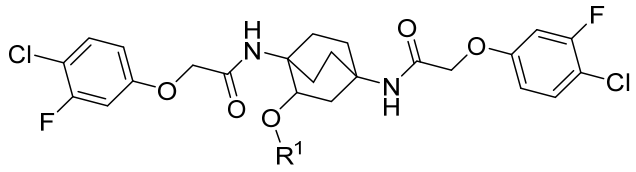
exchange of GDP with GTP in eIF2 is catalyzed by its dedicated guanine nucleotide exchange factor (GEF) eIF2B. eIF2B exists as a decamer ($B1_2\ B2_2\ B3_2\ B4_2\ B5_2$) or dimer of two pentamers in cells (Gordiyenko, Y. et al, *Nat Commun* (2014) 5:3902; Wortham, N.C. et al, *FASEB J* (2014) 28:2225-2237). Molecules such as ISRIB interact with and stabilize the eIF2B dimer conformation, thereby enhancing intrinsic GEF activity and making cells less sensitive to the cellular effects of phosphorylation of eIF2α (Sidrauski, C. et al, *eLife* (2015) e07314; Sekine, Y. et al, *Science* (2015) 348:1027-1030). As such, small molecule therapeutics that can modulate eIF2B activity may have the potential to attenuate the PERK branch of the UPR and the overall ISR, and therefore may be used in the prevention and/or treatment of various diseases, such as a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, or a metabolic disease.

SUMMARY

[004a] In one aspect of the present disclosure, there is provided a compound represented by Formula (I):

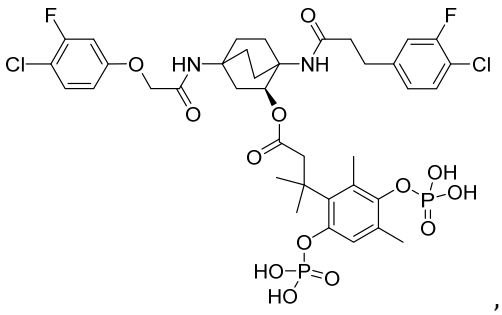
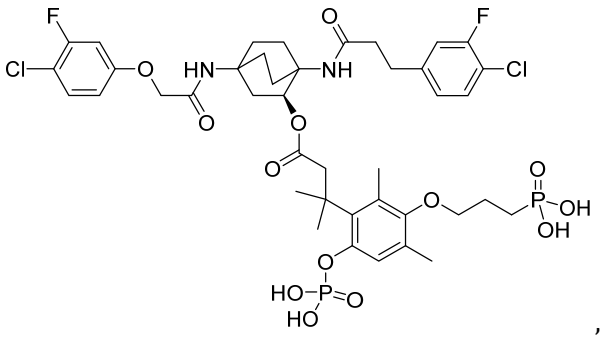
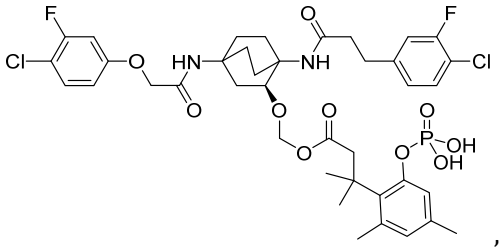
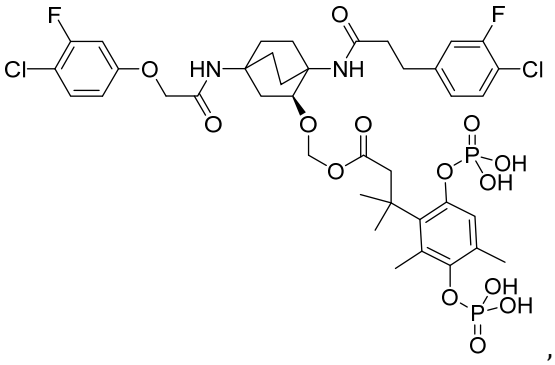


(I);

or a pharmaceutically acceptable salt~~, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer~~ thereof, wherein:

R^1 is selected from the group consisting of -C(O)-C_{1-4}alkyl, -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-4}alkoxy, -methylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-O-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2$)(O-C_{1-5}alkylene-P(O)$(OH)_2$), -methylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$ or -methylene-O-C(O)C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-O-C_{1-5}alkylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-heteroarylene-C_{1-2}alkylene-O-P(O)$(OH)_2$, -P(O)$(OH)_2$, -SO_3H, -$SO_2NR^aR^b$, -C(O)-heteroaryl, -C(O)-C_{1-5}alkylene-O-C_{1-5}alkylene-phenyl and methylene-C_{1-5}alkoxide;

wherein -C(O)-C_{1-4}alkyl is substituted by one or two substituents each independently selected from the group consisting of –NR^aR^b and -CO_2H; and wherein -C(O)-O-C_{1-4}alkyl, -


,

,

,

,

or a pharmaceutically acceptable salt~~, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer~~ thereof.

~~**[004c]** In a further aspect of the present disclosure, there is provided a pharmaceutically acceptable composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier.~~

~~**[004d]** In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating a neurodegenerative dpisease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, or a mitochondrial disease in a patient in need thereof.~~

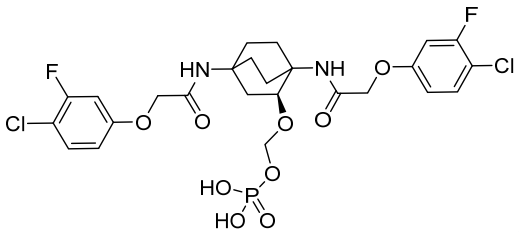
~~**[004e]** In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating a disease related to a modulation of eIF2B activity or levels, eIF2α activity or levels, or the activity or levels of a component of the eIF2 pathway or the ISR pathway in a patient in need thereof.~~

~~**[004f]** In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating a cancer in a patient in need thereof, wherein the compound is to be administered with an immunotherapeutic agent.~~

~~**[004g]** In a further aspect of the present disclosure, there is provided a compound disclosed herein for use in treating a neurodegenerative disease, a leukodystrophy, a cancer, an~~

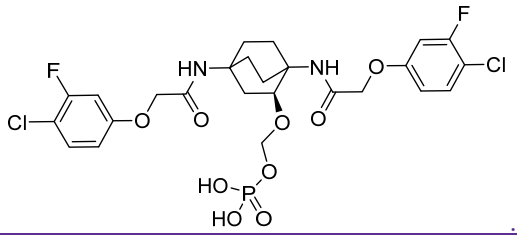
~~inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, a mitochondrial disease or a disease related to a modulation of eIF2B activity or levels, eIF2α activity or levels, or the activity or levels of a component of the eIF2 pathway or the ISR pathway in a patient in need thereof.~~

[004c] In another aspect of the present disclosure, there is provided a compound, wherein the compound is:



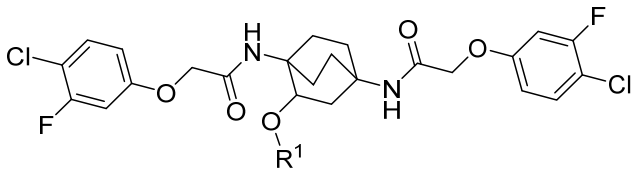
, or a pharmaceutically acceptable salt, thereof.

[004d] In a further aspect of the present disclosure, there is provided a compound, wherein the compound is



.

[005] In one example, described herein is a compound represented by Formula (I):



(I);

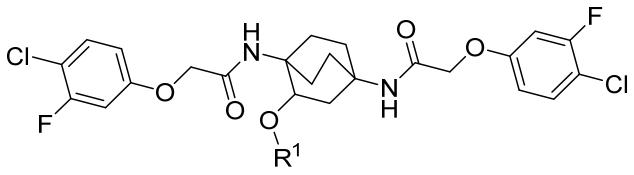
or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein:

R^1 is selected from the group consisting of -C(O)-C_{1-4}alkyl, -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-4}alkoxy, -methylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-O-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2$)(O-C_{1-5}alkylene-P(O)$(OH)_2$), -methylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -methylene-O-C(O)C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-O-C_{1-5}alkylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-heteroarylene-C_{1-2}alkylene-O-P(O)$(OH)_2$, -P(O)$(OH)_2$, -SO_3H, -$SO_2NR^aR^b$, -C(O)-heteroaryl, -C(O)-C_{1-5}alkylene-O-C_{1-5}alkylene-phenyl and methylene-C_{1-5}alkoxide;

wherein -C(O)-C_{1-4}alkyl is substituted by one or two substituents each independently selected from the group consisting of –NR^aR^b and -CO_2H; and wherein -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-}

CLAIMS

1. A compound represented by Formula (I):



(I);

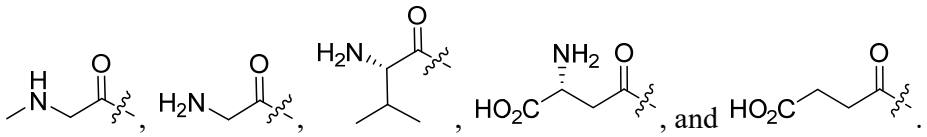
or a pharmaceutically acceptable salt~~, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer~~ thereof, wherein:

R^1 is selected from the group consisting of -C(O)-C_{1-4}alkyl, -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-4}alkoxy, -methylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-O-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2$)(O-C_{1-5}alkylene-P(O)$(OH)_2$), -methylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$ or -methylene-O-C(O)C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-O-C_{1-5}alkylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-heteroarylene-C_{1-2}alkylene-O-P(O)$(OH)_2$, -P(O)$(OH)_2$, -SO_3H, -$SO_2NR^aR^b$, -C(O)-heteroaryl, -C(O)-C_{1-5}alkylene-O-C_{1-5}alkylene-phenyl and methylene-C_{1-5}alkoxide;

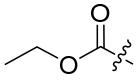
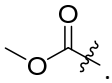
wherein -C(O)-C_{1-4}alkyl is substituted by one or two substituents each independently selected from the group consisting of –NR^aR^b and -CO_2H; and wherein -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-4}alkoxy, methylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-O-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2$)(O-C_{1-5}alkylene-P(O)$(OH)_2$), -methylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$ or -methylene-O-C(O)C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-O-C_{1-5}alkylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-heteroaryl, -C(O)-C_{1-5}alkylene-O-C_{1-5}alkylene-phenyl and -C(O)-N(R^a)-heteroarylene-C_{1-2}alkylene-O-P(O)$(OH)_2$ may optionally be substituted by one, two, three or four substituents each independently selected from the group consisting of halogen, -CO_2H, -NR^aR^b and C_{1-2}alkyl (optionally substituted by one, two or three fluorines) and aryl; and

R^a and R^b are independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-3}alkyl.

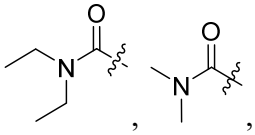
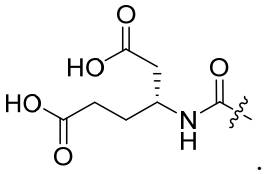
2. The compound of claim 1, wherein R^1 is -C(O)-C_{1-4}alkyl, wherein -C(O)-C_{1-4}alkyl is substituted by one or two substituents each independently selected from the group consisting of $–NR^aR^b$ and $-CO_2H$.

3. The compound of claim 1 or 2, wherein R^1 is selected from the group consisting of .

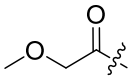
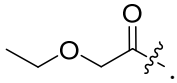
4. The compound of claim 1, wherein R^1 is -C(O)-O-C_{1-4}alkyl.

5. The compound of claim 4, wherein R^1 is selected from the group consisting of  and .

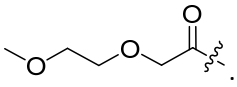
6. The compound of claim 1, wherein R^1 is -C(O)-N(R^a)-C_{1-4}alkyl, wherein -C(O)-N(R^a)-C_{1-4}alkyl may optionally be substituted by one or two $–CO_2H$ groups.

7. The compound of claim 6, wherein R^1 is represented by , and .

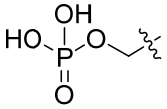
8. The compound of claim 1, wherein R^1 is -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy.

9. The compound of claim 8, wherein R^1 is selected from the group consisting of  and .

10. The compound of claim 1, wherein R^1 is -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-4}alkoxy.

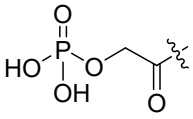
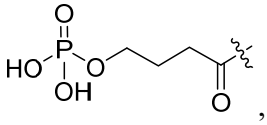
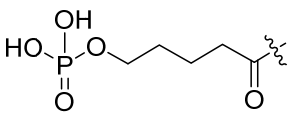
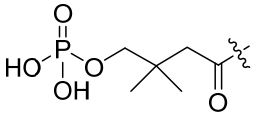
11. The compound of claim 10, wherein R^1 is represented by .

12. The compound of claim 1, wherein R^1 is -methylene-O-P(O)$(OH)_2$.

13. The compound of claim 12, wherein R^1 is represented by .

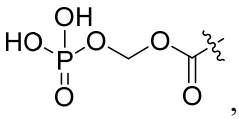
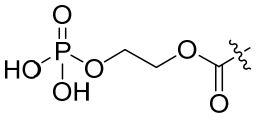
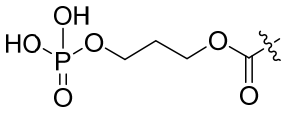
14. The compound of claim 1, wherein R^1 is -C(O)-C_{1-5}alkylene-O-P(O)$(OH)_2$.

15. The compound of claim 14, wherein R^1 is selected from the group consisting of

, ,  and .

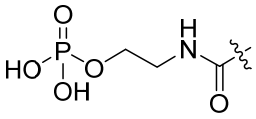
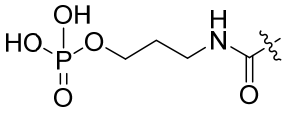
16. The compound of claim 1, wherein R^1 is -C(O)-O-C_{1-5}alkylene-O-P(O)(OH)$_2$.

17. The compound of claim 16, wherein R^1 is selected from the group consisting of

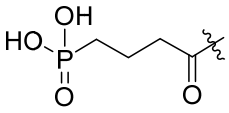
, , and .

18. The compound of claim 1,wherein R^1 is -C(O)-N(R^a)-C_{1-5}alkylene-O-P(O)(OH)$_2$.

19. The compound of claim 18, wherein R^1 is selected from the group consisting of

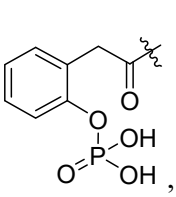
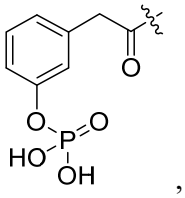
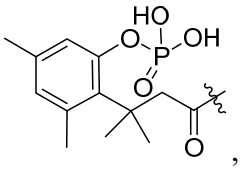
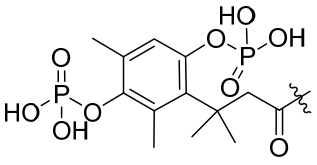
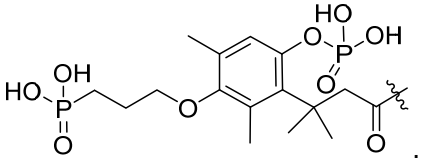
 and .

20. The compound of claim 1, wherein R^1 is -C(O)-C_{1-5}alkylene-P(O)(OH)$_2$.

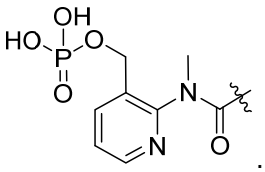
21. The compound of claim 20, wherein R^1 is represented by .

22. The compound of claim 1, wherein R^1 is -C(O)-C_{1-5}alkylene-phenylene-O-P(O)(OH)$_2$ -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)(OH)$_2$)$_2$ or -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)(OH)$_2$)(O-C_{1-5}alkylene-P(O)(OH)$_2$).

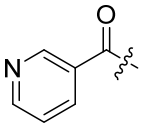
23. The compound of claim 22, wherein R^1 is selected from the group consisting of

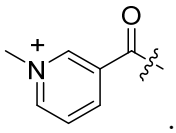
, , ,  and .

24. The compound of claim 1, wherein R^1 is -C(O)-N(R^a)-heteroarylene-C_{1-2}alkylene-O-P(O)(OH)$_2$.

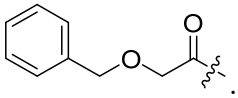
25. The compound of claim 24, wherein R^1 is represented by .

26. The compound of claim 1, wherein R^1 is -C(O)-heteroaryl.

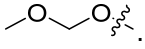
27. The compound of claim 26, wherein R^1 is selected from the group consisting of 

and .

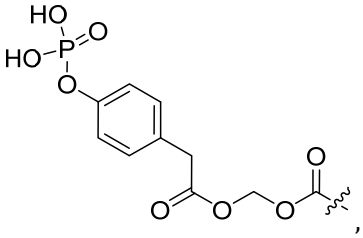
28. The compound of claim 1, wherein R^1 is -C(O)-$C_{1\text{-}5}$alkylene-O-$C_{1\text{-}5}$alkylene-phenyl.

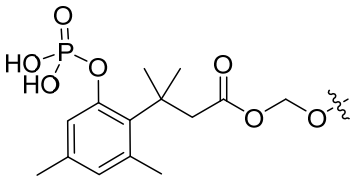
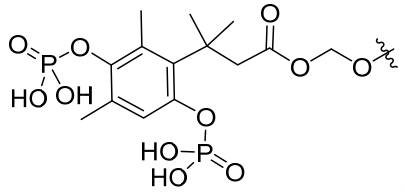
29. The compound of claim 28, wherein R^1 is represented by .

30. The compound of claim 1, wherein R^1 is methylene-$C_{1\text{-}5}$alkoxide.

31. The compound of claim 30, wherein R^1 is represented by .

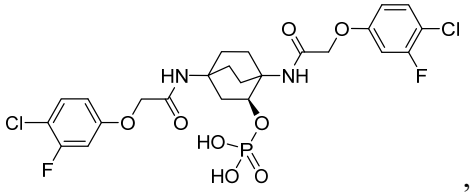
32. The compound of claim 1, wherein R^1 is -C(O)-O-$C_{1\text{-}5}$alkylene-O-C(O)$C_{1\text{-}5}$alkylene-phenylene-O-P(O)$(OH)_2$, -methylene-O-C(O)$C_{1\text{-}5}$alkylene-phenylene-O-P(O)$(OH)_2$ or -methylene-O-C(O)$C_{1\text{-}5}$alkylene-phenylene-(O-P(O)$(OH)_2)_2$.

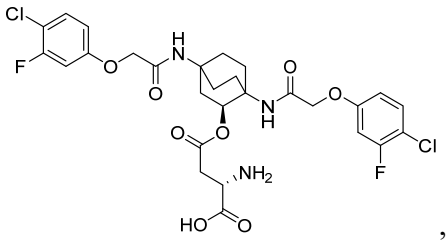
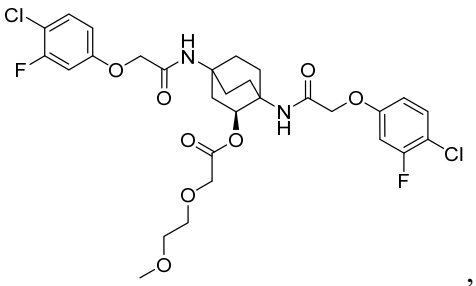
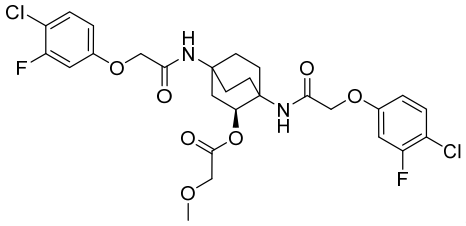
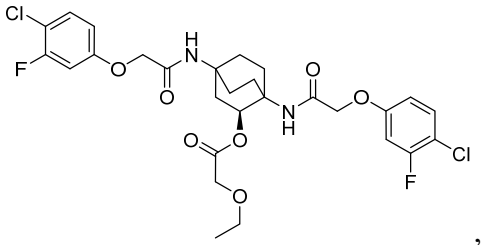
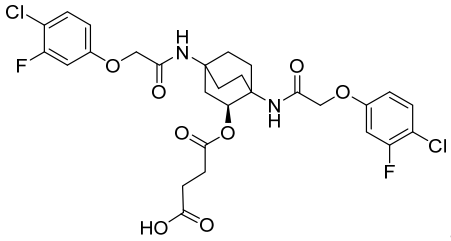
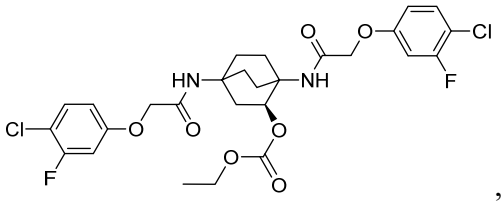
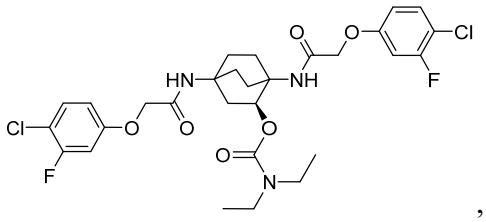
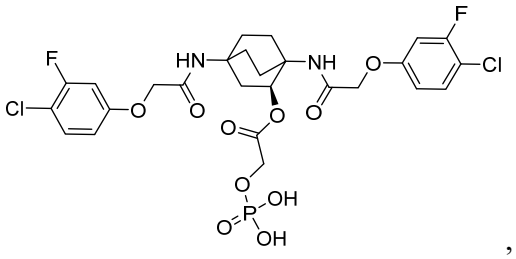
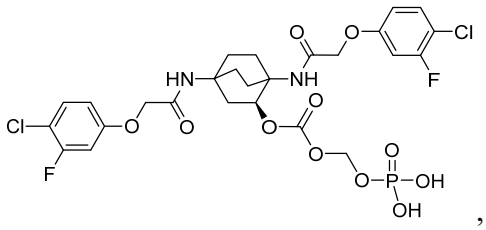
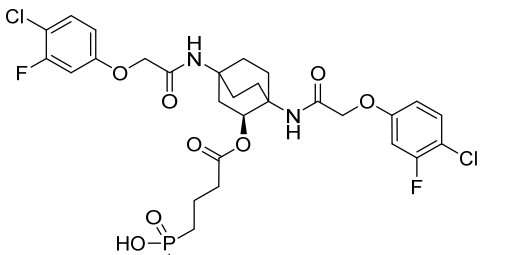
33. The compound of claim 32, wherein R^1 is represented by ,

, and .

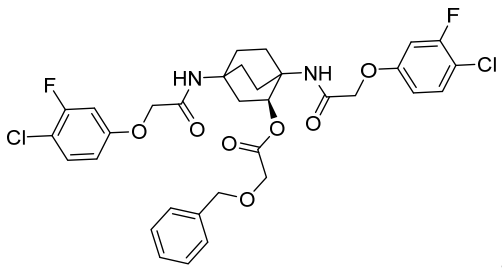
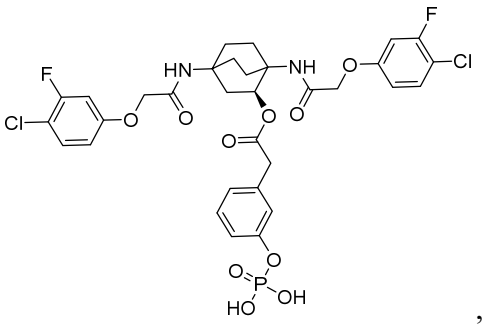
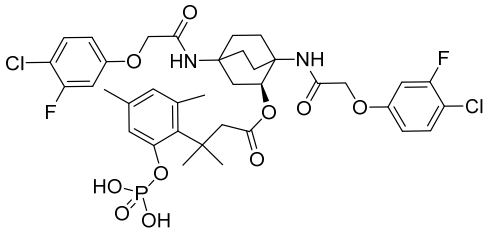
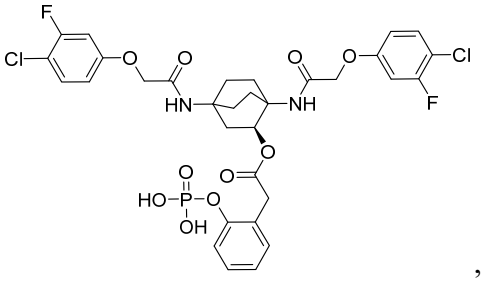
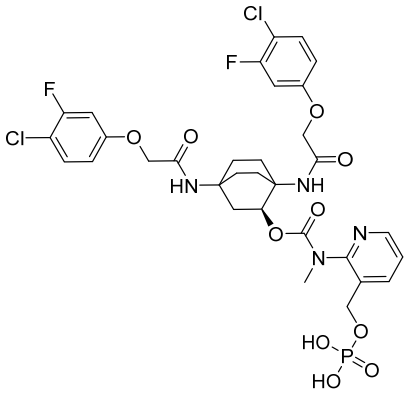
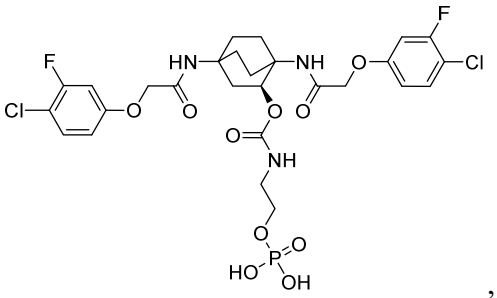
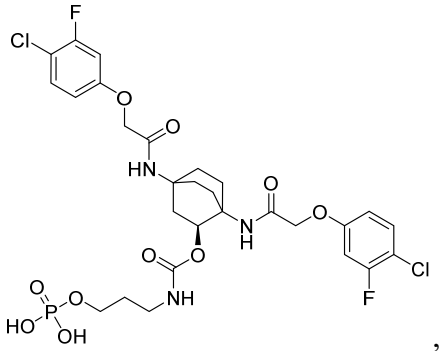
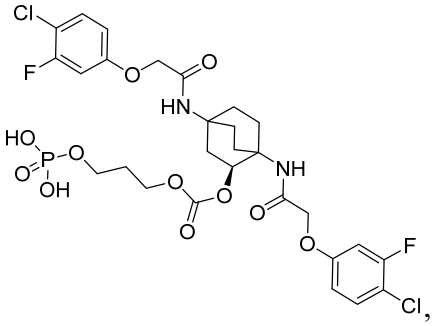
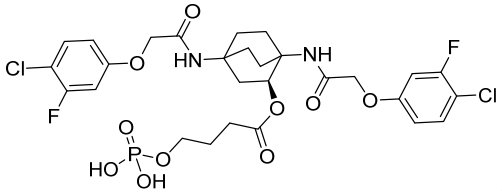
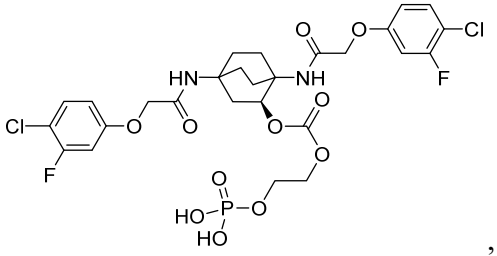
34. The compound of claim 1, wherein R^1 is selected from the group consisting of -P(O)$(OH)_2$, -SO_3H, and -SO_2NH_2.

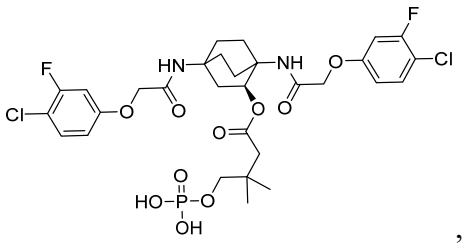
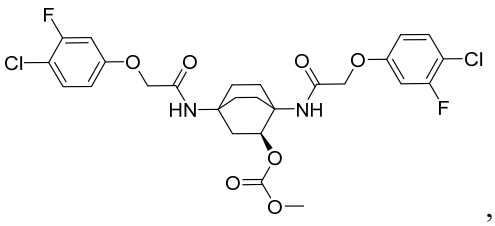
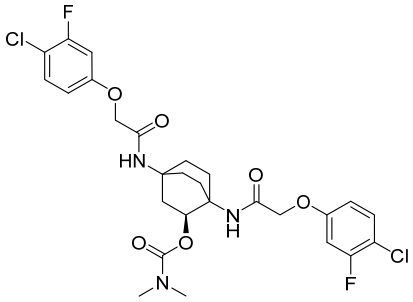
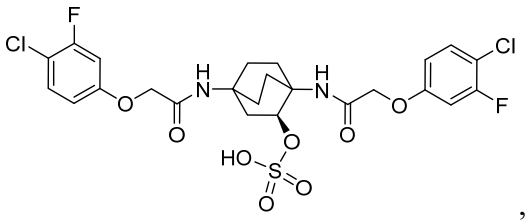
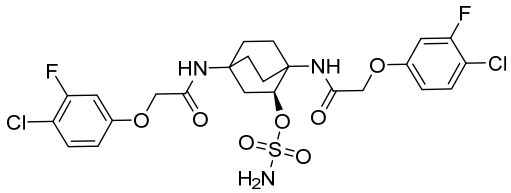
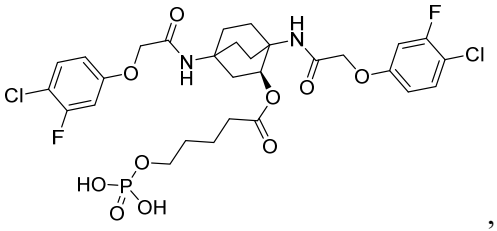
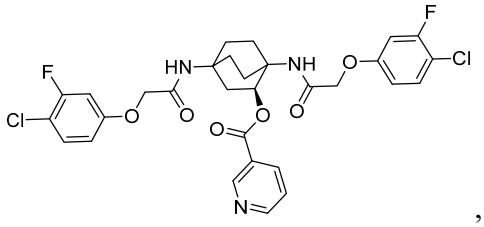
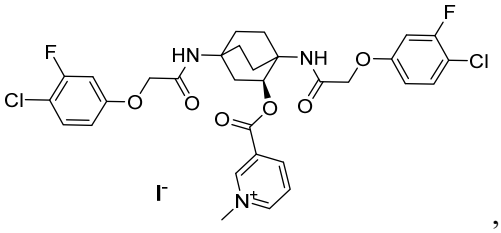
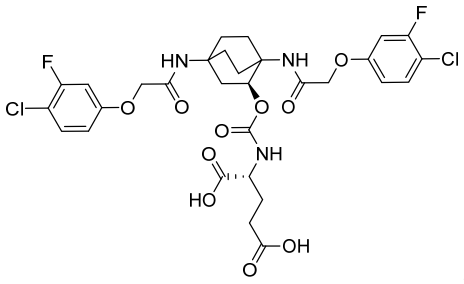
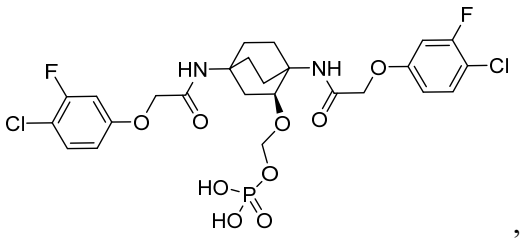
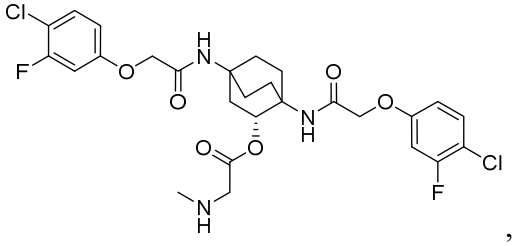
35. A compound selected from the group consisting of:

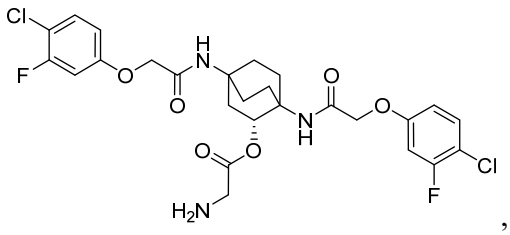
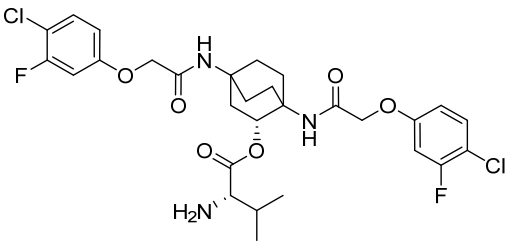
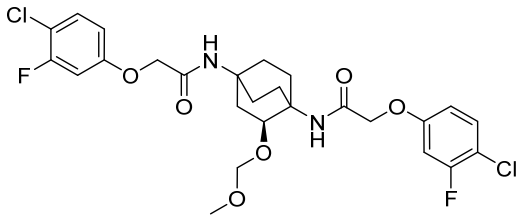
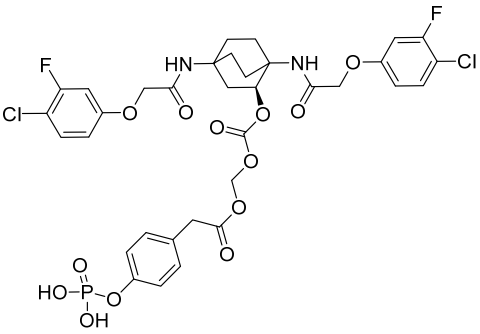
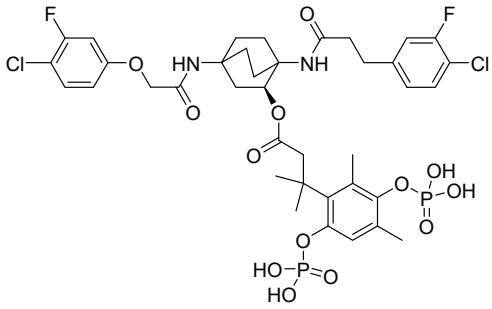
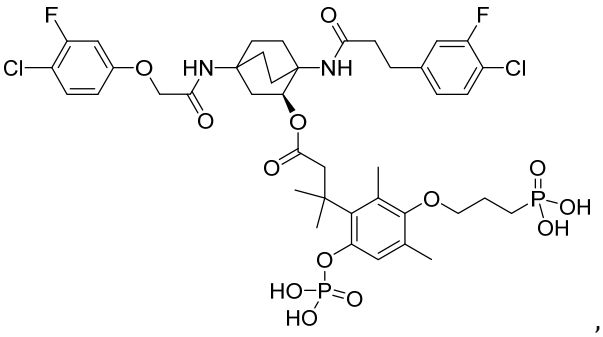
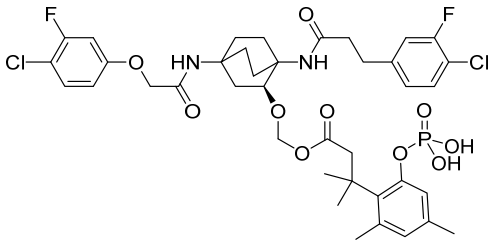
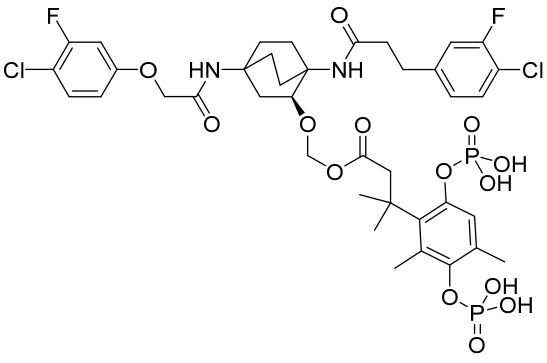
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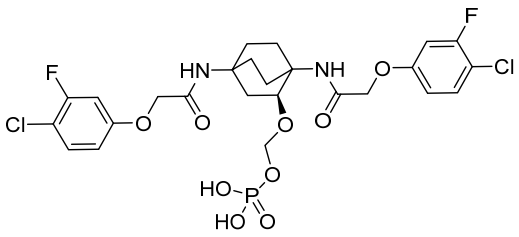

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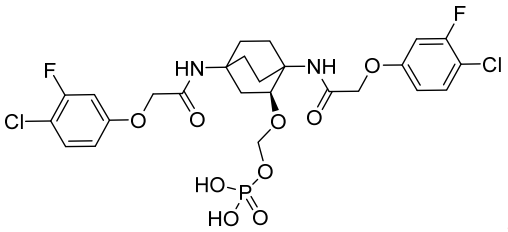

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or a pharmaceutically acceptable salt~~, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer~~ thereof.

36. A compound, wherein the compound is:



, or a pharmaceutically acceptable salt, thereof.



37. A compound, wherein the compound is .

~~36. A pharmaceutically acceptable composition comprising a compound of any one of claims 1-35 and a pharmaceutically acceptable carrier.~~

~~37. The composition of claim 36, wherein the composition is formulated for oral administration.~~

~~38. Use of a compound of any one of claims 1-35 in the manufacture of a medicament for treating a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, or a mitochondrial disease in a patient in need thereof.~~

~~39. The use of claim 38, wherein the neurodegenerative disease comprises a leukodystrophy, a leukoencephalopathy, a hypomyelinating or demyelinating disease, an intellectual disability syndrome (e.g., Fragile X syndrome), a cognitive impairment, a glial cell dysfunction, or a brain injury (e.g., a traumatic brain injury, hypoxia induced brain injury or toxin induced brain injury).~~

~~40. The use of claim 38 or 39, wherein the neurodegenerative disease comprises vanishing white matter disease, childhood ataxia with CNS hypo myelination, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Creutzfeldt-Jakob disease, frontotemporal dementia (FTD), Gerstmann-Straussler-Scheinker disease, Huntington's disease, dementia (e.g., HIV-associated dementia or Lewy body dementia), kuru, multiple sclerosis, Parkinson's disease, or a prion disease.~~

~~41. The use of any one of claims 38-40, wherein the neurodegenerative disease comprises vanishing white matter disease.~~

~~42. The use of claim 38, wherein the cancer comprises pancreatic cancer, breast cancer, multiple myeloma, or a cancer of the secretory cells.~~

~~43. The use of claim 38, wherein the inflammatory disease comprises postoperative cognitive dysfunction, arthritis (e.g., rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis), systemic lupus erythematosus (SLE), myasthenia gravis, diabetes (e.g., juvenile onset diabetes or diabetes mellitus type 1), Guillain-Barre syndrome, Hashimoto's encephalitis,~~

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

44. The use of claim 38, wherein the musculoskeletal disease comprises muscular dystrophy (e.g., Duchenne muscular dystrophy, Becker muscular dystrophy, distal muscular dystrophy, congenital muscular dystrophy, Emery-Dreifuss muscular dystrophy, facioscapulohumeral muscular dystrophy, myotonic muscular dystrophy type 1, or myotonic muscular dystrophy type 2), multiple sclerosis, amyotropic lateral sclerosis (ALS), primary lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, spinal muscular atrophy, progressive spinobulbar muscular atrophy, spinal cord spasticity, spinal muscle atrophy, myasthenia gravis, neuralgia, fibromyalgia, Machado-Joseph disease, cramp-fasciculation syndrome, Freidrich's ataxia, a muscle wasting disorder (e.g., muscle atrophy, sarcopenia, cachexia), an inclusion body myopathy, motor neuron disease, or paralysis.

45. The use of claim 38, wherein the metabolic disease comprises non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes (e.g., Type I diabetes, Type II diabetes, or gestational diabetes), phenylketonuria, proliferative retinopathy, or Kearns-Sayre disease.

46. The use of claim 38, wherein the mitochondrial disease is associated with or is a result of mitochondrial dysfunction, one or more mitochondrial protein mutations, or one or more mitochondrial DNA mutations.

47. The use of claim 38 or 46, wherein the mitochondrial disease is a mitochondrial myopathy.

48. The use of any one of claims 38 and 46-47, wherein the mitochondrial disease is selected from the group consisting of Barth syndrome, chronic progressive external ophthalmoplegia (cPEO), Kearns-Sayre syndrome (KSS), Leigh syndrome (e.g., MILS, or maternally inherited Leigh syndrome), mitochondrial DNA depletion syndromes (MDDS, e.g., Alpers syndrome), mitochondrial encephalomyopathy (e.g., mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), myoclonus epilepsy with ragged-red fibers (MERRF), neuropathy, ataxia, retinitis pigmentosa (NARP), Leber's hereditary optic neuropathy (LHON), and Pearson syndrome.

49. The use of claim 38, wherein the autoimmune disease is selected from the group consisting of Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid

~~syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune orchitis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammalglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neonatal Lupus, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis (peripheral uveitis), Parsonnage-Turner syndrome, Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndrome type I, Polyglandular syndrome type II, Polyglandular syndrome type III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis,~~

Schmidt syndrome, Scleritis, Scleroderma, Sjögren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, Vogt-Koyanagi-Harada Disease, and Wegener's granulomatosis (or Granulomatosis with Polyangiitis (GPA)).

50. The use of claim 38, wherein the viral infection is selected from the group consisting of influenza, human immunodeficiency virus (HIV) and herpes.

51. The use of claim 38, wherein the skin disease is selected from the group consisting of acne, alopecia areata, basal cell carcinoma, Bowen's disease, congenital erythropoietic porphyria, contact dermatitis, Darier's disease, disseminated superficial actinic porokeratosis, dystrophic epidermolysis bullosa, eczema (atopic eczema), extra-mammary Paget's disease, epidermolysis bullosa simplex, erythropoietic protoporphyria, fungal infections of nails, Hailey-Hailey disease, herpes simplex, hidradenitis suppurativa, hirsutism, hyperhidrosis, ichthyosis, impetigo, keloids, keratosis pilaris, lichen planus, lichen sclerosus, melanoma, melasma, mucous membrane pemphigoid, pemphigoid, pemphigus vulgaris, pityriasis lichenoides, pityriasis rubra pilaris, plantar warts (verrucas), polymorphic light eruption, psoriasis, plaque psoriasis, pyoderma gangrenosum, rosacea, scabies, scleroderma, shingles, squamous cell carcinoma, sweet's syndrome, urticaria and angioedema and vitiligo.

52. The use of claim 38, wherein the fibrotic disease is selected from the group consisting of adhesive capsulitis, arterial stiffness, arthrofibrosis, atrial fibrosis, cardiac fibrosis, cirrhosis, congenital hepatic fibrosis, Crohn's disease, cystic fibrosis, Dupuytren's contracture, endomyocardial fibrosis, glial scar, hepatitis C, hypertrophic cardiomyopathy, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, interstitial lung disease, keloid, mediastinal fibrosis, myelofibrosis, nephrogenic systemic fibrosis, non-alcoholic fatty liver disease, old myocardial infarction, Peyronie's disease, pneumoconiosis, pneumonitis, progressive massive fibrosis, pulmonary fibrosis, radiation-induced lung injury, retroperitoneal fibrosis, scleroderma/systemic sclerosis, silicosis and ventricular remodeling.

53. The use of claim 38, wherein the hemoglobin disease is selected from the group consisting of "dominant" β-thalassemia, acquired (toxic) methemoglobinemia, carboxyhemoglobinemia, congenital Heinz body hemolytic anemia, HbH disease, HbS/β-thalassemia, HbE/β-thalassemia, HbSC disease, homozygous α^{+}-thalassemia (phenotype of α^{0}-thalassemia), Hydrops fetalis with Hb Bart's, sickle cell anemia/disease, sickle cell trait, sickle β-thalassemia disease, α^{+}-thalassemia, α^{0}-thalassemia, α-Thalassemia associated with myelodysplastic syndromes, α-

~~Thalassemia with mental retardation syndrome (ATR), β^0-Thalassemia, β^+-Thalassemia, δ-Thalassemia, γ-Thalassemia, β-Thalassemia major, β-Thalassemia intermedia, δβ-Thalassemia, and εγδβ-Thalassemia.~~

~~54. The use of claim 38, wherein the kidney disease is selected from the group consisting of Abderhalden-Kaufmann-Lignac syndrome (Nephropathic Cystinosis), Abdominal Compartment Syndrome, Acetaminophen-induced Nephrotoxicity, Acute Kidney Failure/Acute Kidney Injury, Acute Lobar Nephronia, Acute Phosphate Nephropathy, Acute Tubular Necrosis, Adenine Phosphoribosyltransferase Deficiency, Adenovirus Nephritis, Alagille Syndrome, Alport Syndrome, Amyloidosis, ANCA-Vasculitis Related to Endocarditis and Other Infections, Angiomyolipoma, Analgesic Nephropathy, Anorexia Nervosa and Kidney Disease, Angiotensin Antibodies and Focal Segmental Glomerulosclerosis, Antiphospholipid Syndrome, Anti-TNF-α Therapy-related Glomerulonephritis, APOL1 Mutations, Apparent Mineralocorticoid Excess Syndrome, Aristolochic Acid Nephropathy, Chinese Herbal Nephropathy, Balkan Endemic Nephropathy, Arteriovenous Malformations and Fistulas of the Urologic Tract, Autosomal Dominant Hypocalcemia, Bardet-Biedl Syndrome, Bartter Syndrome, Bath Salts and Acute Kidney Injury, Beer Potomania, Beeturia, β-Thalassemia Renal Disease, Bile Cast Nephropathy, BK Polyoma Virus Nephropathy in the Native Kidney, Bladder Rupture, Bladder Sphincter Dyssynergia, Bladder Tamponade, Border-Crossers' Nephropathy, Bourbon Virus and Acute Kidney Injury, Burnt Sugarcane Harvesting and Acute Renal Dysfunction, Byetta and Renal Failure, C1q Nephropathy, C3 Glomerulopathy, C3 Glomerulopathy with Monoclonal Gammopathy, C4 Glomerulopathy, Calcineurin Inhibitor Nephrotoxicity, Callilepsis Laureola Poisoning, Cannabinoid Hyperemesis Acute Renal Failure, Cardiorenal syndrome, Carfilzomib-Induced Renal Injury, CFHR5 nephropathy, Charcot-Marie-Tooth Disease with Glomerulopathy, Chinese Herbal Medicines and Nephrotoxicity, Cherry Concentrate and Acute Kidney Injury, Cholesterol Emboli, Churg-Strauss syndrome, Chyluria, Ciliopathy, Cocaine and the Kidney, Cold Diuresis, Colistin Nephrotoxicity, Collagenofibrotic Glomerulopathy, Collapsing Glomerulopathy, Collapsing Glomerulopathy Related to CMV, Combination Antiretroviral (cART) Related Nephropathy, Congenital Anomalies of the Kidney and Urinary Tract (CAKUT), Congenital Nephrotic Syndrome, Congestive Renal Failure, Conorenal syndrome (Mainzer-Saldino Syndrome or Saldino-Mainzer Disease), Contrast Nephropathy, Copper Sulphate Intoxication, Cortical Necrosis, Crizotinib-related Acute Kidney Injury, Cryocrystalglobulinemia, Cryoglobuinemia, Crystalglobulin-Induced Nephropathy, Crystal-Induced Acute Kidney injury, Crystal-Storing Histiocytosis, Cystic Kidney Disease, Acquired, Cystinuria, Dasatinib-Induced Nephrotic-Range Proteinuria, Dense Deposit Disease (MPGN Type 2), Dent Disease (X-linked Recessive Nephrolithiasis), DHA-Crystalline Nephropathy,~~

~~Dialysis Disequilibrium Syndrome, Diabetes and Diabetic Kidney Disease, Diabetes Insipidus, Dietary Supplements and Renal Failure, Diffuse Mesangial Sclerosis, Diuresis, Djenkol Bean Poisoning (Djenkolism), Down Syndrome and Kidney Disease, Drugs of Abuse and Kidney Disease, Duplicated Ureter, EAST syndrome, Ebola and the Kidney, Ectopic Kidney, Ectopic Ureter, Edema, Swelling, Erdheim-Chester Disease, Fabry's Disease, Familial Hypocalciuric Hypercalcemia, Fanconi Syndrome, Fraser syndrome, Fibronectin Glomerulopathy, Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy, Fraley syndrome, Fluid Overload, Hypervolemia, Focal Segmental Glomerulosclerosis, Focal Sclerosis, Focal Glomerulosclerosis, Galloway Mowat syndrome, Giant Cell (Temporal) Arteritis with Kidney Involvement, Gestational Hypertension, Gitelman Syndrome, Glomerular Diseases, Glomerular Tubular Reflux, Glycosuria, Goodpasture Syndrome, Green Smoothie Cleanse Nephropathy, HANAC Syndrome, Harvoni (Ledipasvir with Sofosbuvir) Induced Renal Injury, Hair Dye Ingestion and Acute Kidney Injury, Hantavirus Infection Podocytopathy, Heat Stress Nephropathy, Hematuria (Blood in Urine), Hemolytic Uremic Syndrome (HUS), Atypical Hemolytic Uremic Syndrome (aHUS), Hemophagocytic Syndrome, Hemorrhagic Cystitis, Hemorrhagic Fever with Renal Syndrome (HFRS, Hantavirus Renal Disease, Korean Hemorrhagic Fever, Epidemic Hemorrhagic Fever, Nephropathis Epidemica), Hemosiderinuria, Hemosiderosis related to Paroxysmal Nocturnal Hemoglobinuria and Hemolytic Anemia, Hepatic Glomerulopathy, Hepatic Veno-Occlusive Disease, Sinusoidal Obstruction Syndrome, Hepatitis C-Associated Renal Disease, Hepatocyte Nuclear Factor 1β-Associated Kidney Disease, Hepatorenal Syndrome, Herbal Supplements and Kidney Disease, High-Altitude Renal Syndrome, High Blood Pressure and Kidney Disease, HIV-Associated Immune Complex Kidney Disease (HIVICK), HIV-Associated Nephropathy (HIVAN), HNF1B-related Autosomal Dominant Tubulointerstitial Kidney Disease, Horseshoe Kidney (Renal Fusion), Hunner's Ulcer, Hydroxychloroquine-induced Renal Phospholipidosis, Hyperaldosteronism, Hypercalcemia, Hyperkalemia, Hypermagnesemia, Hypernatremia, Hyperoxaluria, Hyperphosphatemia, Hypocalcemia, Hypocomplementemic Urticarial Vasculitic Syndrome, Hypokalemia, Hypokalemia-induced renal dysfunction, Hypokalemic Periodic Paralysis, Hypomagnesemia, Hyponatremia, Hypophosphatemia, Hypophosphatemia in Users of Cannabis, Hypertension, Hypertension, Monogenic, Iced Tea Nephropathy, Ifosfamide Nephrotoxicity, IgA Nephropathy, IgG4 Nephropathy, Immersion Diuresis, Immune-Checkpoint Therapy-Related Interstitial Nephritis, Infliximab-Related Renal Disease, Interstitial Cystitis, Painful Bladder Syndrome (Questionnaire), Interstitial Nephritis, Interstitial Nephritis, Karyomegalic, Ivemark's syndrome, JC Virus Nephropathy, Joubert Syndrome, Ketamine-Associated Bladder Dysfunction, Kidney Stones, Nephrolithiasis, Kombucha Tea Toxicity, Lead Nephropathy and Lead-Related~~

~~Nephrotoxicity, Lecithin-Cholesterol Acyltransferase Deficiency (LCAT Deficiency), Leptospirosis Renal Disease, Light Chain Deposition Disease, Monoclonal Immunoglobulin Deposition Disease, Light Chain Proximal Tubulopathy, Liddle Syndrome, Lightwood-Albright Syndrome, Lipoprotein Glomerulopathy, Lithium Nephrotoxicity, LMX1B Mutations Cause Hereditary FSGS, Loin Pain Hematuria, Lupus, Systemic Lupus Erythematosis, Lupus Kidney Disease, Lupus Nephritis, Lupus Nephritis with Antineutrophil Cytoplasmic Antibody Seropositivity, Lupus Podocytopathy, Lyme Disease-Associated Glomerulonephritis, Lysinuric Protein Intolerance, Lysozyme Nephropathy, Malarial Nephropathy, Malignancy-Associated Renal Disease, Malignant Hypertension, Malakoplakia, McKittrick-Wheelock Syndrome, MDMA (Molly; Ecstacy; 3,4-Methylenedioxymethamphetamine) and Kidney Failure, Meatal Stenosis, Medullary Cystic Kidney Disease, Urolodulin-Associated Nephropathy, Juvenile Hyperuricemic Nephropathy Type 1, Medullary Sponge Kidney, Megaureter, Melamine Toxicity and the Kidney, MELAS Syndrome, Membranoproliferative Glomerulonephritis, Membranous Nephropathy, Membranous-like Glomerulopathy with Masked IgG Kappa Deposits, MesoAmerican Nephropathy, Metabolic Acidosis, Metabolic Alkalosis, Methotrexate-related Renal Failure, Microscopic Polyangiitis, Milk-alkalai syndrome, Minimal Change Disease, Monoclonal Gammopathy of Renal Significance, Dysproteinemia, Mouthwash Toxicity, MUC1 Nephropathy, Multicystic dysplastic kidney, Multiple Myeloma, Myeloproliferative Neoplasms and Glomerulopathy, Nail-patella Syndrome, NARP Syndrome, Nephrocalcinosis, Nephrogenic Systemic Fibrosis, Nephroptosis (Floating Kidney, Renal Ptosis), Nephrotic Syndrome, Neurogenic Bladder, 9/11 and Kidney Disease, Nodular Glomerulosclerosis, Non-Gonococcal Urethritis, Nuteracker syndrome, Oligomeganephronia, Orofaciodigital Syndrome, Orotic Aciduria, Orthostatic Hypotension, Orthostatic Proteinuria, Osmotic Diuresis, Osmotic Nephrosis, Ovarian Hyperstimulation Syndrome, Oxalate Nephropathy, Page Kidney, Papillary Necrosis, Papillorenal Syndrome (Renal-Coloboma Syndrome, Isolated Renal Hypoplasia), PARN Mutations and Kidney Disease, Parvovirus B19 and the Kidney, The Peritoneal-Renal Syndrome, POEMS Syndrome, Posterior Urethral Valve, Podocyte Infolding Glomerulopathy, Post-infectious Glomerulonephritis, Post-streptococcal Glomerulonephritis, Post-infectious Glomerulonephritis, Atypical, Post-Infectious Glomerulonephritis (IgA-Dominant), Mimicking IgA Nephropathy, Polyarteritis Nodosa, Polycystic Kidney Disease, Posterior Urethral Valves, Post-Obstructive Diuresis, Preeclampsia, Propofol infusion syndrome, Proliferative Glomerulonephritis with Monoclonal IgG Deposits (Nasr Disease), Propolis (Honeybee Resin) Related Renal Failure, Proteinuria (Protein in Urine), Pseudohyperaldosteronism, Pseudohypobicarbonatemia, Pseudohypoparathyroidism, Pulmonary-Renal Syndrome, Pyelonephritis (Kidney Infection), Pyonephrosis, Pyridium and Kidney Failure, Radiation~~

Nephropathy, Ranolazine and the Kidney, Refeeding syndrome, Reflux Nephropathy, Rapidly Progressive Glomerulonephritis, Renal Abscess, Peripnephric Abscess, Renal Agenesis, Renal Arcuate Vein Microthrombi-Associated Acute Kidney Injury, Renal Artery Aneurysm, Renal Artery Dissection, Spontaneous, Renal Artery Stenosis, Renal Cell Cancer, Renal Cyst, Renal Hypouricemia with Exercise-induced Acute Renal Failure, Renal Infarction, Renal Osteodystrophy, Renal Tubular Acidosis, Renin Mutations and Autosomal Dominant Tubulointerstitial Kidney Disease, Renin Secreting Tumors (Juxtaglomerular Cell Tumor), Reset Osmostat, Retrocaval Ureter, Retroperitoneal Fibrosis, Rhabdomyolysis, Rhabdomyolysis related to Bariatric Sugery, Rheumatoid Arthritis-Associated Renal Disease, Sarcoidosis Renal Disease, Salt Wasting, Renal and Cerebral, Schistosomiasis and Glomerular Disease, Schimke immuno-osseous dysplasia, Scleroderma Renal Crisis, Serpentine Fibula-Polycystic Kidney Syndrome, Exner Syndrome, Sickle Cell Nephropathy, Silica Exposure and Chronic Kidney Disease, Sri Lankan Farmers' Kidney Disease, Sjögren's Syndrome and Renal Disease, Synthetic Cannabinoid Use and Acute Kidney Injury, Kidney Disease Following Hematopoietic Cell Transplantation, Kidney Disease Related to Stem Cell Transplantation, TAFRO Syndrome, Tea and Toast Hyponatremia, Tenofovir-Induced Nephrotoxicity, Thin Basement Membrane Disease, Benign Familial Hematuria, Thrombotic Microangiopathy Associated with Monoclonal Gammopathy, Trench Nephritis, Trigonitis, Tuberculosis, Genitourinary, Tuberous Sclerosis, Tubular Dysgenesis, Immune Complex Tubulointerstitial Nephritis Due to Autoantibodies to the Proximal Tubule Brush Border, Tumor Lysis Syndrome, Uremia, Uremic Optic Neuropathy, Ureteritis Cystica, Ureterocele, Urethral Caruncle, Urethral Stricture, Urinary Incontinence, Urinary Tract Infection, Urinary Tract Obstruction, Urogenital Fistula, Uromodulin-Associated Kidney Disease, Vancomycin-Associated Cast Nephropathy, Vasomotor Nephropathy, Vesicointestinal Fistula, Vesicoureteral Reflux, VGEF Inhibition and Renal Thrombotic Microangiopathy, Volatile Anesthetics and Acute Kidney Injury, Von Hippel-Lindau Disease, Waldenstrom's Macroglobulinemic Glomerulonephritis, Warfarin-Related Nephropathy, Wasp Stings and Acute Kidney Injury, Wegener’s Granulomatosis, Granulomatosis with Polyangiitis, West Nile Virus and Chronic Kidney Disease, Wunderlich syndrome, Zellweger Syndrome, or Cerebrohepatorenal Syndrome.

55. The use of claim 38, wherein the hearing loss condition is selected from the group consisting of mitochondrial nonsyndromic hearing loss and deafness, hair cell death, age-related hearing loss, noise-induced hearing loss, genetic or inherited hearing loss, hearing loss experienced as a result of ototoxic exposure, hearing loss resulting from disease, and hearing loss resulting from trauma.

56. The use of claim 38, wherein the ocular disease cataracts, glaucoma, endoplasmic reticulum (ER) stress, autophagy deficiency, age-related macular degeneration (AMD), or diabetic retinopathy.

57. The use of any one of claims 38-56, wherein the compound of any one of claims 1-35 is to be administered with a second agent (e.g., agent for treating cancer, a neurodegenerative disease, a leukodystrophy, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, a mitochondrial disease, or a disease or disorder associated with impaired function of eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway).

58. Use of a compound of any one of claims 1-35 in the manufacture of a medicament for treating a disease related to a modulation of eIF2B activity or levels, eIF2α activity or levels, or the activity or levels of a component of the eIF2 pathway or the ISR pathway in a patient in need thereof.

59. The use of claim 58, wherein the modulation comprises an increase in eIF2B activity or levels, increase in eIF2α activity or levels, or increase in activity or levels of a component of the eIF2 pathway or the ISR pathway.

60. The use of claim 58, wherein the disease may be caused by a mutation to a gene or protein sequence related to a member of the eIF2 pathway (e.g., the eIF2α signaling pathway).

61. Use of a compound of any one of claims 1-35 in the manufacture of a medicament for treating a cancer in a patient in need thereof, wherein the compound is to be administered with an immunotherapeutic agent.

62. A compound of any one of claims 1-35 for use in treating a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, a mitochondrial disease or a disease related to a modulation of eIF2B activity or levels, eIF2α activity or levels, or the activity or levels of a component of the eIF2 pathway or the ISR pathway in a patient in need thereof.

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