining whether an overexpression of a biomarker, e.g., retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA, e.g., LINE-1 RNA, ORF1p, or ORF2p, is present or absent in a biological sample taken from the subject; and (b) identifying the subject as being a candidate for treatment if an overexpression of the biomarker is present; or (c) identifying the subject as not being a candidate for treatment if an overexpression of the biomarker is absent.

[0008] In another aspect, the present disclosure provides methods of predicting treatment outcome in a subject having a disease, condition, or disorder, the method comprising determining whether an overexpression of a biomarker, e.g., retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA, e.g., LINE-1 RNA, ORF1p, or ORF2p, is present or absent in a biological sample taken from the subject, wherein (a) the presence of an overexpression of the biomarker in the biological sample indicates that administering a Compound of the Disclosure, or a pharmaceutical composition thereof, to the subject will likely cause a favorable therapeutic response; and (b) the absence of an overexpression of the biomarker in the biological sample indicates that administering a Compound of the Disclosure, or a pharmaceutical composition thereof, to the subject will likely cause an unfavorable therapeutic response.

[0009] In another aspect, the present disclosure provides methods, comprising administering a therapeutically effective amount of a Compound of the Disclosure, or a pharmaceutical composition thereof, to a subject in need thereof, wherein (a) the subject has a disease, disorder, or condition; and (b) the disease, disorder, or condition is characterized as having an overexpression of a biomarker, e.g., retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA, e.g., LINE-1 RNA, ORF1p, or ORF2p.

[0010] In another aspect, the present disclosure provides a kit comprising a Compound of the Disclosure, or a pharmaceutical composition thereof, and instructions for administering the compound or composition to a subject having a disease, condition, or disorder caused by a pathophysiological retrotransposon-associated process.

[0011] In another aspect, the present disclosure provides a Compound of the Disclosure, or a pharmaceutical composition thereof, for use in treating or preventing a disease, disorder, or condition caused by a pathophysiological retrotransposon-associated process.

[0012] In another aspect, the present disclosure provides a Compound of the Disclosure, or a pharmaceutical composition thereof, for use in treating or preventing a symptom of a disease, disorder, or condition caused by a pathophysiological retrotransposon-associated process

[0013] In another aspect, the present disclosure provides the use of Compound of the Disclosure, or a pharmaceutical composition thereof, for the manufacture of a medicament for treating or preventing a disease, disorder, or condition caused by a pathophysiological retrotransposon-associated process.

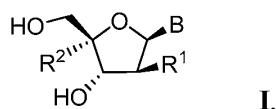
[0014] In another aspect, the present disclosure provides the use of Compound of the Disclosure, or a pharmaceutical composition thereof, for the manufacture of a medicament for treating or preventing a symptom of a disease, disorder, or condition caused by a pathophysiological retrotransposon-associated process.

DETAILED DESCRIPTION OF THE INVENTION

I. Compounds of the Disclosure

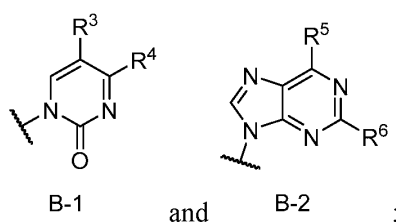
[0015] Applicant has discovered that compounds having any one of Formulae **I-III** are surprisingly potent LINE-1 inhibitors. As such, these compounds can be used to treat diseases, disorders, or conditions wherein LINE-1 retrotransposition plays a causative role.

[0016] In one embodiment, Compounds of the Disclosure are compounds of Formula **I**:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

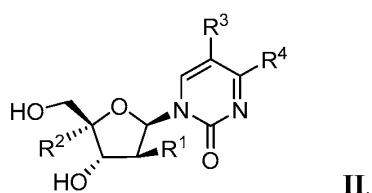
[0017] B is selected from the group consisting of:



[0018] R¹ is selected from the group consisting of hydrogen and -OH;

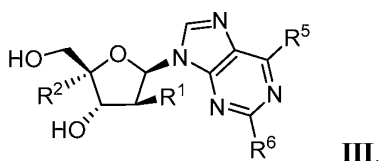
[0019] R² is selected from the group consisting of methyl, ethynyl, and -CN;

- [0020] R^3 is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;
- [0021] R^4 is selected from the group consisting of $-NH_2$ and $-OH$;
- [0022] R^5 is selected from the group consisting of $-NH_2$ and $-OH$; and
- [0023] R^6 is selected from the group consisting of hydrogen, chloro, and $-NH_2$.
- [0024] In another embodiment, Compounds of the Disclosure are compounds of Formula II:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^1 , R^2 , R^3 , and R^4 are as defined in connection with Formula I.

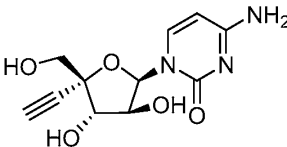
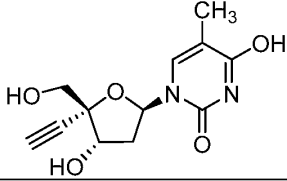
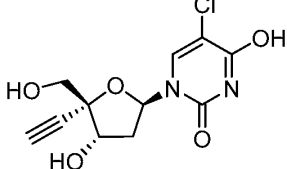
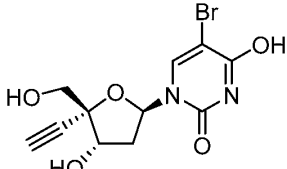
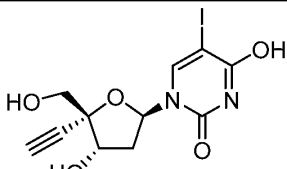
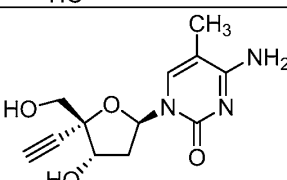
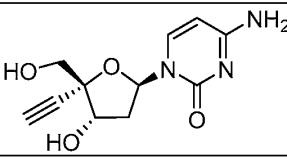
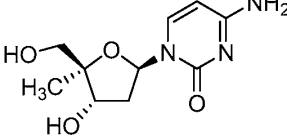
- [0025] In another embodiment, Compounds of the Disclosure are compounds of Formula II, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^3 is hydrogen.
- [0026] In another embodiment, Compounds of the Disclosure are compounds of Formula II, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^3 is methyl.
- [0027] In another embodiment, Compounds of the Disclosure are compounds of Formula II, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^4 is $-NH_2$.
- [0028] In another embodiment, Compounds of the Disclosure are compounds of Formula III:

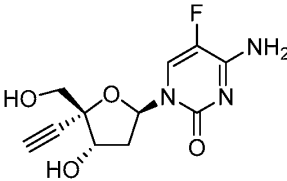
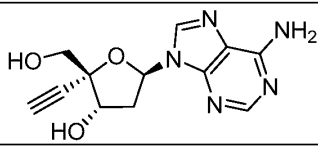
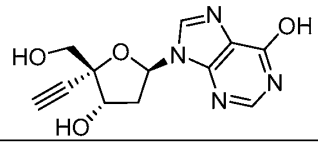
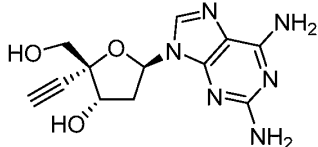
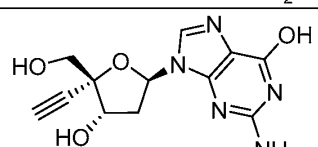
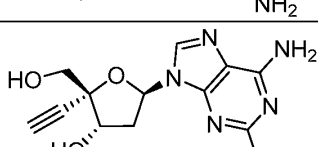
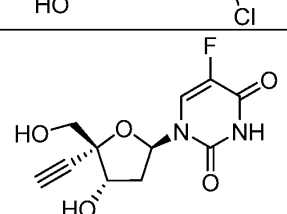


or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^1 , R^2 , R^5 , and R^6 are as defined in connection with Formula I.

- [0029] In another embodiment, Compounds of the Disclosure are compounds of Formula **III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R⁵ is -NH₂.
- [0030] In another embodiment, Compounds of the Disclosure are compounds of Formula **III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R⁵ is -OH.
- [0031] In another embodiment, Compounds of the Disclosure are compounds of Formula **III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R⁶ is hydrogen.
- [0032] In another embodiment, Compounds of the Disclosure are compounds of Formula **III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R⁶ is chloro.
- [0033] In another embodiment, Compounds of the Disclosure are compounds of Formula **III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R⁶ is -NH₂.
- [0034] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R¹ is hydrogen.
- [0035] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R¹ is -OH.
- [0036] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R² is methyl.
- [0037] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R² is ethynyl, i.e., $\text{---C}\equiv\text{CH}$.
- [0038] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I-III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R² is -CN.
- [0039] In another embodiment, Compounds of the Disclosure are compounds of Table 1, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

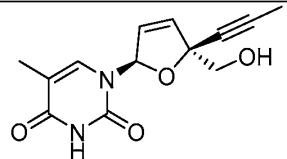
Table 1

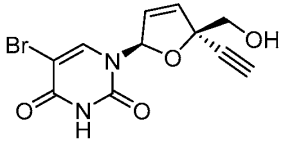
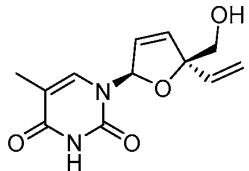
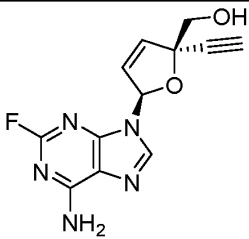
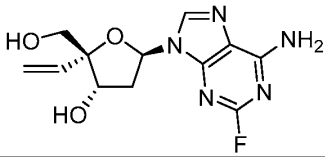
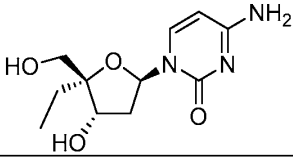
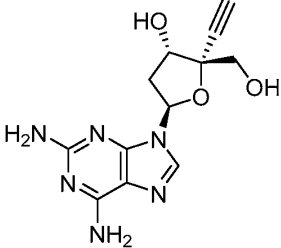
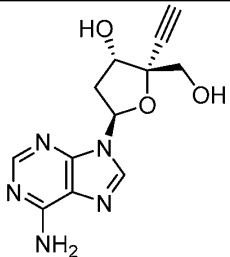
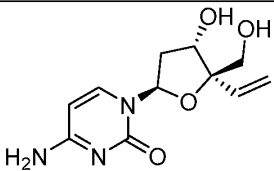
Compound Number	Structure
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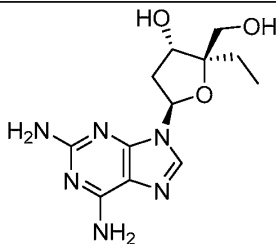
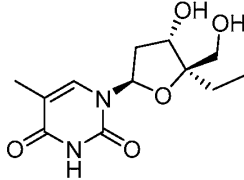
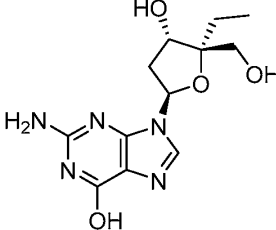
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[0040] In another embodiment, Compounds of the Disclosure are compounds of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

Table 1A

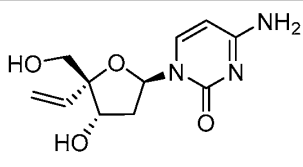
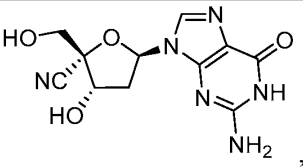
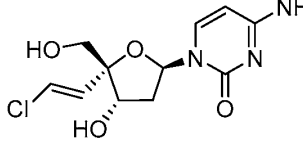
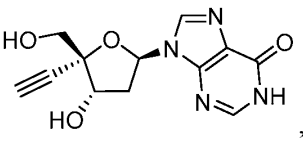
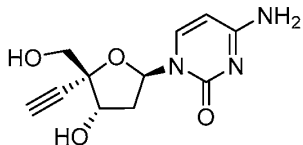
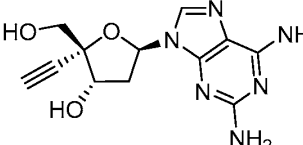
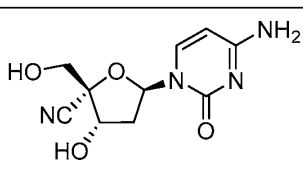
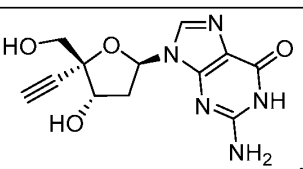
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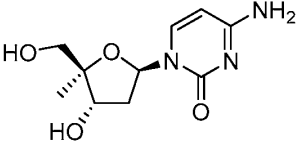
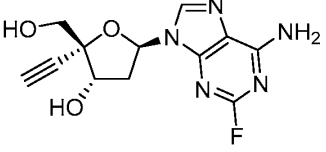
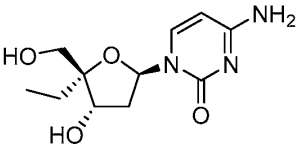
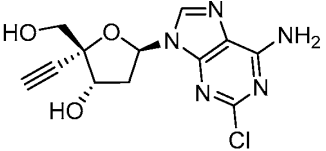
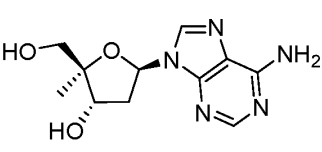
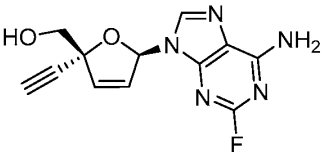
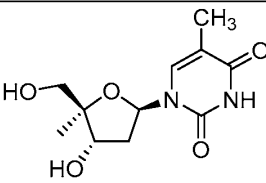
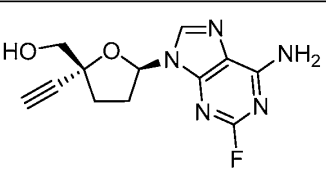
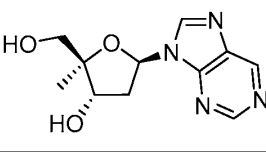
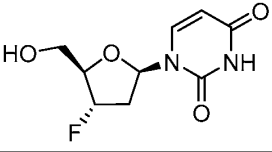
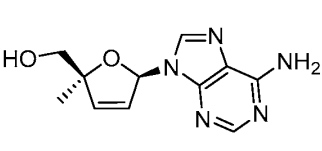
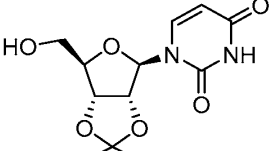
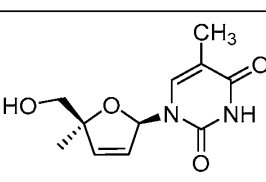
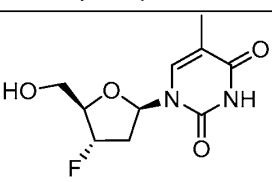
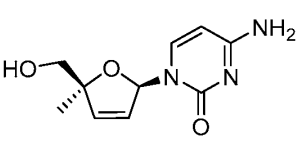
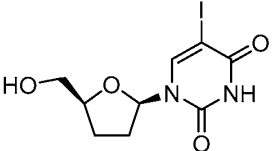
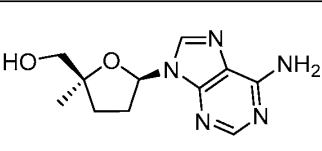
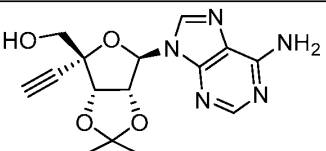
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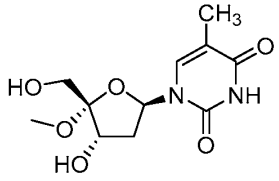
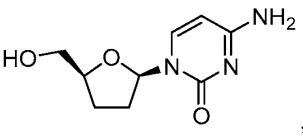
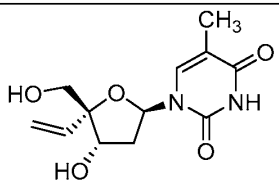
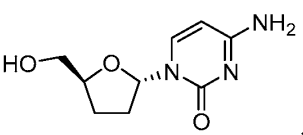
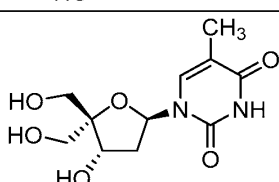
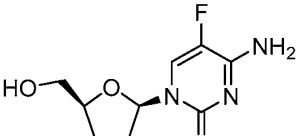
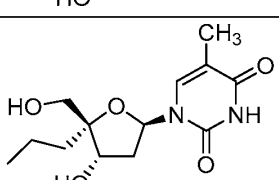
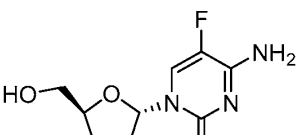
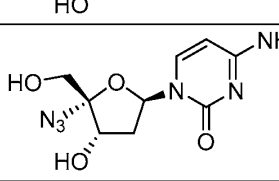
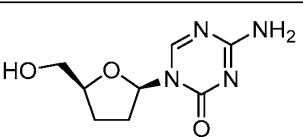
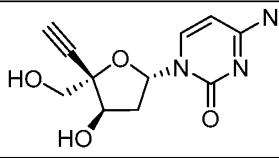
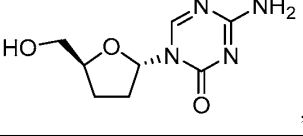
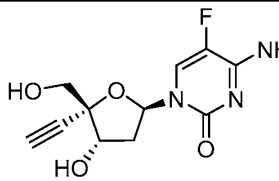
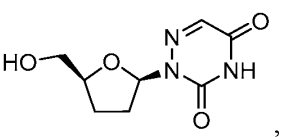
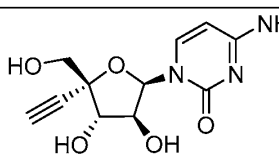
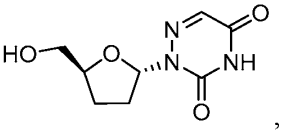
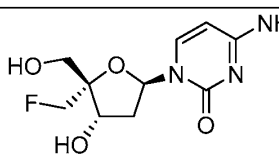
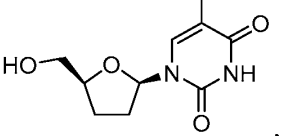
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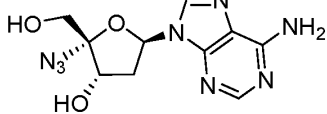
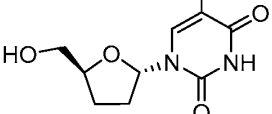
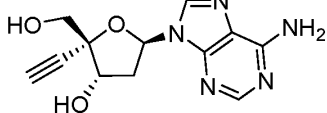
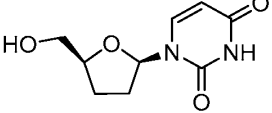
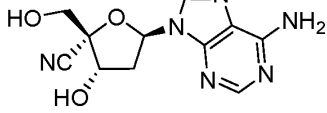
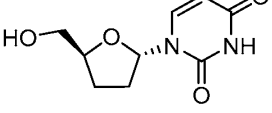
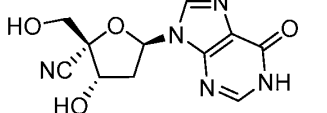
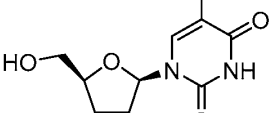
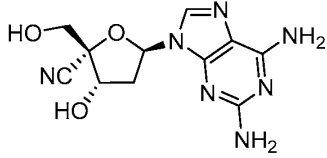
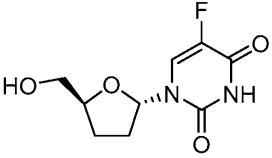
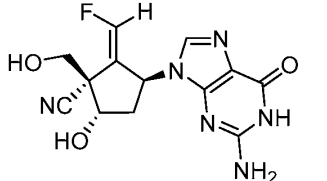
[0041] In another embodiment, Compounds of the Disclosure are compounds of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

Table 1B

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	or

[0042] The compounds Table 1, Table 1A, and Table 1B may be found and prepared as described, for example, in Nomura et al., *J. Med. Chem.* 42:2901-2908 (1999); Ohruai et al., *J. Med. Chem.* 43:4516-4525 (2000), Ohruai, H., *Proc. Jpn. Acad. Ser. B* 87:53-65 (2011); Banuelos-Sanchez et al., *Cell Chemical Biology* 26:1095-1109 (2019); Kirby et al., *Antimicrobial Agents and Chemotherapy* 57:6254-6264 (2013), Higashi-Kuwata et al., *Journal of Hepatology* 74:1075-1086 (2021), JP Patent No. 6767011, US Patent No. 10,933,067, and/or as described in EXAMPLES 2-4, below.

[0043] In another embodiment, the Compound of the Disclosure is tenofovir alafenamide.

II. Therapeutic Methods and Uses

[0044] A Compound of the Disclosure, or pharmaceutical composition thereof, can be administered to a subject in need thereof, e.g., a subject already suffering from a disease,

condition, or disorder; a subject suspected of having a disease, condition, or disorder; or a subject at risk of acquiring a disease, condition, or disorder. When a Compound of the Disclosure is administered to a subject at risk of acquiring a disease, condition, or disorder, the intention is to try to avoid the disease, condition, or disorder in the subject, e.g. by preventing or reducing the LINE-1 retrotransposition activity that causes the disease, condition, or disorder.

[0045] In one embodiment, the disclosure provides a method of treating or preventing a disease, disorder, or condition in a subject in need thereof, and/or treating or preventing a symptom of the disease, disorder, or condition, the method comprising administering a therapeutically effective amount of a Compound of the Disclosure, or pharmaceutical composition thereof, to the subject.

[0046] In another embodiment, the disclosure provides a method of treating a disease, disorder, or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a Compound of the Disclosure, or pharmaceutical composition thereof, to the subject.

[0047] In another embodiment, the disclosure provides a method of preventing a disease, disorder, or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a Compound of the Disclosure, or pharmaceutical composition thereof, to the subject.

[0048] In another embodiment, the disclosure provides a method of treating a symptom of a disease, disorder, or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a Compound of the Disclosure, or pharmaceutical composition thereof, to the subject.

[0049] In another embodiment, the disclosure provides a method of preventing a symptom of a disease, disorder, or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a Compound of the Disclosure, or pharmaceutical composition thereof, to the subject.

[0050] In another embodiment, the disclosure provides a Compound of the Disclosure, or pharmaceutical composition thereof, for use in treating or preventing a disease, disorder, or condition in a subject and/or treating or preventing a symptom of the disease, disorder, or condition.

- [0051] In another embodiment, the disclosure provides a Compound of the Disclosure, or pharmaceutical composition thereof, for use in treating a disease, disorder, or condition in a subject.
- [0052] In another embodiment, the disclosure provides a Compound of the Disclosure, or pharmaceutical composition thereof, for use in preventing a disease, disorder, or condition in a subject.
- [0053] In another embodiment, the disclosure provides a Compound of the Disclosure, or pharmaceutical composition thereof, for use in treating a symptom of a disease, disorder, or condition in a subject.
- [0054] In another embodiment, the disclosure provides a Compound of the Disclosure, or pharmaceutical composition thereof, for use preventing a symptom of a disease, disorder, or condition in a subject.
- [0055] In another embodiment, the disclosure provides the use of a Compound of the Disclosure, or pharmaceutical composition thereof, in the manufacture of a medicament for treating or preventing a disease, disorder, or condition in a subject and/or treating or preventing a symptom of the disease, disorder, or condition.
- [0056] In another embodiment, the disclosure provides the use of a Compound of the Disclosure, or pharmaceutical composition thereof, in the manufacture of a medicament for treating a disease, disorder, or condition in a subject.
- [0057] In another embodiment, the disclosure provides the use of a Compound of the Disclosure, or pharmaceutical composition thereof, in the manufacture of a medicament for preventing a disease, disorder, or condition in a subject.
- [0058] In another embodiment, the disclosure provides the use of a Compound of the Disclosure, or pharmaceutical composition thereof, in the manufacture of a medicament for treating a symptom of a disease, disorder, or condition in a subject.
- [0059] In another embodiment, the disclosure provides the use of a Compound of the Disclosure, or pharmaceutical composition thereof, in the manufacture of a medicament for preventing a symptom of the disease, disorder, or condition in a subject.
- [0060] In another embodiment, the subject is (a) not infected with the HIV virus, (b) not suspected of being infected with the HIV virus, (c) not being treated for the HIV virus, and/or (d) not being treated to prevent the HIV virus.

[0061] In another embodiment, the disclosure provides a method of inhibiting a LINE-1 retrotransposition event that causes a disease, disorder, or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a Compound of the Disclosure.

III. Diseases, Disorders, and Conditions

[0062] Compounds of the Disclosure inhibit LINE-1 retrotransposition activity and thus can be used to treat or prevent diseases, disorders, or conditions in a subject. In some embodiments, the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.

[0063] In one embodiment, Compounds of the Disclosure inhibit human LINE-1 retrotransposition activity with a half maximal inhibitory concentration (IC_{50}) of 1 μ M or less in an in vitro HeLa cell-based dual-luciferase assay as described in EXAMPLE 2, *see below*. *See also* Jones et al., (2008) *PLoS ONE* 3(2): e1547. doi:10.1371/journal.pone.0001547; Xie et al., (2011) *Nucleic Acids Res.* 39(3): e16. doi: 10.1093/nar/gkq1076; Kopera et al., *Methods Mol Biol* 1400:139-156 (2016). In another embodiment, the IC_{50} is 0.5 μ M or less. In another embodiment, the IC_{50} is 0.25 μ M or less. In another embodiment, the IC_{50} is 0.15 μ M or less. In another embodiment, the IC_{50} is 0.1 μ M or less. In another embodiment, the IC_{50} is 0.05 μ M or less. In another embodiment, the IC_{50} is 0.01 μ M or less. In another embodiment, the IC_{50} is 0.005 μ M or less.

[0064] In one embodiment, the disease, disorder, or condition, and/or symptom(s) thereof is caused by a pathophysiological retrotransposon-associated process, wherein the disease, disorder, or condition is not cancer and/or not an infectious disease.

[0065] In another embodiment, the disease, disorder, or condition, and/or symptom(s) thereof is caused by a pathophysiological LINE-1-associated process, wherein the disease, disorder, or condition is not cancer and/or not an infectious disease.

[0066] In another embodiment, the disease, disorder, or condition is a neurodegenerative disease. *See, e.g.*, Dugger and Dickson, *Cold Spring Harb Perspect Biol* 2016;9:a028035. Exemplary neurodegenerative diseases include, but are not limited to, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, dementia with Lewy Bodies (DLB), multi systems atrophy (MSA), Huntington's disease, frontotemporal lobar degeneration (FTLD), mild cognitive impairment (MCI), corticobasal degeneration (CDB),

progressive supra nuclear palsy (PSP), Rett Syndrome, peripheral degenerative disease, or Aicardi-Goutières syndrome (AGS). In another embodiment, the frontotemporal lobar degeneration is frontotemporal dementia. *See, e.g.,* Mohandas and Rajmohan, *Indian J Psychiatry* 51(Suppl 1):S65–S69 (2009).

[0067] In another embodiment, symptoms of the neurodegenerative disease include, but are not limited to, memory loss, forgetfulness, apathy, anxiety, agitation, a loss of inhibition, or mood changes,

[0068] In another embodiment, the disease, disorder, or condition is an autoimmune disease. *See, e.g.,* Wang et al., *J Intern Med* 278:369–395 (2016). Exemplary autoimmune diseases include, but are not limited to, lupus, rheumatoid arthritis (RA), Sjogrens syndrome, or multiple sclerosis (MS).

[0069] In another embodiment, symptoms of the autoimmune disease include, but are not limited to, fatigue, achy muscles, swelling and redness, low-grade fever, trouble concentrating, numbness and tingling in the hands and feet, hair loss, or skin rash.

[0070] In another embodiment, the disease, disorder, or condition is an age-associated disease. *See, e.g.,* Franceschi et al., *Front. Med.* 5:61. doi: 10.3389/fmed.2018.00061; De Cecco et al., *Nature* 566:73-78 (2019); WO 2020/154656. Exemplary age-associated diseases include, but are not limited to, Alzheimer's disease, Parkinson's disease, atherosclerosis, osteoarthritis, osteoporosis, rheumatoid arthritis (RA), macular degeneration, peripheral degenerative disease, or skin aging. In one embodiment, the subject having the age-associated disease is at least 40 years old. In one embodiment, the subject having the age-associated disease is at least 45 years old. In one embodiment, the subject having the age-associated disease is at least 50 years old. In one embodiment, the subject having the age-associated disease is at least 55 years old. In one embodiment, the subject having the age-associated disease is at least 60 years old. In one embodiment, the subject having the age-associated disease is at least 65 years old. In one embodiment, the subject having the age-associated disease is at least 70 years old. In one embodiment, the subject having the age-associated disease is at least 75 years old.

[0071] In another embodiment, the disease, disorder, or condition is autism spectrum disorder (ADS), cardiovascular dysfunction, hearing loss, hematopoietic stem cell function, pulmonary fibrosis, schizophrenia, or vision loss.

- [0072] In another embodiment, the disease, disorder, or condition is wound healing in a subject in need thereof.
- [0073] In another embodiment, the disease, disorder, or condition is tissue regeneration in a subject in need thereof.
- [0074] In another embodiment, the disease, disorder, or condition is Alzheimer's disease.
- [0075] In another embodiment, the symptom of Alzheimer's disease any one or more of memory loss, misplacing items, forgetting the names of places or objects, repeating questions, being less flexible, confusion, disorientation, obsessive behavior, compulsive behavior, delusions, aphasia, disturbed sleep, mood swings, depression, anxiety, frustration, agitation, difficulty in performing spatial tasks, agnosia, difficulty with ambulation, weight loss, loss of speech, loss of short term memory, or loss of long term memory, and combinations thereof.
- [0076] In another embodiment, the symptom(s) of Alzheimer's disease are determined using the cognitive subscale of the Alzheimer's disease Assessment Scale (ADAS-cog), the Clinician's Interview-Based Impression of Change (CIBIC-plus), or the Activities of Daily Living Scale (ADL).
- [0077] In another embodiment, the disease, disorder, or condition is Alzheimer's disease, and one or more optional therapeutic agents are administered to the subject. In another embodiment, the optional therapeutic agents are donepezil, galantamine, rivastigmine, memantine, bapineuzumab, ABBV-8E12, CTS-21166, verubecestat (MK-8931), lanabecestat (AZD3293), LY2886721, nicotinamide, or MPT0G211.
- [0078] In another embodiment, the disease, disorder, or condition is amyotrophic lateral sclerosis.
- [0079] In another embodiment, the disease, disorder, or condition is amyotrophic lateral sclerosis and one or more optional therapeutic agents are administered to the subject. In another embodiment, the optional therapeutic agents are edaravone, riluzole, raltegravir, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-25 870810, MK-0518, BMS-538158, or GSK364735C.

- [0080] In another embodiment, the disease is ataxia-telangiectasia.
- [0081] In another embodiment, the disease is age-related macular degeneration, systemic lupus erythematosus, IFN-associated autoimmune disease, e.g., rheumatoid arthritis, psoriasis, vitiligo, hypothyroidism, hyperthyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, myasthenia gravis, Addison disease, celiac disease, polymyositis, or superimposed autoimmune hepatitis, Fanconi Anemia, idiopathic pulmonary fibrosis, or cardiovascular disease. In another embodiment, the systemic disease is age-related macular degeneration. In another embodiment, the systemic disease is systemic lupus erythematosus. In another embodiment, the systemic disease is an IFN-associated autoimmune disease, e.g., psoriasis. In another embodiment, the systemic disease is Fanconi Anemia. In another embodiment, the systemic disease is idiopathic pulmonary fibrosis. In another embodiment, the systemic disease is cardiovascular disease.
- [0082] In one embodiment, a Compound of the Disclosure is administered to a subject having a disease, disorder, or condition as a single agent.
- [0083] In another embodiment, a Compound of the Disclosure is administered to a subject having a disease, disorder, or condition in combination with one or more optional therapeutic agents. *See, e.g.,* Durães et al., *Pharmaceuticals* 2018, 11, 44; doi:10.3390/ph11020044 for optionally therapeutic agents to treat neurodegenerative diseases.
- [0084] In another embodiment, a Compound of the Disclosure is administered to a subject having a disease, disorder, or condition in combination with one optional therapeutic agent. In another embodiment, a Compound of the Disclosure is administered to a subject having a disease, disorder, or condition in combination with two optional therapeutic agents. In another embodiment, a Compound of the Disclosure is administered to a subject having a disease, disorder, or condition in combination with three optional therapeutic agents.
- [0085] The Compound of the Disclosure and the one or more optional therapeutic agents can be administered in combination under one or more of the following conditions: at different periodicities, at different durations, at different concentrations, by different administration routes, *etc.*
- [0086] In one embodiment, the Compound of the Disclosure and the one or more optional therapeutic agents are administered in combination to a subject as part of a single pharmaceutical composition.

- [0087] In another embodiment, the Compound of the Disclosure and the one or more optional therapeutic agents are administered in combination to a subject separately, e.g., as two or more separate pharmaceutical compositions. In this case, two separate pharmaceutical compositions – one comprising the Compound of the Disclosure and one comprising the optional therapeutic agent – are administered to a subject. The separate pharmaceutical compositions can be administered to the subject, for example, at different periodicities, at different durations, or by the same or different administration routes, e.g., the Compound of the Disclosure can be administered orally and the optionally therapeutic agent can be administered intravenously.
- [0088] In another embodiments, the Compound of the Disclosure is administered to the subject prior to the one or more optional therapeutic agents, e.g., 0.5, 1, 2, 3, 4, 5, 10, 12, or 18 hours, 1, 2, 3, 4, 5, or 6 days, or 1, 2, 3, or 4 weeks prior to the administration of the one or more optional therapeutic agents.
- [0089] In another embodiments, the Compound of the Disclosure is administered to the subject after the one or more optional therapeutic agents, e.g., 0.5, 1, 2, 3, 4, 5, 10, 12, or 18 hours, 1, 2, 3, 4, 5, or 6 days, or 1, 2, 3, or 4 weeks after the administration of the one or more optional therapeutic agents.
- [0090] In another embodiments, the Compound of the Disclosure and the one or more optional therapeutic agents are administered concurrently.
- [0091] In one embodiment, the Compound of the Disclosure is administered to the subject according to a continuous dosing schedule.
- [0092] In one embodiment, the Compound of the Disclosure is administered to the subject according to an intermittent dosing schedule.
- [0093] In one embodiment, the Compound of the Disclosure is orally administered to the subject.
- [0094] The therapeutic methods provided herein comprise administering a Compound of the Disclosure to a subject having a disease, disorder, or condition in an amount which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the Compound of the Disclosure is administered in an amount from about 0.01 mg/kg to about 500 mg/kg, about 0.05 mg/kg to about 100 mg/kg, about 0.05 mg/kg to about 50 mg/kg, or about 0.05 mg/kg to about 10 mg/kg. In one embodiment, the

Compound of the Disclosure is administered once a day. In another embodiment, the Compound of the Disclosure is administered twice a day. In one embodiment, the Compound of the Disclosure is administered three times a day. In one embodiment, the Compound of the Disclosure is administered four times a day. These dosages are exemplary, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this disclosure. In practice, the physician determines the actual dosing regimen that is most suitable for an individual subject, which can vary with the age, weight, and response of the particular subject.

[0095] The unit dose may comprise from about 0.01 mg to about 1000 mg, e.g., about 1 mg to about 500 mg, e.g., about 1 mg to about 250 mg, e.g., about 1 mg to about 100 mg of the Compound of the Disclosure. For example, the unit oral dose of the Compound of the Disclosure may comprise, for example 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, or 10 mg. The unit dose may be administered one or more times daily, e.g., as one or more tablets or capsules. The unit dose may also be administered by any suitable route, e.g., orally, by IV, inhalation or subcutaneously to the subject. In practice, the physician determines the actual dosing regimen that is most suitable for an individual subject, which can vary with the age, weight, and response of the particular subject.

[0096] In one embodiment, the Compound of the Disclosure is administered to a subject in an amount from about 0.1 mg to about 100 mg once a day, twice a day, three times a day, or four times a day. In another embodiment, the Compound of the Disclosure is administered to a subject in an amount from about 1 mg to about 50 mg per day.

[0097] In one embodiment, the Compound of the Disclosure is administered to the subject in a single dose. In another embodiment, the Compound of the Disclosure is administered to the subject in two divided doses. In another embodiment, the Compound of the Disclosure is administered to the subject in three divided doses. In another embodiment, the Compound of the Disclosure is administered to the subject in four divided doses.

[0098] The Compound of the Disclosure can be administered to a subject in the form of a raw chemical or as part of a pharmaceutical composition containing the Compound of the Disclosure combined with a suitable pharmaceutically acceptable carrier. Such a carrier can be selected from pharmaceutically acceptable excipients, vehicles, and auxiliaries. The term "pharmaceutically acceptable carrier," "pharmaceutically acceptable vehicle," or "pharmaceutically acceptable vehicle" encompasses any of the standard pharmaceutical

carriers, solvents, surfactants, or vehicles. Suitable pharmaceutically acceptable vehicles include aqueous vehicles and nonaqueous vehicles. Standard pharmaceutical carriers and their formulations are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995.

[0099] A pharmaceutical composition comprising the Compound of the Disclosure can contain from about 0.01 to 99 percent by weight, e.g., from about 0.25 to 75 percent by weight, of the Compound of the Disclosure, e.g., about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, or about 75% by weight of the Compound of the Disclosure.

[0100] The Compound of the Disclosure, or pharmaceutical composition comprising the Compound of the Disclosure, can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, intracisternal or intrathecal through lumbar puncture, transurethral, nasal, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, intracoronary, intradermal, intramammary, intraperitoneal, intraarticular, intrathecal, retrobulbar, intrapulmonary injection and/or surgical implantation at a particular site) administration to a subject. Dosage forms depend on the route administration. Dosage forms include, but are not limited to, tablets, dragees, slow release lozenges, capsules, liquid solutions, liquid suspensions, oral/nasal spray, transdermal patch, thin dissolvable film, ointments, sustained or controlled release implants, mouth rinses and mouth washes, gels, hair rinses, hair gels, and shampoos, and suppositories, as well as suitable solutions for administration by intravenous infusion, and suitable suspensions for administration subcutaneous injection, and suitable powders for reconstitution. Parenteral administration can be accomplished using a needle and syringe or using other technique known in the art. In one embodiment, the Compound of the Disclosure is administered orally to the subject. In one embodiment, the Compound of the Disclosure is administered subcutaneously to the subject. In one embodiment, the Compound of the Disclosure is administered intravenously to the subject.

[0101] The Compound of the Disclosure and pharmaceutical compositions comprising the Compound of the Disclosure may be administered to any subject which may experience the beneficial effects of inhibiting LINE-1 retrotransposition activity. The term "subject" as used herein refers to any human or animal that is in need of or might benefit from

administration of the Compound of the Disclosure. Foremost among such subjects are mammals, e.g., humans, although the methods and compositions provided herein are not intended to be so limited. Other subjects include veterinary animals, e.g., cows, sheep, pigs, horses, dogs, cats and the like. In one embodiment, the subject is a human. In one embodiment, the subject is an animal. In another embodiment, the subject is a human having a disease, condition, or disorder responsive to LINE-1 inhibition.

[0102] The pharmaceutical preparations provided herein are manufactured by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[0103] Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries can be suitable flow-regulating agents and lubricants. Suitable auxiliaries include, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

- [0104] Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are in one embodiment dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.
- [0105] Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.
- [0106] Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of a Compound of the Disclosure may be administered to a subject. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers and other additives.
- [0107] Therapeutically effective amounts of a Compound of the Disclosure formulated in accordance with standard pharmaceutical practices are administered to a subject in need thereof. Whether such a treatment is indicated depends on the individual case and is subject to medical assessment (diagnosis) that takes into consideration signs, symptoms, and/or malfunctions that are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.
- [0108] Pharmaceutical compositions include those wherein a Compound of the Disclosure is administered in an effective amount to achieve its intended purpose. The exact formulation, route of administration, and dosage is determined by an individual physician

in view of the diagnosed condition or disease. Dosage amount and interval can be adjusted individually to provide levels of the Compound of the Disclosure that is sufficient to maintain therapeutic effects.

[0109] Toxicity and therapeutic efficacy of the Compound of the Disclosure can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) of a compound, which defines as the highest dose that causes no toxicity in a subject. The dose ratio between the maximum tolerated dose and therapeutic effects is the therapeutic index. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0110] A therapeutically effective amount of the Compound of the Disclosure required for use in therapy varies with the nature of the disease being treated, the length of time that activity is desired, and the age and the condition of the subject, and ultimately is determined by the attendant physician. For example, dosage amounts and intervals can be adjusted individually to provide plasma levels of a Compound of the Disclosure that are sufficient to maintain the desired therapeutic effects. The desired dose conveniently can be administered in a single dose, or as multiple doses administered at appropriate intervals, for example as one, two, three, four or more subdoses per day.

IV. Kits

[0111] In another embodiment, the present disclosure provides kits comprising a Compound of the Disclosure, or a pharmaceutical composition thereof, and instructions for administering the compound or composition to a subject having a disease, disorder, or condition.

[0112] In another embodiment, the present disclosure provides kits comprising a Compound of the Disclosure, or a pharmaceutical composition thereof, packaged in a manner that facilitates their use to practice methods of the present disclosure.

[0113] In one embodiment, the kit includes a Compound of the Disclosure, or a pharmaceutical composition thereof, packaged in a container, such as a sealed bottle or vessel, with a label affixed to the container or included in the kit that describes use of the compound or composition to practice the method of the disclosure. In one embodiment, the compound or composition is packaged in a unit dosage form. The kit may include a

single dose or multiple doses of a Compound of the Disclosure, or a pharmaceutical composition thereof.

- [0114] In another embodiment, the kit includes a Compound of the Disclosure, or a composition thereof, and one or more optional therapeutic agents.

V. Biomarkers

- [0115] In another embodiment, present disclosure provides methods of treating a subject having a disease, condition, or disorder, the method comprising (a) determining whether a biomarker is present or absent in a biological sample taken from the subject; and (b) administering a therapeutically effective amount of a Compound of the Disclosure to the subject if the biomarker is present in the biological sample.

- [0116] The term "biomarker" as used herein refers to any biological compound, such as a gene, a protein, a fragment of a protein, a peptide, a polypeptide, a nucleic acid, etc., or chromosome abnormality, such as a chromosome translocation, that can be detected and/or quantified in a subject in vivo or in a biological sample obtained from a subject. A biomarker can be the entire intact molecule, or it can be a portion or fragment thereof. In one embodiment, the expression level of the biomarker is measured. The expression level of the biomarker can be measured, for example, by detecting the protein or RNA, e.g., mRNA, level of the biomarker. In some embodiments, portions or fragments of biomarkers can be detected or measured, for example, by an antibody or other specific binding agent. In some embodiments, a measurable aspect of the biomarker is associated with a given state of the subject, such as the subject's age. For biomarkers that are detected at the protein or RNA level, such measurable aspects may include, for example, the presence, absence, or concentration, i.e., expression level, of the biomarker in the subject, or biological sample obtained from the subject. For biomarkers that are detected at the nucleic acid level, such measurable aspects may include, for example, allelic versions of the biomarker or type, rate, and/or degree of mutation of the biomarker, also referred to herein as mutation status.

- [0117] For biomarkers that are detected based on expression level of protein or RNA, expression level measured between different phenotypic statuses can be considered different, for example, if the mean or median expression level of the biomarker in the different groups is calculated to be statistically significant. Common tests for statistical significance include, among others, t-test, ANOVA, Kruskal-Wallis, Wilcoxon, Mann-Whitney, Significance Analysis of Microarrays, odds ratio, etc. Biomarkers, alone or in

combination, provide measures of relative likelihood that a subject belongs to one phenotypic status or another. Therefore, they are useful, inter alia, as markers for disease and as indicators that particular therapeutic treatment regimens will likely result in beneficial patient outcomes. The term "overexpression" indicates that the expression level of the biomarker in the subject having a disease, condition, or disorder is above the mean or median expression level of the biomarker in, e.g., a normal undiseased subject.

[0118] Biomarkers include, but are not limited to, retrotransposon RNA, retrotransposon reverse transcriptase e.g., ORF1p, ORF2p, and/or retrotransposon DNA. In one embodiment, the measurable aspect of the biomarker is its expression status. In another embodiment, the measurable aspect of the biomarker is elevated levels of the biomarker. In one embodiment, the measurable aspect of the biomarker is its mutation status.

[0119] In one embodiment, the biomarker is the expression level of LINE-1. Methods of determining the expression level of LINE-1 are described in US 2020/0253888, and may comprise, for example, determining the level of ORF1p, determining the level of LINE-1 mRNA, determining the amount of LINE-1 in a cell sample of the subject, or determining the level of ORF2p, or a combination thereof.

[0120] In one embodiment, the biomarker is retrotransposon RNA expression which is differentially present in a subject of one phenotypic status, e.g., a subject having an age-associated disease or a neurodegenerative disease, as compared with another phenotypic status, e.g., a normal undiseased subject or a subject having a disease, disorder, or condition without overexpression retrotransposon RNA. In one embodiment, the biomarker is overexpression of retrotransposon RNA.

[0121] In one embodiment, the biomarker is LINE-1 RNA expression which is differentially present in a subject of one phenotypic status, e.g., a subject having an age-associated disease or a neurodegenerative disease, as compared with another phenotypic status, e.g., a normal undiseased subject or a subject having a disease, disorder, or condition without overexpression LINE-1 RNA. In one embodiment, the biomarker is overexpression of LINE-1 RNA.

[0122] In another embodiment, the biomarker is retrotransposon reverse transcriptase which is differentially present in a subject of one phenotypic status, e.g., a subject having an age-associated disease or a neurodegenerative disease, as compared with another phenotypic status, e.g., a normal undiseased subject or a subject having a disease, disorder,

or condition without overexpression of the retrotransposon reverse transcriptase. In one embodiment, the biomarker is overexpression of retrotransposon reverse transcriptase.

[0123] In another embodiment, the biomarker is ORF1p expression which is differentially present in a subject of one phenotypic status, e.g., a subject having an age-associated disease or a neurodegenerative disease, as compared with another phenotypic status, e.g., a normal undiseased subject or a subject having a disease, disorder, or condition without overexpression ORF1p. In one embodiment, the biomarker is overexpression of ORF1p.

[0124] In another embodiment, the biomarker is ORF2p expression which is differentially present in a subject of one phenotypic status, e.g., a subject having an age-associated disease or a neurodegenerative disease, as compared with another phenotypic status, e.g., a normal undiseased subject or a subject having a disease, disorder, or condition without overexpression ORF2p. In one embodiment, the biomarker is overexpression of ORF2p.

[0125] Biomarker standards can be predetermined, determined concurrently, or determined after a biological sample is obtained from the subject. Biomarker standards for use with the methods described herein can, for example, include data from samples from subjects without a neurodegenerative disease; data from samples from subjects with a neurodegenerative disease. Comparisons can be made to establish predetermined threshold biomarker standards for different classes of subjects, e.g., diseased vs. non-diseased subjects. The standards can be run in the same assay or can be known standards from a previous assay.

[0126] In one embodiment, the biomarker is retrotransposon DNA expression which is differentially present in a subject of one phenotypic status, e.g., a subject having an age-associated disease or a neurodegenerative disease, as compared with another phenotypic status, e.g., a normal undiseased subject or a subject having a disease, disorder, or condition without overexpression retrotransposon DNA. In one embodiment, the biomarker is overexpression of retrotransposon DNA. In another embodiment, the biomarker is overexpression of retrotransposon nuclear DNA. In another embodiment, the biomarker is overexpression of retrotransposon cytoplasmic DNA.

[0127] In one embodiment, the biomarker is LINE-1 DNA expression which is differentially present in a subject of one phenotypic status, e.g., a subject having an age-associated disease or a neurodegenerative disease, as compared with another phenotypic status, e.g., a normal undiseased subject or a subject having a disease, disorder,

or condition without overexpression LINE-1 DNA. In one embodiment, the biomarker is overexpression of LINE-1 DNA. In another embodiment, the biomarker is overexpression of LINE-1 nuclear DNA. In another embodiment, the biomarker is overexpression of LINE-1 cytoplasmic DNA.

[0128] A biomarker is differentially present between different phenotypic status groups if the mean or median expression or mutation levels of the biomarker is calculated to be different, i.e., higher or lower, between the groups. Thus, biomarkers provide an indication that a subject, e.g., a subject having ALS, belongs to one phenotypic status or another.

[0129] In addition to individual biological compounds, e.g., LINE-1 RNA, the term "biomarker" as used herein is meant to include groups, sets, or arrays of multiple biological compounds. For example, the combination of LINE-1 RNA overexpression and ORF1p overexpression may comprise a biomarker, or the overexpression of LINE-1 RNA and LINE-1 DNA may comprise a biomarker. The term "biomarker" may comprise one, two, three, four, five, six, seven, eight, nine, ten, fifteen, twenty, twenty five, thirty, or more, biological compounds. In embodiment, the biomarker comprises one, two, or three biological compounds.

[0130] The determination of the expression level or mutation status of a biomarker in a subject can be performed using any of the many methods known in the art. Any method known in the art for quantitating specific proteins and/or detecting biomarker expression, e.g., LINE-1 RNA expression, ORF1p expression, and/or ORF2p expression, or the expression or mutation levels of any other biomarker(s) in a patient or a biological sample may be used in the methods of the disclosure. Examples include, but are not limited to, PCR (polymerase chain reaction), or RT-PCR, flow cytometry, Northern blot, Western blot, ELISA (enzyme linked immunosorbent assay), RIA (radioimmunoassay), gene chip analysis of RNA expression, immunohistochemistry or immunofluorescence. See, e.g., Slagle et al. Cancer 83:1401 (1998). Certain embodiments of the disclosure include methods wherein biomarker RNA expression (transcription) is determined. Other embodiments of the disclosure include methods wherein protein expression in the biological sample is determined. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, (1988); Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, New York 3rd Edition, (1995); Kamel and Al-Amodi, Genomics Proteomics Bioinformatics 15:220–235 (2017).

For northern blot or RT-PCR analysis, RNA is isolated from tissue sample using RNase free techniques. Such techniques are commonly known in the art.

[0131] In one embodiment of the disclosure, a biological sample is obtained from the subject and the biological sample is assayed for determination of a biomarker expression or mutation status.

[0132] In another embodiment of the disclosure, Northern blot analysis of biomarker transcription in a tumor cell sample is performed. Northern analysis is a standard method for detection and/or quantitation of mRNA levels in a sample. Initially, RNA is isolated from a sample to be assayed using Northern blot analysis. In the analysis, the RNA samples are first separated by size via electrophoresis in an agarose gel under denaturing conditions. The RNA is then transferred to a membrane, crosslinked and hybridized with a labeled probe. Typically, Northern hybridization involves polymerizing radiolabeled or nonisotopically labeled DNA, in vitro, or generation of oligonucleotides as hybridization probes. Typically, the membrane holding the RNA sample is prehybridized or blocked prior to probe hybridization to prevent the probe from coating the membrane and, thus, to reduce non-specific background signal. After hybridization, typically, unhybridized probe is removed by washing in several changes of buffer. Stringency of the wash and hybridization conditions can be designed, selected and implemented by any practitioner of ordinary skill in the art. Detection is accomplished using detectably labeled probes and a suitable detection method. Radiolabeled and non-radiolabeled probes and their use are well known in the art. The presence and or relative levels of expression of the biomarker being assayed can be quantified using, for example, densitometry.

[0133] In another embodiment, biomarker expression and/or mutation status is determined using RT-PCR. RT-PCR allows detection of the progress of a PCR amplification of a target gene in real time. Design of the primers and probes required to detect expression and/or mutation status of a biomarker of the disclosure is within the skill of a practitioner of ordinary skill in the art. RT-PCR can be used, for example, to determine the level of RNA encoding a biomarker of the disclosure in a tissue sample. In an embodiment of the disclosure, RNA from the biological sample is isolated, under RNase free conditions, than converted to DNA by treatment with reverse transcriptase. Methods for reverse transcriptase conversion of RNA to DNA are well known in the art. A description of PCR is provided in the following references: Mullis et al., Cold Spring Harbor Symp. Quant.

Biol. 51:263 (1986); EP 50,424; EP 84,796; EP 258,017; EP 237,362; EP 201,184; U.S. Patent Nos. 4,683,202; 4,582,788; 4,683,194.

[0134] RT-PCR probes depend on the 5'-3' nuclease activity of the DNA polymerase used for PCR to hydrolyze an oligonucleotide that is hybridized to the target amplicon (biomarker gene). RT-PCR probes are oligonucleotides that have a fluorescent reporter dye attached to the 5' end and a quencher moiety coupled to the 3' end (or vice versa). These probes are designed to hybridize to an internal region of a PCR product. In the unhybridized state, the proximity of the fluor and the quench molecules prevents the detection of fluorescent signal from the probe. During PCR amplification, when the polymerase replicates a template on which an RT-PCR probe is bound, the 5'-3' nuclease activity of the polymerase cleaves the probe. This decouples the fluorescent and quenching dyes and FRET no longer occurs. Thus, fluorescence increases in each cycle, in a manner proportional to the amount of probe cleavage. Fluorescence signal emitted from the reaction can be measured or followed over time using equipment which is commercially available using routine and conventional techniques.

[0135] In another embodiment of the disclosure, expression of proteins encoded by biomarkers are detected by western blot analysis. A western blot (also known as an immunoblot) is a method for protein detection in a given sample of tissue homogenate or extract. It uses gel electrophoresis to separate denatured proteins by mass. The proteins are then transferred out of the gel and onto a membrane (e.g., nitrocellulose or polyvinylidene fluoride (PVDF)), where they are detected using a primary antibody that specifically bind to the protein. The bound antibody can then detected by a secondary antibody that is conjugated with a detectable label (e.g., biotin, horseradish peroxidase or alkaline phosphatase). Detection of the secondary label signal indicates the presence of the protein.

[0136] In another embodiment of the disclosure, the expression of a protein encoded by a biomarker is detected by enzyme-linked immunosorbent assay (ELISA). In one embodiment of the disclosure, "sandwich ELISA" comprises coating a plate with a capture antibody; adding sample wherein any antigen present binds to the capture antibody; adding a detecting antibody which also binds the antigen; adding an enzyme-linked secondary antibody which binds to detecting antibody; and adding substrate which is converted by an enzyme on the secondary antibody to a detectable form. Detection of the signal from the secondary antibody indicates presence of the biomarker antigen protein.

- [0137] In another embodiment of the disclosure, the expression of a protein, e.g., ORF1p, ORF2p, encoded by a biomarker is detected by a single molecule array assay (Simoa™).
- [0138] In another embodiment of the disclosure, the expression of a protein, e.g., ORF1p, ORF2p, encoded by a biomarker is detected by droplet digital ELISA (ddELISA). Using ddELISA, LINE-1/ORF1p protein can be measured in serum. *See* Cohen et al., *ACS Nano* 14:9491-9501 (2020).

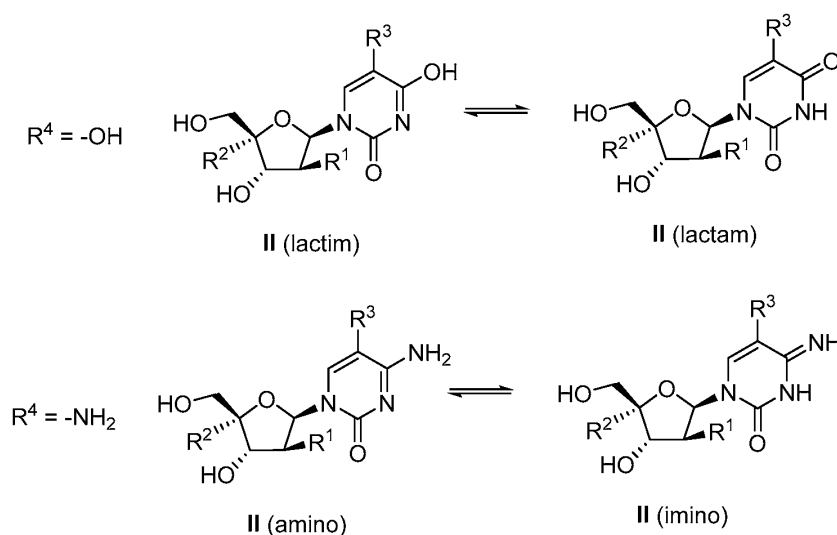
VI. Definitions

- [0139] The term "pathophysiological retrotransposon-associated process" as used herein refers to a disordered physiological process relating to aberrant retrotransposition activity of at least one retrotransposon. Exemplary retrotransposons include, but are not limited to, LINE-1 and human endogenous retroviruses (HERVs), e.g., HERV-K and HERV-E. *See, e.g.,* Saleh et al, (2019) *Front. Neurol.* 10:894. doi: 10.3389/fneur.2019.00894. Diseases, disorders, or conditions caused by a pathophysiological retrotransposon-associated process include, but are not limited to, neurodegenerative diseases, autoimmune diseases, age-associated diseases, autism spectrum disorder (ADS), cardiovascular dysfunction, hearing loss, hematopoietic stem cell function, pulmonary fibrosis, schizophrenia, or vision loss.
- [0140] The term "pathophysiological LINE-1-associated process" as used herein refers to a disordered physiological process relating to aberrant LINE-1 (L1) retrotransposition activity. *See, e.g.,* Saleh et al, (2019) *Front. Neurol.* 10:894. doi: 10.3389/fneur.2019.00894; Zhao et al., *PLoS Genet* 15(4): e1008043. <https://doi.org/10.1371/journal.pgen.1008043>; Bundo et al., *Neuron* 81:306-313 (2014).
- [0141] The term "LINE-1 retrotransposition event that causes a disease, disorder, or condition" as used herein refers to any causal factor, e.g., aberrant transcription, alternative splicing, insertional mutagenesis, DNA damage, chromosomal translocation, increased expression of LINE-1 RNA, ORF1p (a 40 kDa RNA-binding protein), ORF2p (a ~150 kDa protein with endonuclease (EN) and reverse transcriptase (RT) activities) associated with LINE-1 retrotransposition that results in or promotes a pathological condition, e.g., a disease or disorder, in a subject. *See, e.g.,* Beck et al., *Annu Rev Genomics Hum Genet* 12:187-215 (2011); Pizarro and Cristofari (2016) *Front. Cell Dev. Biol.* 4:14, <https://doi.org/10.3389/fcell.2016.00014>. In one embodiment, the LINE-1

retrotransposition event is a somatic LINE-1 insertion. In another embodiment, LINE-1 retrotransposition event is increased expression of LINE-1 RNA in the subject.

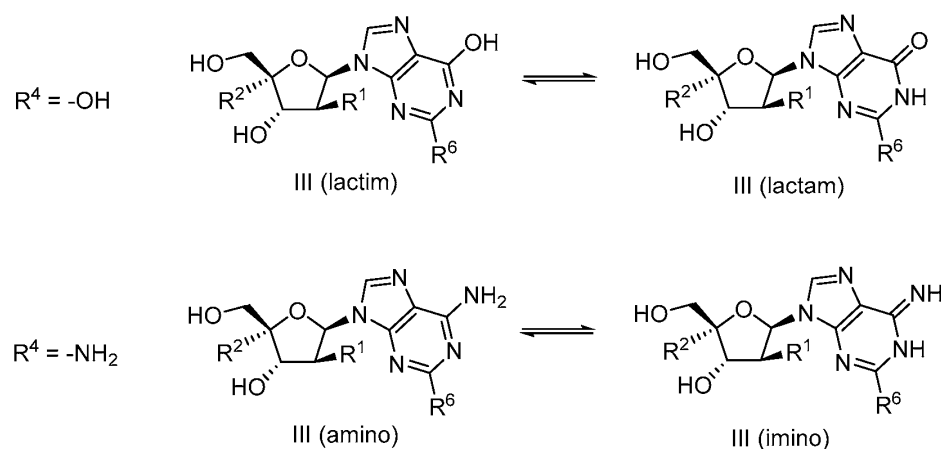
[0142] The term "tautomer" as used herein refers to each of two or more isomers of a compound which exist together in equilibrium, and are interchanged by migration of an atom, e.g., a hydrogen, or group within the molecule. Certain Compounds of the Disclosure may exist as tautomers. In situations where tautomers are possible, the present disclosure includes all tautomeric forms. For example, as illustrated in Chart 1, both the lactim and lactam tautomers are encompassed by Formula II when R⁴ is -OH, and both the amino and imino tautomers are encompassed by Formula II when R⁴ is -NH₂.

Chart 1



Likewise, as illustrated in Chart 2, both the lactim and lactam tautomers are encompassed by Formula III when R⁵ is -OH, and both the amino and imino tautomers are encompassed by Formula III when R⁵ is -NH₂.

Chart 2



The equilibrium arrows in Charts 1 and 2 are not intended to show the position of the equilibrium, only that an equilibrium exists between the two tautomeric forms.

[0143] The term "biological sample" as used herein refers any tissue or fluid from a subject that is suitable for detecting a biomarker. Examples of useful biological samples include, but are not limited to, biopsied tissues and/or cells, e.g., solid tumor, lymph gland, inflamed tissue, tissue and/or cells involved in a condition or disease, blood, plasma, serous fluid, cerebrospinal fluid, saliva, urine, lymph, cerebral spinal fluid, and the like. Other suitable biological samples will be familiar to those of ordinary skill in the relevant arts. A biological sample can be analyzed for the expression level of a biological compound, e.g., LINE-1 RNA, ORF1p protein, ORF2p protein, using any technique known in the art. Such techniques include, but are not limited to, polymerase chain reaction (PCR) methodology, reverse transcription-polymerase chain reaction (RT-PCR) methodology, or cytoplasmic light chain immunofluorescence combined with fluorescence in situ hybridization (cIg-FISH). A biological sample can be obtained using techniques that are well within the scope of ordinary knowledge of a clinical practitioner. In one embodiment of the disclosure, the biological sample comprises a tissue or blood sample.

[0144] The terms "a", "an", "the", and similar referents in the context of describing the disclosure (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated. Recitation of ranges of values herein merely are intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The use

of any and all examples, or exemplary language, e.g., "such as," provided herein, is intended to better illustrate the disclosure and is not a limitation on the scope of the disclosure unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the disclosure.

[0145] The term "about," as used herein, includes the recited number $\pm 10\%$. Thus, "about 10" means 9 to 11.

[0146] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease, disorder, or condition, and/or the symptoms associated therewith. Although not precluded, treating a disease, disorder, or condition does not require that the disease, disorder, or condition, and/or symptom(s) associated therewith be completely eliminated. However, in one embodiment, administration of a Compound of the Disclosure leads to complete elimination of the disease and associated symptoms.

[0147] As used herein, the terms "prevent," "preventing," "prevention" and the like refer to a method of preventing the onset of a disease, disorder, or condition and/or symptom(s) associated therewith, or barring a subject from acquiring the disease, disorder, or condition. The terms "prevent," "preventing," and "prevention" also include delaying the onset of disease, disorder, or condition and/or its attendant symptom(s), and reducing a subject's risk of acquiring the disease, disorder, or condition. The terms "prevent," "preventing" and "prevention" also includes "prophylactic treatment," which refers to reducing the probability of redeveloping the disease, disorder, or condition, or of a recurrence of a previously-controlled disease, disorder, or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping the disease, disorder, or condition or a recurrence of the disease, disorder, or condition. The terms "prevent," "preventing" and "prevention" also include delaying or reversing the progression of the underlying pathology of the disease, disorder, or condition, e.g., a mutation caused by a somatic LINE-1 insertion.

[0148] The term "therapeutically effective amount," as used herein, refers to that amount of a Compound of the Disclosure and, optionally, one or more optional therapeutic agents sufficient to result in amelioration of one or more symptoms of a disease, disorder, or condition, or prevent advancement of a disease, disorder, or condition, or cause regression of a disease, disorder, or condition. For example, a therapeutically effective amount will refer to the amount of a Compound of the Disclosure that causes a therapeutic response,

e.g., delay the progression of the disease, disorder, or condition in subject by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100%, or more.

[0149] The term "container" means any receptacle and closure therefore suitable for storing, shipping, dispensing, and/or handling the Compound of the Disclosure. Non-limiting exemplary containers include vials, ampules, bottles, and syringes.

[0150] The term "insert" means information accompanying a pharmaceutical product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and subject to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

[0151] In some embodiments, when administered in combination, two or more therapeutic agents can have a synergistic effect. The terms "synergy," "synergistic," "synergistically" and derivations thereof, such as in a "synergistic effect" or a "synergistic combination" or a "synergistic composition" as used herein refer to circumstances under which the biological activity of a combination of an agent and at least one additional therapeutic agent is greater than the sum of the biological activities of the respective agents when administered individually. For example, the term "synergistically effective" as used herein refers to the interaction between a Compound of the Disclosure and another therapeutic agent that causes the total effect of the drugs to be greater than the sum of the individual effects of each drug. Berenbaum, *Pharmacological Reviews* 41:93-141 (1989).

[0152] Synergy can be expressed in terms of a "Synergy Index (SI)," which generally can be determined by the method described by F. C. Kull et al. *Applied Microbiology* 9, 538 (1961), from the ratio determined by:

$$Q_a Q_A + Q_b Q_B = \text{Synergy Index (SI)}$$

wherein:

[0153] Q_A is the concentration of a component A, acting alone, which produced an end point in relation to component A;

[0154] Q_a is the concentration of component A, in a mixture, which produced an end point;

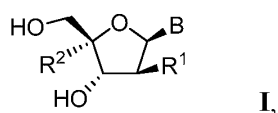
- [0155] Q_B is the concentration of a component B, acting alone, which produced an end point in relation to component B; and
- [0156] Q_b is the concentration of component B, in a mixture, which produced an end point.
- [0157] Generally, when the sum of Q_a/Q_A and Q_b/Q_B is greater than one, antagonism is indicated. When the sum is equal to one, additivity is indicated. When the sum is less than one, synergism is demonstrated. The lower the SI, the greater the synergy shown by that particular mixture. Thus, a "synergistic combination" has an activity higher than what can be expected based on the observed activities of the individual components when used alone. Further, a "synergistically effective amount" of a component refers to the amount of the component necessary to elicit a synergistic effect in, for example, another therapeutic agent present in the composition.
- [0158] The terms "intermittent dose administration," "intermittent dosing schedule," and similar terms as used herein refer to, i.e., not continuous, administration, of a Compound of the Disclosure to a subject.
- [0159] Intermittent dose administration of a Compound of the Disclosure may maintain or efficacy achieved with continuous dosing, but with less side-effects, e.g., less body weight loss. Intermittent dose administration regimens useful in the present disclosure encompass any discontinuous administration regimen that provides a therapeutically effective amount of a Compound of the Disclosure to a subject in need thereof. Intermittent dosing regimens can use equivalent, lower, or higher doses of the Compound of the Disclosure than would be used in continuous dosing regimens. Advantages of intermittent dose administration of a Compound of the Disclosure include, but are not limited to, improved safety, decreased toxicity, e.g., decreased weight loss, increased exposure, increased efficacy, and/or increased subject compliance. These advantages may be realized when the Compound of the Disclosure is administered as a single agent or when administered in combination with one or more optional therapeutic agents. On the day a Compound of the Disclosure is scheduled to be administered to the subject, administration can occur in a single or in divided doses, e.g., once-a-day, twice-a-day, three times a day, four times a day or more. Dosing can also occur via any suitable route, e.g., orally, intravenously, or subcutaneously. In one embodiment, the Compound of the Disclosure is administered to the subject once (QD) or twice (BID) on the day the compound is scheduled to be administered.

[0160] The phrase "in combination" as used in connection with the administration of a Compound of the Disclosure and one or more optional therapeutic agents to a subject means that the Compound of the Disclosure and the one or more optional therapeutic agents can be administered to the subject together, e.g., as part of a single pharmaceutical composition or formulation, or separately, e.g., as part of two or more separate pharmaceutical compositions or formulations. The phrase "in combination" as used in connection with the administration of a Compound of the Disclosure and the one or more optional therapeutic agents to a subject is thus intended to embrace administration of the Compound of the Disclosure and the one or more optional therapeutic agents in a sequential manner, wherein the Compound of the Disclosure and the one or more optional therapeutic agents are administered to the subject at a different time, as well as administration concurrently, or in a substantially simultaneous manner, e.g., less than 30 minutes apart. Simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each of the Compound of the Disclosure and the one or more optional therapeutic agents or in multiple, single capsules for each of the Compound of the Disclosure and the one or more optional therapeutic agents. Sequential or substantially simultaneous administration of the Compound of the Disclosure and the one or more optional therapeutic agents can be accomplished by any appropriate route including, but not limited to, oral routes, intravenous routes, subcutaneous routes, intramuscular routes, etc. The Compound of the Disclosure and the one or more optional therapeutic agents can be administered by the same route or by different routes. For example, the one or more optional therapeutic agents and the Compound of the Disclosure of the combination may be administered orally. Alternatively, for example, the Compound of the Disclosure may be administered orally and the one or more optional therapeutic agents may be administered by intravenous injection. The Compound of the Disclosure and the one or more optional therapeutic agents may also be administered in alternation. In one embodiment, the Compound of the Disclosure and the one or more optional therapeutic agents are administered to a subject separately, e.g., as part of two or more separate pharmaceutical compositions or formulations.

VII. Particular Embodiments

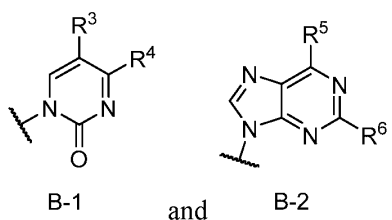
[0161] The disclosure provides the following particular embodiments.

[0162] Embodiment 1. A method of treating or preventing a disease, disorder, or condition caused by a pathophysiological retrotransposon-associated process in a subject in need thereof, and/or treating or preventing a symptom of the disease, disorder, or condition, the method comprising administering to the subject a therapeutically effective amount of (i) a compound of Formula I:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

[0163] B is selected from the group consisting of:



[0164] R¹ is selected from the group consisting of hydrogen and -OH;

[0165] R² is selected from the group consisting of methyl, ethynyl, and -CN;

[0166] R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;

[0167] R⁴ is selected from the group consisting of -NH₂ and -OH;

[0168] R⁵ is selected from the group consisting of -NH₂ and -OH; and

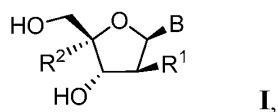
[0169] R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂,

[0170] (ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,

[0171] with provisos that the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.

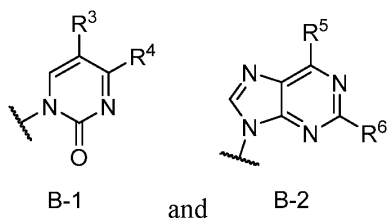
[0172] Embodiment 2. A method of inhibiting a LINE-1 retrotransposition event that causes a disease, disorder, or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of (i) a compound of Formula I:

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or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

[0173] B is selected from the group consisting of:



[0174] R¹ is selected from the group consisting of hydrogen and -OH;

[0175] R² is selected from the group consisting of methyl, ethynyl, and -CN;

[0176] R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;

[0177] R⁴ is selected from the group consisting of -NH₂ and -OH;

[0178] R⁵ is selected from the group consisting of -NH₂ and -OH; and

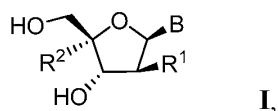
[0179] R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂,

[0180] (ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0181] Embodiment 3. A method of treating a disease, condition, or disorder in a subject, the method comprising:

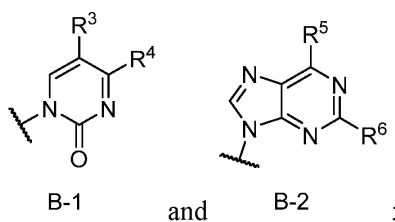
[0182] (a) determining whether an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present or absent in a biological sample taken from the subject; and

[0183] (b) administering a therapeutically effective amount of (i) a compound of Formula I:

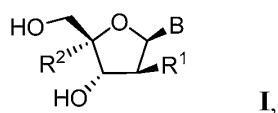


or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

[0184] B is selected from the group consisting of:

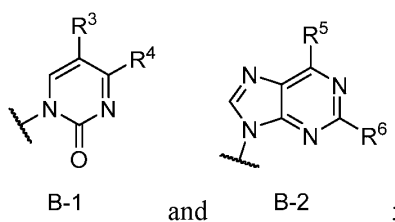


- [0185] R^1 is selected from the group consisting of hydrogen and -OH;
- [0186] R^2 is selected from the group consisting of methyl, ethynyl, and -CN;
- [0187] R^3 is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;
- [0188] R^4 is selected from the group consisting of -NH₂ and -OH;
- [0189] R^5 is selected from the group consisting of -NH₂ and -OH; and
- [0190] R^6 is selected from the group consisting of hydrogen, chloro, and -NH₂;
- [0191] (ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,
- [0192] to the subject if an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present in the biological sample.
- [0193] Embodiment 4. A method of identifying whether a subject having a disease, condition, or disorder is a candidate for treatment with (i) a compound of Formula I:



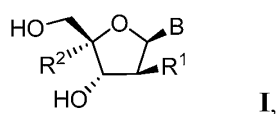
or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

- [0194] B is selected from the group consisting of:



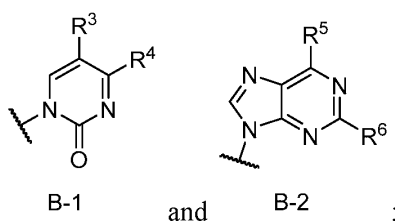
- [0195] R^1 is selected from the group consisting of hydrogen and -OH;
- [0196] R^2 is selected from the group consisting of methyl, ethynyl, and -CN;
- [0197] R^3 is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;

- [0198] R^4 is selected from the group consisting of $-NH_2$ and $-OH$;
- [0199] R^5 is selected from the group consisting of $-NH_2$ and $-OH$; and
- [0200] R^6 is selected from the group consisting of hydrogen, chloro, and $-NH_2$,
- [0201] (ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, the method comprising:
- [0202] (a) determining whether an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present or absent in a biological sample taken from the subject; and
- [0203] (b) identifying the subject as being a candidate for treatment if an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present; or
- [0204] (c) identifying the subject as not being a candidate for treatment if an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is absent.
- [0205] Embodiment 5. A method of predicting treatment outcome in a subject having a disease, condition, or disorder, the method comprising determining whether an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present or absent in a biological sample taken from the subject, wherein:
- [0206] (a) the presence of an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA in the biological sample indicates that administering (i) a compound of Formula I:

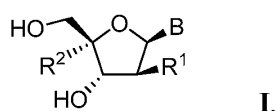


or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

- [0207] B is selected from the group consisting of:

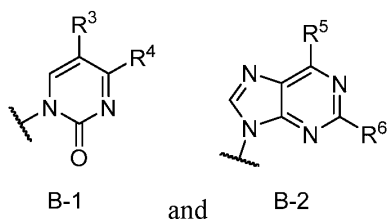


- [0208] R^1 is selected from the group consisting of hydrogen and -OH;
- [0209] R^2 is selected from the group consisting of methyl, ethynyl, and -CN;
- [0210] R^3 is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;
- [0211] R^4 is selected from the group consisting of -NH₂ and -OH;
- [0212] R^5 is selected from the group consisting of -NH₂ and -OH; and
- [0213] R^6 is selected from the group consisting of hydrogen, chloro, and -NH₂,
- [0214] (ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, to the subject will likely cause a favorable therapeutic response; and
- [0215] (b) the absence of an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA in the biological sample indicates that administering (i) the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, (ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, to the subject will likely cause an unfavorable therapeutic response.
- [0216] Embodiment 6. A method, comprising administering a therapeutically effective amount of (i) a compound Formula I:



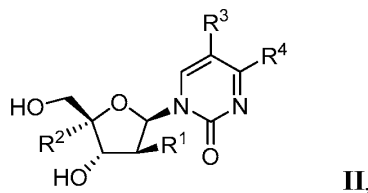
or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

- [0217] B is selected from the group consisting of:



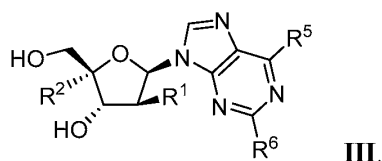
- [0218] R^1 is selected from the group consisting of hydrogen and -OH;
- [0219] R^2 is selected from the group consisting of methyl, ethynyl, and -CN;

- [0220] R^3 is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;
- [0221] R^4 is selected from the group consisting of $-NH_2$ and $-OH$;
- [0222] R^5 is selected from the group consisting of $-NH_2$ and $-OH$; and
- [0223] R^6 is selected from the group consisting of hydrogen, chloro, and $-NH_2$,
- [0224] (ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, to a subject, wherein:
- [0225] (a) the subject has a disease, condition, or disorder; and
- [0226] (b) the disease, condition, or disorder is characterized as having an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA.
- [0227] Embodiment 7. The method of any one of Embodiments 1-6, wherein the compound of Formula I is a compound of Formula II:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

- [0228] Embodiment 8. The method of Embodiment 7, wherein R^3 is hydrogen.
- [0229] Embodiment 9. The method of Embodiment 7, wherein R^3 is selected from the group consisting of fluoro and chloro.
- [0230] Embodiment 10. The method of Embodiment 7, wherein R^3 is methyl.
- [0231] Embodiment 11. The method of any one of Embodiments 7-10, wherein R^4 is $-NH_2$.
- [0232] Embodiment 12. The method of any one of Embodiments 7-10, wherein R^4 is $-OH$.
- [0233] Embodiment 13. The method of any one of Embodiments 1-6, wherein the compound of Formula I is a compound of Formula III:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

- [0234] Embodiment 14. The method of Embodiment 13, wherein R⁵ is -NH₂.
- [0235] Embodiment 15. The method of Embodiment 13, wherein R⁵ is -OH.
- [0236] Embodiment 16. The method of any one of Embodiments 13-15, wherein R⁶ is hydrogen.
- [0237] Embodiment 17. The method of any one of Embodiments 13-15, wherein R⁶ is chloro.
- [0238] Embodiment 18. The method of any one of Embodiments 13-15, wherein R⁶ is -NH₂.
- [0239] Embodiment 19. The method of any one of Embodiments 1-18, wherein R¹ is hydrogen.
- [0240] Embodiment 20. The method of any one of Embodiments 1-18, wherein R¹ is -OH.
- [0241] Embodiment 21. The method of any one of Embodiments 1-20, wherein R² is methyl.
- [0242] Embodiment 22. The method of any one of Embodiments 1-20, wherein R² is ethynyl.
- [0243] Embodiment 23. The method of any one of Embodiments 1-20, wherein R² is -CN.
- [0244] Embodiment 24. The method of any one of Embodiments 1-6, wherein the compound of Formula I is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.
- [0245] Embodiment 25. The method of any one of Embodiments 1 or 7-24 for treating the disease, disorder, or condition in a subject.
- [0246] Embodiment 26. The method of any one of Embodiments 1 or 7-24 for preventing the disease, disorder, or condition in a subject.
- [0247] Embodiment 27. The method of any one of Embodiments 1 or 7-24, for treating the symptom of a disease, disorder, or condition in a subject.
- [0248] Embodiment 28. The method of any one of Embodiments 1 or 7-24, for preventing the symptom of a disease, disorder, or condition in a subject.

- [0249] Embodiment 29. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is a neurodegenerative disease.
- [0250] Embodiment 30. The method of Embodiment 29, wherein the neurodegenerative disease is Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, dementia with Lewy Bodies, multi systems atrophy, Huntington's disease, frontotemporal lobar degeneration, mild cognitive impairment, corticobasal degeneration, progressive supra nuclear palsy, Rett Syndrome, peripheral degenerative disease, or Aicardi-Goutières syndrome.
- [0251] Embodiment 31. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is an autoimmune disease.
- [0252] Embodiment 32. The method of Embodiment 31, wherein the autoimmune disease is lupus, rheumatoid arthritis, Sjogrens syndrome, or multiple sclerosis.
- [0253] Embodiment 33. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is an age-associated disease.
- [0254] Embodiment 34. The method of Embodiment 33, wherein the age-associated disease is Alzheimer's disease, Parkinson's disease, atherosclerosis, osteoarthritis, osteoporosis, rheumatoid arthritis, macular degeneration, peripheral degenerative disease, or skin aging.
- [0255] Embodiment 35. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is autism spectrum disorder (ADS), cardiovascular dysfunction, hearing loss, hematopoietic stem cell function, pulmonary fibrosis, schizophrenia, or vision loss.
- [0256] Embodiment 36. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is progressive supra nuclear palsy.
- [0257] Embodiment 37. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is amyotrophic lateral sclerosis.
- [0258] Embodiment 38. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is Aicardi-Goutières syndrome.
- [0259] Embodiment 39. The method of any one of Embodiments 1-3 or 5-38 further comprising one or more optional therapeutic agents to the subject.
- [0260] Embodiment 40. The method of any one of Embodiments 1-39, wherein the subject is (a) not infected with the HIV virus; (b) not suspected of being infected with the

HIV virus; (c) not being treated for the HIV virus; and/or (d) not being treated to prevent the HIV virus.

- [0261] Embodiment 41. The method of any one of Embodiments 1-40, wherein the compound inhibits human LINE-1 retrotransposition activity with a half maximal inhibitory concentration of 1 μ M or less in an in vitro HeLa cell-based dual-luciferase assay.
- [0262] Embodiment 42. A kit comprising a compound of Formula **I**, *see* Embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:
- [0263] B is selected from the group consisting of B-1 and B-2, *see* Embodiment 1;
- [0264] R¹ is selected from the group consisting of hydrogen and -OH;
- [0265] R² is selected from the group consisting of methyl, ethynyl, and -CN;
- [0266] R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;
- [0267] R⁴ is selected from the group consisting of -NH₂ and -OH;
- [0268] R⁵ is selected from the group consisting of -NH₂ and -OH; and
- [0269] R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂,
- [0270] (ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,
- [0271] and instructions for administering the compound to a subject having a disease, condition, or disorder caused by a pathophysiological retrotransposon-associated process.
- [0272] Embodiment 43. The kit of Embodiment 42, wherein the compound of Formula **I** is a compound of Formula **II**, *see* Embodiment 7, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.
- [0273] Embodiment 44. The kit of Embodiment 43, wherein R³ is hydrogen.
- [0274] Embodiment 45. The kit of Embodiment 43, wherein R³ is selected from the group consisting of fluoro and chloro.
- [0275] Embodiment 46. The kit of Embodiment 43, wherein R³ is methyl.
- [0276] Embodiment 47. The kit of any one of Embodiments 43-46, wherein R⁴ is -NH₂.

- [0277] Embodiment 48. The kit of any one of Embodiments 43-46, wherein R^4 is -OH.
- [0278] Embodiment 49. The kit of Embodiment 42, wherein the compound of Formula **I** is a compound of Formula **III**, *see* Embodiment 13, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.
- [0279] Embodiment 50. The kit of Embodiment 49, wherein R^5 is -NH₂.
- [0280] Embodiment 51. The kit of Embodiment 49, wherein R^5 is -OH.
- [0281] Embodiment 52. The kit of any one of Embodiments 49-51, wherein R^6 is hydrogen.
- [0282] Embodiment 53. The kit of any one of Embodiments 49-51, wherein R^6 is chloro.
- [0283] Embodiment 54. The kit of any one of Embodiments 49-51, wherein R^6 is -NH₂.
- [0284] Embodiment 55. The kit of any one of Embodiments 42-54, wherein R^1 is hydrogen.
- [0285] Embodiment 56. The kit of any one of Embodiments 42-54, wherein R^1 is -OH.
- [0286] Embodiment 57. The kit of any one of Embodiments 42-56, wherein R^2 is methyl.
- [0287] Embodiment 58. The kit of any one of Embodiments 42-56, wherein R^2 is ethynyl.
- [0288] Embodiment 59. The kit of any one of Embodiments 42-56, wherein R^2 is -CN.
- [0289] Embodiment 60. A (i) compound of Formula **I**, *see* Embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:
- [0290] B is selected from the group consisting of B-1 and B-2, *see* Embodiment 1;
- [0291] R^1 is selected from the group consisting of hydrogen and -OH;
- [0292] R^2 is selected from the group consisting of methyl, ethynyl, and -CN;
- [0293] R^3 is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;
- [0294] R^4 is selected from the group consisting of -NH₂ and -OH;
- [0295] R^5 is selected from the group consisting of -NH₂ and -OH; and

- [0296] R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂,
[0297] or a pharmaceutical composition thereof, (ii) compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,
[0298] for use in treating or preventing a disease, disorder, or condition caused by a pathophysiological retrotransposon-associated process in a subject in need thereof, and/or treating or preventing a symptom of the disease, disorder, or condition,
[0299] with provisos that the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.
- [0300] Embodiment 61. A (i) compound of Formula I, *see* Embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:
[0301] B is selected from the group consisting of B-1 and B-2, *see* Embodiment 1;
[0302] R¹ is selected from the group consisting of hydrogen and -OH;
[0303] R² is selected from the group consisting of methyl, ethynyl, and -CN;
[0304] R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;
[0305] R⁴ is selected from the group consisting of -NH₂ and -OH;
[0306] R⁵ is selected from the group consisting of -NH₂ and -OH; and
[0307] R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂,
[0308] or a pharmaceutical composition thereof, (ii) compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,
[0309] for use in inhibiting a LINE-1 retrotransposition event that causes a disease, disorder, or condition in a subject in need thereof.
- [0310] Embodiment 62. A (i) compound of Formula I, *see* Embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:
[0311] B is selected from the group consisting of B-1 and B-2, *see* Embodiment 1;
[0312] R¹ is selected from the group consisting of hydrogen and -OH;
[0313] R² is selected from the group consisting of methyl, ethynyl, and -CN;
[0314] R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;
[0315] R⁴ is selected from the group consisting of -NH₂ and -OH;

- [0316] R⁵ is selected from the group consisting of -NH₂ and -OH; and
- [0317] R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂,
- [0318] or a pharmaceutical composition thereof, (ii) compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,
- [0319] for use in treating a disease, condition, or disorder is characterized as having an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA.
- [0320] Embodiment 63. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-62, wherein the compound of Formula **I** is a compound of Formula **II**, *see* Embodiment 7, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.
- [0321] Embodiment 64. The compound, or pharmaceutical composition thereof, for use of Embodiment 63, wherein R³ is hydrogen.
- [0322] Embodiment 65. The compound, or pharmaceutical composition thereof, for use of Embodiment 63, wherein R³ is selected from the group consisting of fluoro and chloro.
- [0323] Embodiment 66. The compound, or pharmaceutical composition thereof, for use of Embodiment 63, wherein R³ is methyl.
- [0324] Embodiment 67. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 63-66, wherein R⁴ is -NH₂.
- [0325] Embodiment 68. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 63-66, wherein R⁴ is -OH.
- [0326] Embodiment 69. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-62, wherein the compound of Formula **I** is a compound of Formula **III**, *see* Embodiment 13, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.
- [0327] Embodiment 70. The compound, or pharmaceutical composition thereof, for use of Embodiment 69, wherein R⁵ is -NH₂.
- [0328] Embodiment 71. The compound, or pharmaceutical composition thereof, for use of Embodiment 69, wherein R⁵ is -OH.

- [0329] Embodiment 72. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 69-71, wherein R^6 is hydrogen.
- [0330] Embodiment 73. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 69-71, wherein R^6 is chloro.
- [0331] Embodiment 74. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 69-71, wherein R^6 is $-NH_2$.
- [0332] Embodiment 75. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-75, wherein R^1 is hydrogen.
- [0333] Embodiment 76. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-75, wherein R^1 is $-OH$.
- [0334] Embodiment 77. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-76, wherein R^2 is methyl.
- [0335] Embodiment 78. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-76, wherein R^2 is ethynyl.
- [0336] Embodiment 79. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-76, wherein R^2 is $-CN$.
- [0337] Embodiment 80. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-62, wherein the compound of Formula I is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.
- [0338] Embodiment 81. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60 or 63-80 for treating the disease, disorder, or condition in a subject.
- [0339] Embodiment 82. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60 or 63-80 for preventing the disease, disorder, or condition in a subject.
- [0340] Embodiment 83. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60 or 63-80, for treating the symptom of a disease, disorder, or condition in a subject.
- [0341] Embodiment 84. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60 or 63-80, for preventing the symptom of a disease, disorder, or condition in a subject.

- [0342] Embodiment 85. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-84, wherein the disease, disorder, or condition is a neurodegenerative disease.
- [0343] Embodiment 86. The compound, or pharmaceutical composition thereof, for use of Embodiment 85, wherein the neurodegenerative disease is Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, dementia with Lewy Bodies, multi systems atrophy, Huntington's disease, frontotemporal lobar degeneration, mild cognitive impairment, corticobasal degeneration, progressive supra nuclear palsy, Rett Syndrome, peripheral degenerative disease, or Aicardi-Goutières syndrome.
- [0344] Embodiment 87. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-84, wherein the disease, disorder, or condition is an autoimmune disease.
- [0345] Embodiment 88. The compound, or pharmaceutical composition thereof, for use of Embodiment 87, wherein the autoimmune disease is lupus, rheumatoid arthritis, Sjogrens syndrome, or multiple sclerosis.
- [0346] Embodiment 89. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-84, wherein the disease, disorder, or condition is an age-associated disease.
- [0347] Embodiment 90. The compound, or pharmaceutical composition thereof, for use of Embodiment 89, wherein the age-associated disease is Alzheimer's disease, Parkinson's disease, atherosclerosis, osteoarthritis, osteoporosis, rheumatoid arthritis, macular degeneration, peripheral degenerative disease, or skin aging.
- [0348] Embodiment 91. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-84, wherein the disease, disorder, or condition is autism spectrum disorder (ADS), cardiovascular dysfunction, hearing loss, hematopoietic stem cell function, pulmonary fibrosis, schizophrenia, or vision loss.
- [0349] Embodiment 92. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-84, wherein the disease, disorder, or condition is progressive supra nuclear palsy.
- [0350] Embodiment 93. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-84, wherein the disease, disorder, or condition is amyotrophic lateral sclerosis.

- [0351] Embodiment 94. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-84, wherein the disease, disorder, or condition is Aicardi-Goutières syndrome.
- [0352] Embodiment 95. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-94 wherein one or more optional therapeutic agents is to be administered to the subject.
- [0353] Embodiment 96. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-95, wherein the subject is (a) not infected with the HIV virus; (b) not suspected of being infected with the HIV virus; (c) not being treated for the HIV virus; and/or (d) not being treated to prevent the HIV virus.
- [0354] Embodiment 97. The compound, or pharmaceutical composition thereof, for use of any one of Embodiments 60-96, wherein the compound inhibits human LINE-1 retrotransposition activity with a half maximal inhibitory concentration of 1 μ M or less in an in vitro HeLa cell-based dual-luciferase assay.
- [0355] Embodiment 98. The compound, or pharmaceutical composition thereof, for use of Embodiment 97, wherein the compound inhibits human LINE-1 retrotransposition activity with a half maximal inhibitory concentration of 0.25 μ M or less in an in vitro HeLa cell-based dual-luciferase assay.
- [0356] Embodiment 99. The compound for use of any one of Embodiments 60-98.
- [0357] Embodiment 100. The pharmaceutical composition for use of any one of Embodiments 60-98.
- [0358] Embodiment 101. Use of (i) a compound of Formula I, *see* Embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:
- [0359] B is selected from the group consisting of B-1 and B-2, *see* above;
- [0360] R¹ is selected from the group consisting of hydrogen and -OH;
- [0361] R² is selected from the group consisting of methyl, ethynyl, and -CN;
- [0362] R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;
- [0363] R⁴ is selected from the group consisting of -NH₂ and -OH;
- [0364] R⁵ is selected from the group consisting of -NH₂ and -OH; and
- [0365] R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂,

- [0366] or a pharmaceutical composition thereof, (ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,
- [0367] for the manufacture of a medicament for treating or preventing a disease, disorder, or condition caused by a pathophysiological retrotransposon-associated process in a subject in need thereof, and/or treating or preventing a symptom of the disease, disorder, or condition, with provisos that the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.
- [0368] Embodiment 102. Use of (i) a compound of Formula I, *see* Embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:
- [0369] B is selected from the group consisting of B-1 and B-2, *see* above;
- [0370] R¹ is selected from the group consisting of hydrogen and -OH;
- [0371] R² is selected from the group consisting of methyl, ethynyl, and -CN;
- [0372] R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;
- [0373] R⁴ is selected from the group consisting of -NH₂ and -OH;
- [0374] R⁵ is selected from the group consisting of -NH₂ and -OH; and
- [0375] R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂,
- [0376] or a pharmaceutical composition thereof, (ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, for the manufacture of a medicament for inhibiting a LINE-1 retrotransposition event that causes a disease, disorder, or condition in a subject in need thereof.
- [0377] Embodiment 103. Use of (i) a compound of Formula I, *see* Embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:
- [0378] B is selected from the group consisting of B-1 and B-2, *see* above;
- [0379] R¹ is selected from the group consisting of hydrogen and -OH;
- [0380] R² is selected from the group consisting of methyl, ethynyl, and -CN;
- [0381] R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;

- [0382] R^4 is selected from the group consisting of $-NH_2$ and $-OH$;
- [0383] R^5 is selected from the group consisting of $-NH_2$ and $-OH$; and
- [0384] R^6 is selected from the group consisting of hydrogen, chloro, and $-NH_2$,
- [0385] or a pharmaceutical composition thereof, (ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or (iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, for the manufacture of a medicament for treating a disease, condition, or disorder is characterized as having an overexpression retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA.
- [0386] Embodiment 104. The use of any one of Embodiments 101-103, wherein the compound of Formula **I** is a compound of Formula **II**, *see* Embodiment 7, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.
- [0387] Embodiment 105. The use of Embodiment 104, wherein R^3 is hydrogen.
- [0388] Embodiment 106. The use of Embodiment 104, wherein R^3 is selected from the group consisting of fluoro and chloro.
- [0389] Embodiment 107. The use of Embodiment 104, wherein R^3 is methyl.
- [0390] Embodiment 108. The use of any one of Embodiments 104-107, wherein R^4 is $-NH_2$.
- [0391] Embodiment 109. The use of any one of Embodiments 104-107, wherein R^4 is $-OH$.
- [0392] Embodiment 110. The use of any one of Embodiments 101-103, wherein the compound of Formula **I** is a compound of Formula **III**, *see* Embodiment 13, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.
- [0393] Embodiment 111. The use of Embodiment 110, wherein R^5 is $-NH_2$.
- [0394] Embodiment 112. The use of Embodiment 110, wherein R^5 is $-OH$.
- [0395] Embodiment 113. The use of any one of Embodiments 110-112, wherein R^6 is hydrogen.
- [0396] Embodiment 114. The use of any one of Embodiments 110-112, wherein R^6 is chloro.
- [0397] Embodiment 115. The use of any one of Embodiments 110-112, wherein R^6 is $-NH_2$.

- [0398] Embodiment 116. The use of any one of Embodiments 101-115, wherein R^1 is hydrogen.
- [0399] Embodiment 117. The use of any one of Embodiments 101-115, wherein R^1 is -OH.
- [0400] Embodiment 118. The use of any one of Embodiments 1-117, wherein R^2 is methyl.
- [0401] Embodiment 119. The use of any one of Embodiments 101-117, wherein R^2 is ethynyl.
- [0402] Embodiment 120. The use of any one of Embodiments 101-117, wherein R^2 is -CN.
- [0403] Embodiment 121. The use of any one of Embodiments 101-103, wherein the compound of Formula I is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.
- [0404] Embodiment 122. The use of any one of Embodiments 101 or 104-121 for treating the disease, disorder, or condition in a subject.
- [0405] Embodiment 123. The use of any one of Embodiments 101 or 104-121 for preventing the disease, disorder, or condition in a subject.
- [0406] Embodiment 124. The use of any one of Embodiments 101 or 104-121, for treating the symptom of a disease, disorder, or condition in a subject.
- [0407] Embodiment 125. The use of any one of Embodiments 101 or 104-121, for preventing the symptom of a disease, disorder, or condition in a subject.
- [0408] Embodiment 126. The use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is a neurodegenerative disease.
- [0409] Embodiment 127. The use of Embodiment 126, wherein the neurodegenerative disease is Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, dementia with Lewy Bodies, multi systems atrophy, Huntington's disease, frontotemporal lobar degeneration, mild cognitive impairment, corticobasal degeneration, progressive supra nuclear palsy, Rett Syndrome, peripheral degenerative disease, or Aicardi-Goutières syndrome.
- [0410] Embodiment 128. The use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is an autoimmune disease.

- [0411] Embodiment 129. The use of Embodiment 128, wherein the autoimmune disease is lupus, rheumatoid arthritis, Sjogrens syndrome, or multiple sclerosis.
- [0412] Embodiment 130. The use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is an age-associated disease.
- [0413] Embodiment 131. The use of Embodiment 130, wherein the age-associated disease is Alzheimer's disease, Parkinson's disease, atherosclerosis, osteoarthritis, osteoporosis, rheumatoid arthritis, macular degeneration, peripheral degenerative disease, or skin aging.
- [0414] Embodiment 132. The use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is autism spectrum disorder (ADS), cardiovascular dysfunction, hearing loss, hematopoietic stem cell function, pulmonary fibrosis, schizophrenia, or vision loss.
- [0415] Embodiment 133. The use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is progressive supra nuclear palsy.
- [0416] Embodiment 134. The use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is amyotrophic lateral sclerosis.
- [0417] Embodiment 135. The use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is Aicardi-Goutières syndrome.
- [0418] Embodiment 136. The use of any one of Embodiments 101-135 wherein one or more optional therapeutic agents is to be administered to the subject.
- [0419] Embodiment 137. The use of any one of Embodiments 101-136, wherein the subject is (a) not infected with the HIV virus; (b) not suspected of being infected with the HIV virus; (c) not being treated for the HIV virus; and/or (d) not being treated to prevent the HIV virus.
- [0420] Embodiment 138. The use of any one of Embodiments 101-137, wherein the compound inhibits human LINE-1 retrotransposition activity with a half maximal inhibitory concentration of 1 μ M or less in an in vitro HeLa cell-based dual-luciferase assay.
- [0421] Embodiment 139. The method of any one of Embodiments 3-6, wherein the retrotransposon RNA is LINE-1 RNA.
- [0422] Embodiment 140. The method of any one of Embodiments 3-6, wherein the retrotransposon reverse transcriptase is ORF2p.

- [0423] Embodiment 141. The method of any one of Embodiments 3-6, wherein the retrotransposon DNA is LINE-1 DNA.
- [0424] Embodiment 142. The compound for use of Embodiment 62, wherein the retrotransposon RNA is LINE-1 RNA.
- [0425] Embodiment 143. The compound for use of Embodiment 62, wherein the retrotransposon reverse transcriptase is ORF2p.
- [0426] Embodiment 144. The compound for use of Embodiment 62, wherein the retrotransposon DNA is LINE-1 DNA.
- [0427] Embodiment 145. The use of Embodiment 103, wherein the retrotransposon RNA is LINE-1 RNA.
- [0428] Embodiment 146. The use of Embodiment 103, wherein the retrotransposon reverse transcriptase is ORF2p.
- [0429] Embodiment 147. The use of Embodiment 103, wherein the retrotransposon DNA is LINE-1 DNA.
- [0430] Embodiment 148. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is ataxia-telangiectasia.
- [0431] Embodiment 149. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is age-related macular degeneration.
- [0432] Embodiment 150. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is systemic lupus erythematosus.
- [0433] Embodiment 151. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is IFN-associated autoimmune disease.
- [0434] Embodiment 152. The method of Embodiment 151, wherein the IFN-associated autoimmune disease is psoriasis.
- [0435] Embodiment 153. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is Fanconi Anemia.
- [0436] Embodiment 154. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is idiopathic pulmonary fibrosis.
- [0437] Embodiment 155. The method of any one of Embodiments 1-28, wherein the disease, disorder, or condition is cardiovascular disease.
- [0438] Embodiment 156. The compound for use of any one of Embodiments 60-82, wherein the disease, disorder, or condition is ataxia-telangiectasia.

- [0439] Embodiment 157. The compound for use of any one of Embodiments 60-82, wherein the disease, disorder, or condition is age-related macular degeneration.
- [0440] Embodiment 158. The compound for use of any one of Embodiments 60-82, wherein the disease, disorder, or condition is systemic lupus erythematosus.
- [0441] Embodiment 159. The compound for use of any one of Embodiments 60-82, wherein the disease, disorder, or condition is IFN-associated autoimmune disease.
- [0442] Embodiment 160. The compound for use of Embodiment 159, wherein the IFN-associated autoimmune disease is psoriasis.
- [0443] Embodiment 161. The compound for use of any one of Embodiments 60-82, wherein the disease, disorder, or condition is Fanconi Anemia.
- [0444] Embodiment 162. The compound for use of any one of Embodiments 60-82, wherein the disease, disorder, or condition is idiopathic pulmonary fibrosis.
- [0445] Embodiment 163. The compound for use of any one of Embodiments 60-82, wherein the disease, disorder, or condition is cardiovascular disease.
- [0446] Embodiment 164. The compound for use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is ataxia-telangiectasia.
- [0447] Embodiment 165. The compound for use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is age-related macular degeneration.
- [0448] Embodiment 166. The compound for use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is systemic lupus erythematosus.
- [0449] Embodiment 167. The compound for use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is IFN-associated autoimmune disease.
- [0450] Embodiment 168. The compound for use of Embodiment 167, wherein the IFN-associated autoimmune disease is psoriasis.
- [0451] Embodiment 169. The compound for use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is Fanconi Anemia.
- [0452] Embodiment 170. The compound for use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is idiopathic pulmonary fibrosis.
- [0453] Embodiment 171. The compound for use of any one of Embodiments 101-125, wherein the disease, disorder, or condition is cardiovascular disease.

- [0454] Embodiment 172. The method, kit, compound for use, or use of any one of Embodiments 2-59, 61-100, or 102-171, wherein the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.
- [0455] The disclosure provides the following particular embodiments.
- [0456] Embodiment 1'. A method of treating or preventing a disease, disorder, or condition caused by a pathophysiological retrotransposon-associated process in a subject in need thereof, and/or treating or preventing a symptom of the disease, disorder, or condition, the method comprising administering to the subject a therapeutically effective amount of a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or tenofovir alafenamide, wherein the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.
- [0457] Embodiment 2'. A method of inhibiting a LINE-1 retrotransposition event that causes a disease, disorder, or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or tenofovir alafenamide wherein the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.
- [0458] Embodiment 3'. A method of treating a disease, condition, or disorder in a subject, the method comprising:
- [0459] (a) determining whether an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present or absent in a biological sample taken from the subject; and
- [0460] (b) administering a therapeutically effective amount of a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or tenofovir alafenamide, to the subject if an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present in the biological sample, wherein the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.

- [0461] Embodiment 4'. A method of identifying whether a subject having a disease, condition, or disorder is a candidate for treatment with a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or tenofovir alafenamide, the method comprising:
- [0462] (a) determining whether an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present or absent in a biological sample taken from the subject; and
- [0463] (b) identifying the subject as being a candidate for treatment if an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present; or
- [0464] (c) identifying the subject as not being a candidate for treatment if an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is absent,
- [0465] wherein the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.
- [0466] Embodiment 5'. A method of predicting treatment outcome in a subject having a disease, condition, or disorder, the method comprising determining whether an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present or absent in a biological sample taken from the subject, wherein:
- [0467] (a) the presence of an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA in the biological sample indicates that administering a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or tenofovir alafenamide, to the subject will likely cause a favorable therapeutic response; and
- [0468] (b) the absence of an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA in the biological sample indicates that administering a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or tenofovir alafenamide, to the subject will likely cause a favorable therapeutic response; and

thereof, or a tautomer thereof, or tenofovir alafenamide, to the subject will likely cause an unfavorable therapeutic response,

[0469] wherein the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.

[0470] Embodiment 6. A method, comprising administering a therapeutically effective amount of a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or tenofovir alafenamide, wherein:

[0471] (a) the subject has a disease, condition, or disorder; and

[0472] (b) the disease, condition, or disorder is characterized as having an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA,

[0473] wherein the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.

[0474] Embodiment 7. The method of Embodiment 1' for treating the disease, disorder, or condition in a subject.

[0475] Embodiment 8. The method of Embodiment 1' for preventing the disease, disorder, or condition in a subject.

[0476] Embodiment 9. The method of Embodiment 1' for treating the symptom of a disease, disorder, or condition in a subject.

[0477] Embodiment 10'. The method of Embodiment 1' for preventing the symptom of a disease, disorder, or condition in a subject.

[0478] Embodiment 11'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is a neurodegenerative disease.

[0479] Embodiment 12'. The method of Embodiment 11', wherein the neurodegenerative disease is Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, dementia with Lewy Bodies, multi systems atrophy, Huntington's disease, frontotemporal lobar degeneration, mild cognitive impairment, corticobasal degeneration, progressive supra nuclear palsy, Rett Syndrome, peripheral degenerative disease, or Aicardi-Goutières syndrome.

[0480] Embodiment 13. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is an autoimmune disease.

- [0481] Embodiment 14'. The method of Embodiment 13', wherein the autoimmune disease is lupus, rheumatoid arthritis, Sjogrens syndrome, or multiple sclerosis.
- [0482] Embodiment 15'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is an age-associated disease.
- [0483] Embodiment 16'. The method of Embodiment 15', wherein the age-associated disease is Alzheimer's disease, Parkinson's disease, atherosclerosis, osteoarthritis, osteoporosis, rheumatoid arthritis, macular degeneration, peripheral degenerative disease, or skin aging.
- [0484] Embodiment 17'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is autism spectrum disorder (ADS), cardiovascular dysfunction, hearing loss, hematopoietic stem cell function, pulmonary fibrosis, schizophrenia, or vision loss.
- [0485] Embodiment 18'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is progressive supra nuclear palsy.
- [0486] Embodiment 19'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is amyotrophic lateral sclerosis.
- [0487] Embodiment 20'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is Aicardi-Goutières syndrome.
- [0488] Embodiment 21'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is ataxia-telangiectasia.
- [0489] Embodiment 22'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is age-related macular degeneration.
- [0490] Embodiment 23'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is systemic lupus erythematosus.
- [0491] Embodiment 24'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is IFN-associated autoimmune disease.
- [0492] Embodiment 25'. The method of Embodiment 24', wherein the IFN-associated autoimmune disease is psoriasis.
- [0493] Embodiment 26'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is Fanconi Anemia.
- [0494] Embodiment 27'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is idiopathic pulmonary fibrosis.

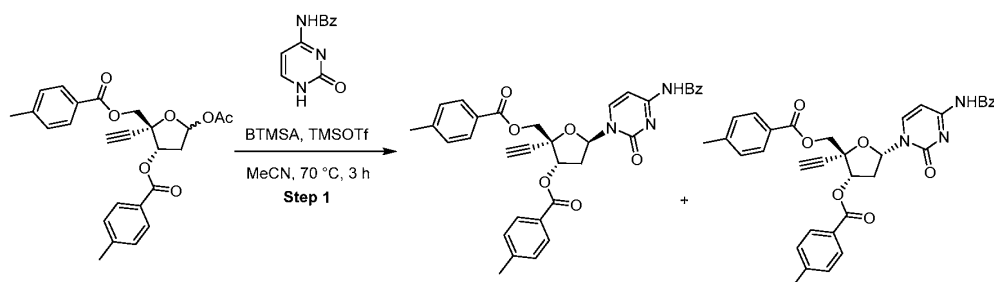
- [0495] Embodiment 28'. The method of any one of Embodiments 1'-10', wherein the disease, disorder, or condition is cardiovascular disease.
- [0496] Embodiment 29'. The method of any one of Embodiments 1'-3 or 5'-28' further comprising one or more optional therapeutic agents to the subject.
- [0497] Embodiment 30'. The method of any one of Embodiments 1'-29', wherein the subject is (a) not infected with the HIV virus; (b) not suspected of being infected with the HIV virus; (c) not being treated for the HIV virus; and/or (d) not being treated to prevent the HIV virus.
- [0498] Embodiment 31'. The method of any one of Embodiments 1'-30', wherein the compound inhibits human LINE-1 retrotransposition activity with a half maximal inhibitory concentration of 1 μ M or less in an in vitro HeLa cell-based dual-luciferase assay.

EXAMPLES

EXAMPLE 1

Synthesis of 4-amino-1-((2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one (Compound 7)

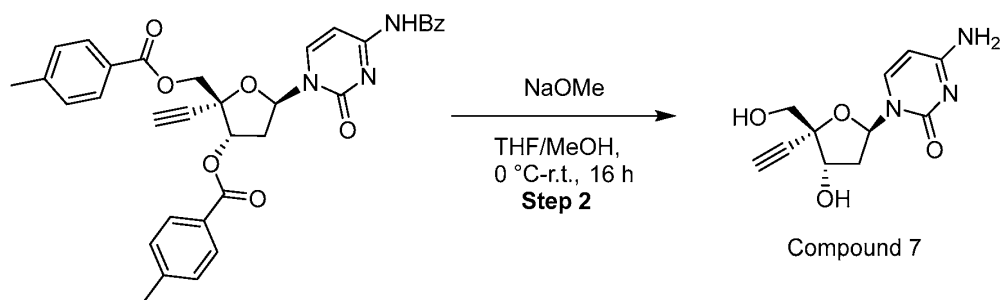
- [0499] Step 1: Synthesis of (2*R*,3*S*,5*R*)-5-(4-benzamido-2-oxopyrimidin-1(2*H*)-yl)-2-ethynyl-2-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate and (2*R*,3*S*,5*S*)-5-(4-benzamido-2-oxopyrimidin-1(2*H*)-yl)-2-ethynyl-2-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate



- [0500] To a solution of *N*-(2-oxo-1*H*-pyrimidin-4-yl)benzamide (118 mg, 0.55 mmol), *see* McLaughlin et al., *Organic Letters* 19:926-929 (2017), in MeCN (20 mL) was added bis(trimethylsilyl)acetylene (BTMSA) (234 mg, 1.37 mmol) at room temperature. The resulting mixture was heated at 70 °C for 1 h. After cooling to room temperature, trimethylsilyl trifluoromethanesulfonate (TMSOTf) (122 mg, 0.55 mmol) was

added and the mixture was reheated to 70 °C, then a solution of [(2*R*,3*S*)-5-acetoxy-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (200 mg, 0.46 mmol) in MeCN (5 mL) was added dropwise. After stirring at 70 °C for 2 h, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (50 mL x 2). The layers were separated, and the organic layer was concentrated. The residue was purified by prep-TLC eluting with 50 % EtOAc in petroleum ether to give [(2*R*,3*S*,5*R*)-5-(4-benzamido-2-oxo-pyrimidin-1-yl)-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (R_f = 0.5) (60 mg, 22% yield) as a white solid and [(2*R*,3*S*,5*S*)-5-(4-benzamido-2-oxo-pyrimidin-1-yl)-2-ethynyl-3-(4-methyl benzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (R_f = 0.4) (60 mg, 22% yield) as a white solid.

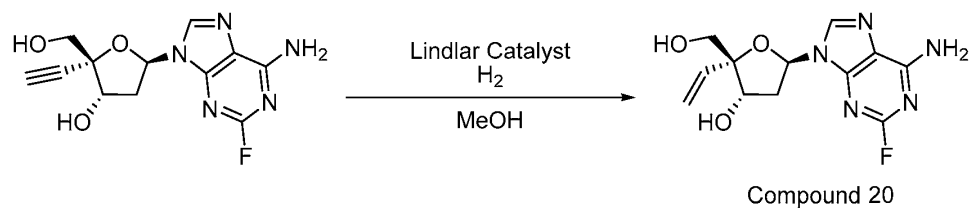
[0501] Step 2: Synthesis of 4-amino-1-((2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one



[0502] To a mixture of [(2*R*,3*S*,5*R*)-5-(4-benzamido-2-oxo-pyrimidin-1-yl)-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (60 mg, 0.1 mmol) in THF (5 mL) was added dropwise a solution of NaOMe (7 mg, 0.13 mmol) in MeOH (2 mL) at 0 °C, then the resulting mixture was stirred at room temperature for 16 h. After that, the reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford Compound 7 (8.8 mg, 34% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 7.77 (d, J = 7.2 Hz, 1H), 7.17 - 7.11 (m, 2H), 6.15 - 6.12 (m, 1H), 5.71 (d, J = 7.2 Hz, 1H), 5.46 (s, 1H), 5.39 (s, 1H), 4.30 - 4.29 (m, 1H), 3.60 - 3.50 (m, 2H), 3.48 (s, 1H), 2.26 - 2.20 (m, 1H), 2.10 - 2.01 (m, 1H). LCMS (ESI): m/z 252.2 ($M+H$) $^+$.

EXAMPLE 2

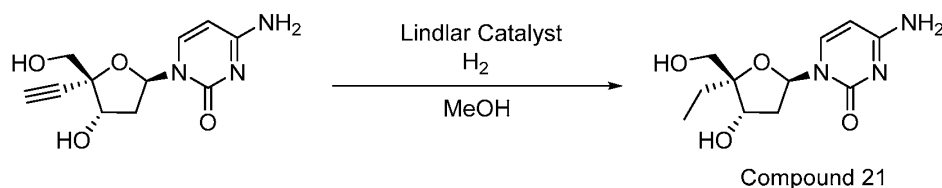
Synthesis of (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-(hydroxymethyl)-2-vinyltetrahydrofuran-3-ol (Compound 20)



[0503] (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (79.3 mg, 270 μ mol) and Lindlar Catalyst (10.0 mg, 270 μ mol) were solubilized in MeOH (5.00 mL) at room temperature. Nitrogen atmosphere was bubbled through the solution for 10 min and then hydrogen was bubbled through the solution for 1 h using a balloon. The reaction was sealed and stirred for 18 h at room temperature. Then, nitrogen atmosphere was bubbled through the solution for 5 min, then the resulting mixture was filtered over a Celite® pad and it was rinsed with MeOH (15 mL). The filtrate was concentrated. The desired product was purified by prep-HPLC using a XBridge Prep C18, 5 μ m 19 x 10 mm pre-column, CSH Prep C18 OBD, 5 μ m, 30 x 75 mm column with MeOH (Eluent B) and AmF pH 3.8 (Eluent A) using an isocratic at 5% B for 1 min pre-run and a gradient of 5% B isocratic for 1min, 5% B to 25% B for 11 minutes, 25% B to 100% B for 0.1 minute, hold 100% B for 2.9 minutes with a 45 mL/min flowrate and a 15 min runtime, affording (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-(hydroxymethyl)-2-vinyltetrahydrofuran-3-ol (42.4 mg, 59%). LC-MS (ESI) m/z calcd for $C_{12}H_{14}FN_5O_3$: 295.1. Found 296.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6): δ 8.36 (s, 1H), 7.82 (br s, 1H), 6.24 - 6.22 (m, 1H), 5.99 - 5.92 (m, 1H), 5.41 - 5.36 (m, 1H), 5.31 - 5.30 (m, 1H), 5.23 - 5.20 (m, 1H), 5.11 (m, 1H), 4.64 (q, J = 6.0 Hz, 1H), 3.52 - 3.48 (m, 2H), 2.60 - 2.57 (m, 1H), 2.29 - 2.22 (m, 1H).

EXAMPLE 3

Synthesis of 4-amino-1-((2R,4S,5R)-5-ethyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (Compound 21)



- [0504]** 4-amino-1-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (7.20 mg, 28.7 μ mol) was dissolved in MeOH in a 5-mL vial with a rubber septum. Then solid Lindlar Catalyst (7.20 mg, 28.7 μ mol) was added and the reaction mixture was flushed with H₂ balloon for 30 min. This reaction was stirred till full conversion to the title compound was observed by LC-MS. Then the reaction mixture was filtered through Celite® and washed with MeOH and the solvent was removed under reduced pressure, affording 4-amino-1-((2R,4S,5R)-5-ethyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (2.85 mg, 39 %) as an off-white powder. LC-MS (ESI) m/z calcd for C₁₁H₁₆N₃O₄: 254.12. Found 254.4 [M-H]⁻. ¹H-NMR (400 MHz, CD₃OD) δ 8.05 (d, J = 7.6 Hz, 1H), 6.21 – 6.06 (m, 1H), 5.95 – 5.77 (d, J = 5.8 Hz, 1H), 4.41 – 4.33 (m, 1H), 3.73 – 3.60 (m, 1H), 3.60 – 3.47 (m, 1H), 2.52 – 2.11 (m, 1H), 1.85 – 1.47 (m, 1H), 1.04 – 0.84 (m, 5H).

EXAMPLE 4

Human LINE-1 Retrotransposition Assay

- [0505]** Representative Compounds of the Disclosure were tested for inhibition of retrotransposition activity of human LINE-1 in HeLa cells according to the following procedure.
- [0506]** HeLa cervical cancer cells were cultivated at 37°C in a humidified 5% CO₂ incubator in Dulbecco's Modified Eagle's Medium (DMEM) - high glucose, with 4500 mg/L glucose, L-glutamine, sodium pyruvate and sodium bicarbonate (Sigma), supplemented with 10 % of heat inactivated fetal bovine serum (Thermo Fisher).
- [0507]** Assays were performed using reporter plasmid pYX017 as described (Xie, et al., 2011) with several modifications. The reporter assay was performed in 96-well white optical bottom plates. HeLa cells were seeded in wells 24 h prior to transfection and compound treatment so that cells were approximately 30% confluent on the day of transfection. Different cell plating densities were tested and a density of 2X10³ cells was determined to be optimal.

[0508] Compounds were resuspended in DMSO. Serial dilutions (1:3) were prepared in DMSO. Medium containing different concentrations of the compounds were prepared by adding 2 μ l of the compound dilution to 1 ml of the culture medium. The final concentration of DMSO in the medium was 0.2%.

[0509] FuGENE® HD transfection reagent (Promega, E2311, Lot 382574 and Lot 397842) was used to transfect the plasmids into the cells. The transfection reagent: DNA mixture was prepared in OpiMEM (Thermo Fisher) according to manufacturer's instructions. Different ratios of transfection reagent to DNA were tested and a ratio of 3:1 was determined to be optimal. Culture medium was removed from the cells and discarded. The transfection reagent: DNA mixture (5 μ l) was mixed with the compound containing medium (100 μ l/well) and this was added onto the cells of each well. Cells were incubated at 37°C/5% CO₂ for different incubation time. A 72 h incubation time was determined to be optimal.

[0510] Luciferase reporter activity was quantified with the Dual-Luciferase® Reporter Assay System (Promega) according to manufacturer's instructions for multiwell plates except that cells were lysed directly on the multiwell plate with 30 μ l of the passive lysis buffer (PLB) for 20 min at room temperature, with gentle shaking to ensure complete cell lysis.

[0511] Firefly and Renilla luciferase signals were measured using a SpectraMax i3x Multi-Mode Microplate Reader. Integration times of 100 ms and 10 ms were used to measure the Firefly and Renilla signals respectively. Relative L1 activity is calculated as Firefly/Renilla *1000 or Firefly/Renilla *10,000. Dose response inhibition data were fit to a four parameter logistic equation using non-linear regression (using Graphpad Prism 8), to determine IC₅₀ values for each inhibitor.

[0512] The results are provided in Table 2.

Table 2: Human LINE-1 Activity Inhibition

Compound Number	Human LINE-1 IC ₅₀ (μ M)
2	0.39
4	0.49
6	18.56
7	0.0097

9	0.021
12	0.0062
13	0.00051
15	0.83
16	>25
17	0.91
18	12.5
19	>12.5
20	0.011
21	0.043
22	23.4
23	>50
24	0.010
25	0.0036
26	2.05
27	0.0026
tenofovir alafenamide	0.01

EXAMPLE 5

Simoa™ ORF1p and ORF2p Assays

[0513] Utilizing the same reagents as a conventional ELISA, the Simoa™ (Single Molecule Array) method has been used to measure proteins in a variety of different matrices (serum, serum/plasma, cerebral spinal fluid, urine, cell extracts etc.) at femtomolar (fg/mL) concentrations, offering a roughly 1000-fold improvement in sensitivity. This approach makes use of arrays of femtoliter-sized reaction chambers, termed single-molecule arrays (Simoa™) that can isolate and detect single enzyme molecules. Because the array volumes are approximately 2 billion times smaller than a conventional ELISA, a rapid buildup of fluorescent product is generated if a labeled protein is present. With diffusion defeated, this high local

concentration of product can be readily observed. Only one single molecule is needed to reach the detection limit.

[0514] In the first step of this single-molecule immunoassay, antibody capture agents are attached to the surface of paramagnetic beads (2.7 μm diameter) that will be used to concentrate a dilute solution of molecules. The beads typically contain approximately 250,000 attachment sites so one can think of each bead as having a "lawn" of capture molecules. The beads are added to the sample solution such that there are many more beads than target molecules. Typically 500,000 beads will be added to a 100 L sample. There are two advantages for adding so many beads. First, at a roughly 10:1 bead to molecule ratio, the percentage of beads that contain a labeled immunocomplex follows a Poisson distribution. At low concentrations of protein, the Poisson distribution indicates that each bead will capture either a single immunocomplex or none. For example, if 1 fM of a protein in 0.1 mL (60,000 molecules) is captured and labeled on 500,000 beads, then 12% of the beads will carry one protein molecule and 88% will not carry any protein molecules. Second, with so many beads in solution, the bead-to-bead distance is small, such that every molecule encounters a bead in less than a minute. Diffusion of the target analyte molecules, even large proteins, occurs on a time scale such that all the molecules should in theory quickly have multiple collisions with multiple beads. In this manner, the slow binding to a fixed capture surface is avoided and the efficiency of binding increases dramatically. Beads are then washed to remove nonspecifically bound proteins, incubated with biotinylated detection antibody and then with β -galactosidase labeled streptavidin. In this manner, each bead that has captured a single protein molecule is labeled with an enzyme. Beads that do not capture a molecule remain label free.

[0515] Rather than ensemble readout, beads are loaded into arrays of 216,000 femtoliter-sized wells that have been sized to hold no more than one bead per well (4.25 μm width, 3.25 μm depth). Beads are added in the presence of substrate, and wells are subsequently sealed with oil and imaged. Simoa permits the detection of very low concentrations of enzyme labels by confining the fluorophores generated by individual enzymes to extremely small volumes (~ 40 fL), ensuring a high local concentration of fluorescent product molecules. If a target analyte has been captured (immunocomplex formed), then the substrate will be converted to a fluorescent product by captured enzyme label. The ratio of the number of wells containing a bead with an enzyme label to the total number of wells containing a bead corresponds to the analyte concentration in the sample. By acquiring

two fluorescence images of the array, it is possible to demonstrate an increase in signal thereby confirming the presence of a true immunocomplex, and those beads associated with a single enzyme molecule ("on" well) can be distinguished from those not associated with an enzyme ("off" well). The protein concentration in the test sample is determined by counting the number of wells containing both a bead and fluorescent product relative to the total number of wells containing beads. As Simoa enables concentration to be determined digitally rather than by using the total analog signal, this approach to detecting single immunocomplexes has been termed digital ELISA. The ability of digital ELISA to measure much lower concentrations of proteins than conventional ELISA derives from two effects: (i) the high sensitivity of Simoa to enzyme label and (ii) the low background signals that can be achieved by digitizing the detection of proteins. For antibodies of given affinity, the sensitivity of the immunoassay will be determined by the assay background. The high label sensitivity and decreased label concentration helps reduce nonspecific binding to the capture surface, resulting in much lower background signals.

[0516] Utilizing ORF1p monoclonal antibodies, a SimoaTM assay to detect ORF1p levels in spiked serum from healthy volunteers (serum from healthy volunteers does not contain detectable concentrations of ORF1p), cancer cell lysates, and peripheral blood mononuclear cell (PBMC) lysates of healthy volunteers. The ORF1p monoclonal antibodies used in these studies were MABC1152 from Millipore-Sigma and ab246317 from Abcam.

[0517] The lower limit of detection (LLOD) was determined at 22 fg/mL and the lower limit of quantitation (LLOQ) was determined at 93 fg/mL in the spiked serum from healthy volunteers. The LLOD was determined at 18 fg/mL and the LLOQ was determined at 70 fg/mL in the cancer cell lysates. The LLOD was determined at 17 fg/mL and the LLOQ was determined at 68 fg/mL in the PBMC lysates of healthy volunteers.

[0518] Using the same procedure with ORF2p monoclonal antibodies, a SimoaTM assay can be used to detect ORF2p levels in biological samples taken from a subject.

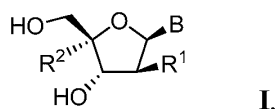
[0519] Having now fully described the compounds, methods, kits, and compositions herein, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the methods, compounds, and compositions provided herein

or any embodiment thereof. All patents, patent applications, and publications cited herein are fully incorporated by reference herein in their entirety.

WHAT IS CLAIMED IS:

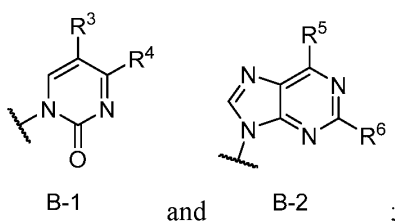
1. A method of treating or preventing a disease, disorder, or condition caused by a pathophysiological retrotransposon-associated process in a subject in need thereof, and/or treating or preventing a symptom of the disease, disorder, or condition, the method comprising administering to the subject a therapeutically effective amount of a compound of:

(i) Formula I:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

B is selected from the group consisting of:



R¹ is selected from the group consisting of hydrogen and -OH;

R² is selected from the group consisting of methyl, ethynyl, and -CN;

R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;

R⁴ is selected from the group consisting of -NH₂ and -OH;

R⁵ is selected from the group consisting of -NH₂ and -OH; and

R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂;

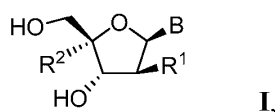
(ii) Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,
or

(iii) Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,

with provisos that the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.

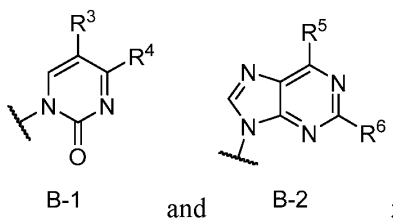
2. A method of inhibiting a LINE-1 retrotransposition event that causes a disease, disorder, or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of:

(i) Formula I:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

B is selected from the group consisting of:



R¹ is selected from the group consisting of hydrogen and -OH;

R² is selected from the group consisting of methyl, ethynyl, and -CN;

R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;

R⁴ is selected from the group consisting of -NH₂ and -OH;

R⁵ is selected from the group consisting of -NH₂ and -OH; and

R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂;

(ii) Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,
or

(iii) Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,

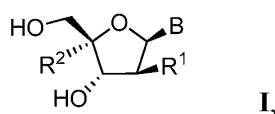
with provisos that the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.

3. A method of treating a disease, condition, or disorder in a subject, the method comprising:

(a) determining whether an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present or absent in a biological sample taken from the subject; and

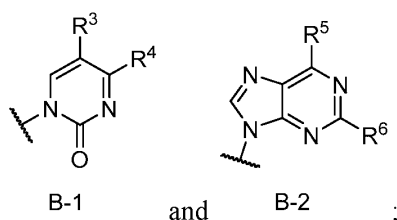
(b) administering a therapeutically effective amount of a compound of:

(i) Formula I:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

B is selected from the group consisting of:



R¹ is selected from the group consisting of hydrogen and -OH;

R² is selected from the group consisting of methyl, ethynyl, and -CN;

R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;

R⁴ is selected from the group consisting of -NH₂ and -OH;

R⁵ is selected from the group consisting of -NH₂ and -OH; and

R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂;

(ii) Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,

or

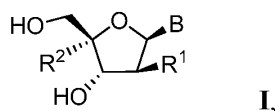
(iii) Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,

to the subject if an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present in the biological sample,

with provisos that the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.

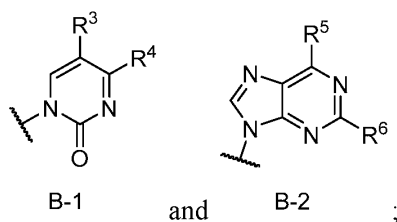
4. A method of identifying whether a subject having a disease, condition, or disorder is a candidate for treatment with a compound of:

(i) Formula **I**:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

B is selected from the group consisting of:



R¹ is selected from the group consisting of hydrogen and -OH;

R² is selected from the group consisting of methyl, ethynyl, and -CN;

R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;

R⁴ is selected from the group consisting of -NH₂ and -OH;

R⁵ is selected from the group consisting of -NH₂ and -OH; and

R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂;

(ii) Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or

(iii) Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,

the method comprising:

(a) determining whether an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present or absent in a biological sample taken from the subject; and

(b) identifying the subject as being a candidate for treatment if an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present; or

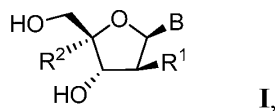
(c) identifying the subject as not being a candidate for treatment if an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is absent,

with provisos that the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.

5. A method of predicting treatment outcome in a subject having a disease, condition, or disorder, the method comprising determining whether an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA is present or absent in a biological sample taken from the subject, wherein:

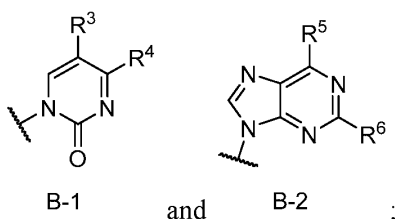
(a) the presence of an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA in the biological sample indicates that administering a compound of:

(i) Formula I:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

B is selected from the group consisting of:



R¹ is selected from the group consisting of hydrogen and -OH;

R² is selected from the group consisting of methyl, ethynyl, and -CN;

R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;

R⁴ is selected from the group consisting of -NH₂ and -OH;

R⁵ is selected from the group consisting of -NH₂ and -OH; and

R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂;

(ii) Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,
or

(iii) Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,

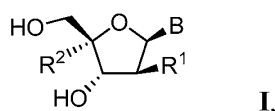
to the subject will likely cause a favorable therapeutic response; and

(b) the absence of an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA in the biological sample indicates that administering the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, to the subject will likely cause an unfavorable therapeutic response,

with provisos that the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.

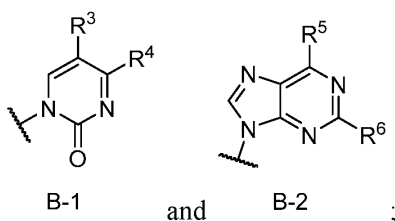
6. A method, comprising administering a therapeutically effective amount of a compound of:

(i) Formula I:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

B is selected from the group consisting of:



R¹ is selected from the group consisting of hydrogen and -OH;

R² is selected from the group consisting of methyl, ethynyl, and -CN;

R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;

R⁴ is selected from the group consisting of -NH₂ and -OH;

R⁵ is selected from the group consisting of -NH₂ and -OH; and

R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂;

(ii) Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,
or

(iii) Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,

to a subject, wherein:

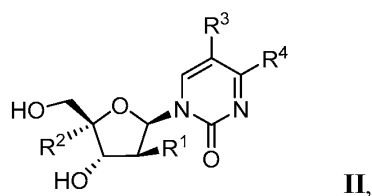
(a) the subject has a disease, condition, or disorder; and

(b) the disease, condition, or disorder is characterized as having an overexpression of retrotransposon RNA, retrotransposon reverse transcriptase, or retrotransposon DNA,

with provisos that the disease, disorder, or condition is not (i) cancer; or (ii) an infectious disease.

7. The method of any one of claims 1-6, wherein the compound is a compound of Formula **I**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

8. The method of claim 7, wherein the compound of Formula **I** is a compound of Formula **II**:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

9. The method of claim 8, wherein R^3 is hydrogen.

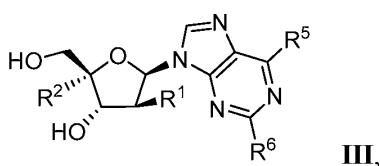
10. The method of claim 8, wherein R^3 is selected from the group consisting of fluoro and chloro.

11. The method of claim 8, wherein R^3 is methyl.

12. The method of any one of claims 8-11, wherein R^4 is $-NH_2$.

13. The method of any one of claims 8-11, wherein R^4 is $-OH$.

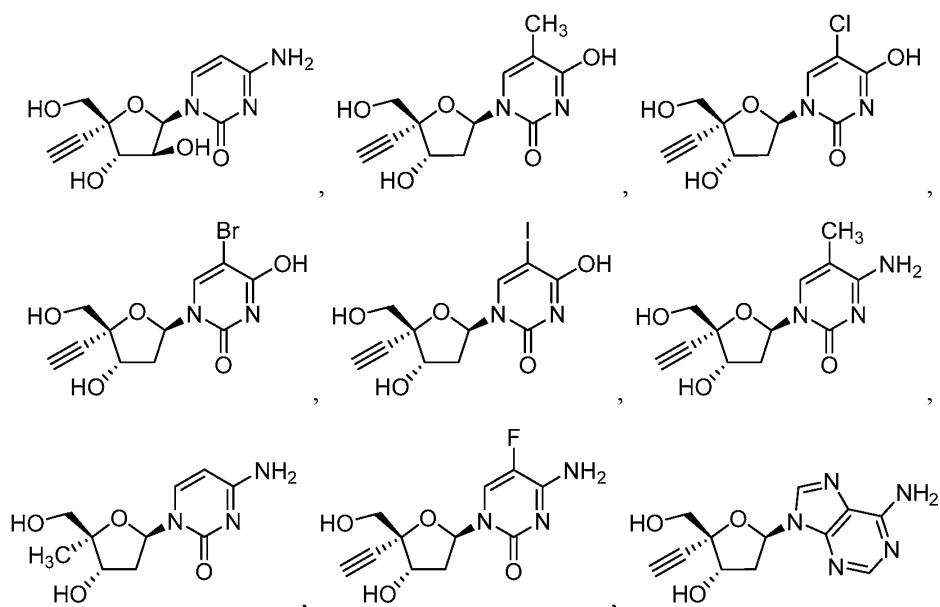
14. The method of claim 7, wherein the compound of Formula **I** is a compound of Formula **III**:

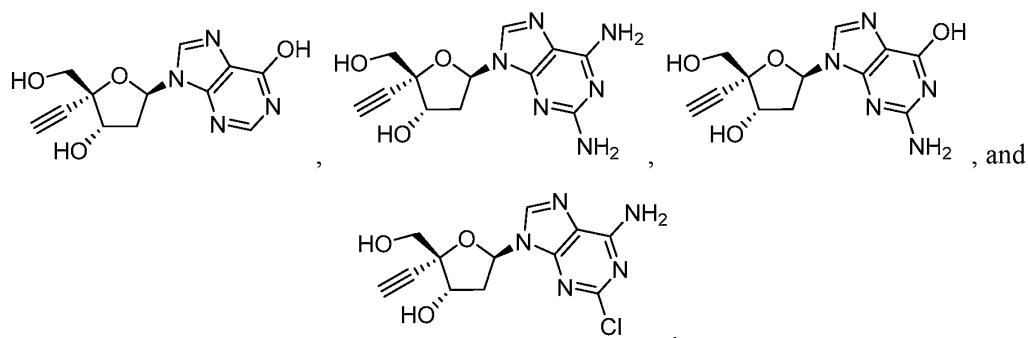


or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

15. The method of claim 14, wherein R^5 is $-NH_2$.

16. The method of claim 14, wherein R^5 is -OH.
17. The method of any one of claims 14-16, wherein R^6 is hydrogen.
18. The method of any one of claims 14-16, wherein R^6 is chloro.
19. The method of any one of claims 14-16, wherein R^6 is -NH₂.
20. The method of any one of claims 7-19, wherein R^1 is hydrogen.
21. The method of any one of claims 7-19, wherein R^1 is -OH.
22. The method of any one of claims 7-21, wherein R^2 is methyl.
23. The method of any one of claims 7-21, wherein R^2 is ethynyl.
24. The method of any one of claims 7-21, wherein R^2 is -CN.
25. The method of claim 7, wherein the compound of Formula I is selected from the group consisting of:





or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

26. The method of any one of claims 1-6, wherein the compound is a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

27. The method of any one of claims 1-6, wherein the compound is a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

28. The method of any one of claims 1 or 7-27 for treating the disease, disorder, or condition in a subject.

29. The method of any one of claims 1 or 7-27 for preventing the disease, disorder, or condition in a subject.

30. The method of any one of claims 1 or 7-27, for treating the symptom of a disease, disorder, or condition in a subject.

31. The method of any one of claims 1 or 7-27, for preventing the symptom of a disease, disorder, or condition in a subject.

32. The method of any one of claims 1-31, wherein the disease, disorder, or condition is a neurodegenerative disease.

33. The method of claim 32, wherein the neurodegenerative disease is Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, dementia with Lewy Bodies, multi systems atrophy, Huntington's disease, frontotemporal lobar degeneration, mild cognitive

impairment, corticobasal degeneration, progressive supra nuclear palsy, Rett Syndrome, peripheral degenerative disease, or Aicardi-Goutières syndrome.

34. The method of any one of claims 1-31, wherein the disease, disorder, or condition is an autoimmune disease.

35. The method of claim 34, wherein the autoimmune disease is lupus, rheumatoid arthritis, Sjogrens syndrome, or multiple sclerosis.

36. The method of any one of claims 1-31, wherein the disease, disorder, or condition is an age-associated disease.

37. The method of claim 36, wherein the age-associated disease is Alzheimer's disease, Parkinson's disease, atherosclerosis, osteoarthritis, osteoporosis, rheumatoid arthritis, macular degeneration, peripheral degenerative disease, or skin aging.

38. The method of any one of claims 1-31, wherein the disease, disorder, or condition is autism spectrum disorder (ADS), cardiovascular dysfunction, hearing loss, hematopoietic stem cell function, pulmonary fibrosis, schizophrenia, or vision loss.

39. The method of any one of claims 1-31, wherein the disease, disorder, or condition is progressive supra nuclear palsy.

40. The method of any one of claims 1-31, wherein the disease, disorder, or condition is amyotrophic lateral sclerosis.

41. The method of any one of claims 1-31, wherein the disease, disorder, or condition is Aicardi-Goutières syndrome.

42. The method of any one of claims 1-31, wherein the disease, disorder, or condition is ataxia-telangiectasia.

43. The method of any one of claims 1-31, wherein the disease, disorder, or condition is age-related macular degeneration.

44. The method of any one of claims 1-31, wherein the disease, disorder, or condition is systemic lupus erythematosus.

45. The method of any one of claims 1-31, wherein the disease, disorder, or condition is IFN-associated autoimmune disease.

46. The method of claim 45, wherein the IFN-associated autoimmune disease is psoriasis.

47. The method of any one of claims 1-31, wherein the disease, disorder, or condition is Fanconi Anemia.

48. The method of any one of claims 1-31, wherein the disease, disorder, or condition is idiopathic pulmonary fibrosis.

49. The method of any one of claims 1-31, wherein the disease, disorder, or condition is cardiovascular disease.

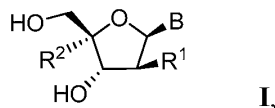
50. The method of any one of claims 1-3 or 5-49 further comprising one or more optional therapeutic agents to the subject.

51. The method of any one of claims 1-50, wherein the subject is (a) not infected with the HIV virus; (b) not suspected of being infected with the HIV virus; (c) not being treated for the HIV virus; and/or (d) not being treated to prevent the HIV virus.

52. The method of any one of claims 1-51, wherein the compound inhibits human LINE-1 retrotransposition activity with a half maximal inhibitory concentration of 1 μ M or less in an in vitro HeLa cell-based dual-luciferase assay.

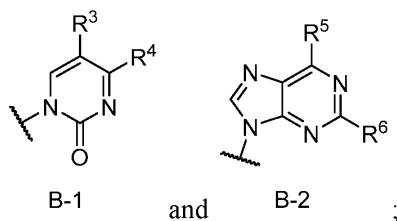
53. A kit comprising:

(i) a compound of Formula I:



or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

B is selected from the group consisting of:



R¹ is selected from the group consisting of hydrogen and -OH;

R² is selected from the group consisting of methyl, ethynyl, and -CN;

R³ is selected from the group consisting of hydrogen fluoro, chloro, bromo, iodo, and methyl;

R⁴ is selected from the group consisting of -NH₂ and -OH;

R⁵ is selected from the group consisting of -NH₂ and -OH; and

R⁶ is selected from the group consisting of hydrogen, chloro, and -NH₂;

(ii) a compound of Table 1A, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, or

(iii) a compound of Table 1B, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof,

and instructions for administering the compound to a subject having a disease, condition, or disorder caused by a pathophysiological retrotransposon-associated process.