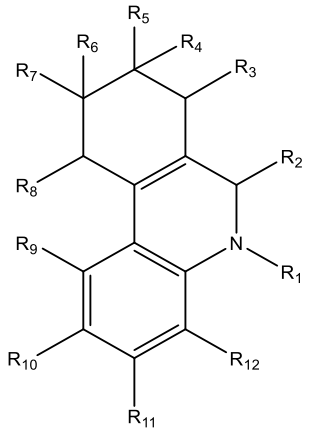
SUMMARY

[0005] Described herein are compounds for use in treating or reducing onset or development of a disease or condition associated with TDP-43 toxicity, and methods of using the same for the treatment, inhibition, amelioration, prevention, or slowing of a disease or condition associated with TDP-43 toxicity.

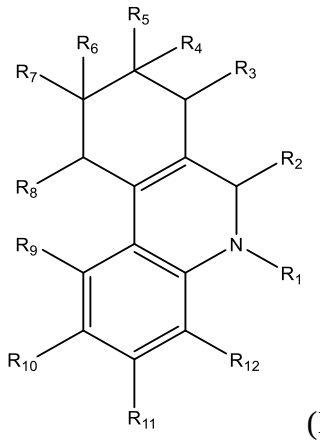
[0005a] In one aspect, the present disclosure provides a use of a pharmaceutical composition in the manufacture of a medicament for use in the treatment of a disease or condition associated with TAR DNA-binding protein 43 (TDP-43) toxicity, wherein the composition comprises a therapeutically effective amount of a compound of Formula (I), an analogue, derivative, or a pharmaceutically acceptable salt thereof:



(I)

wherein: R_1 is H, OH, or lower alkyl; R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; at least one of R_9 and R_{10}, R_{10} and R_{11}, or R_{11} and R_{12}, together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused

rings of Formula (I) is optionally replaced with a nitrogen atom. **[0005b]** In another aspect, the present disclosure provides a use of a pharmaceutical composition in the manufacture of a medicament for use in reducing or inhibiting TAR DNA-binding protein 43 (TDP-43) in a subject, wherein the subject is in need of a compound that reduces or inhibits TDP-43; and wherein the pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula (I), an analogue, derivative, or a pharmaceutically acceptable salt thereof:

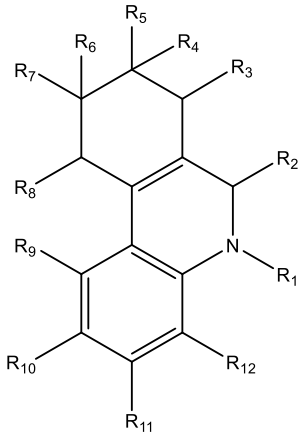


(I)

wherein: R_1 is H, OH, or lower alkyl; R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; at least one of R_9 and R_{10}, R_{10} and R_{11}, or R_{11} and R_{12}, together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formula (I) is optionally replaced with a nitrogen atom.

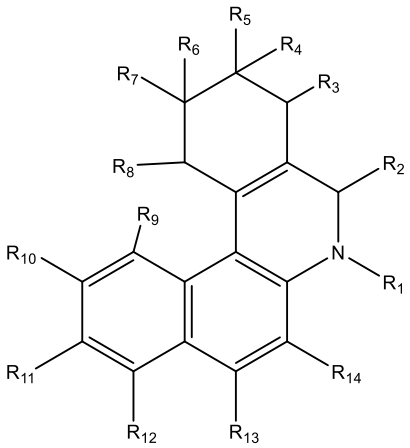
[0006] Some examples provided herein relate to pharmaceutical compositions. In some examples, the pharmaceutical composition is for use in the treatment of a disease or

condition associated with TAR DNA-binding protein 43 (TDP-43) toxicity. In some examples, the composition comprises a therapeutically effective amount of a compound of Formula (I), an analogue, derivative, or a pharmaceutically acceptable salt thereof:

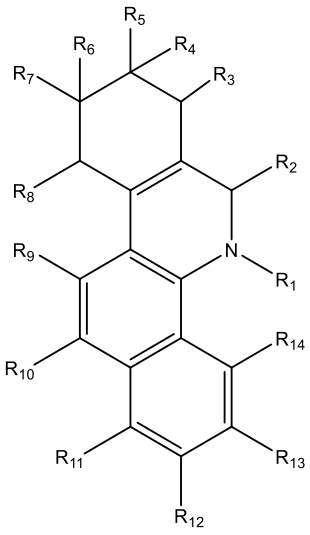


(I)

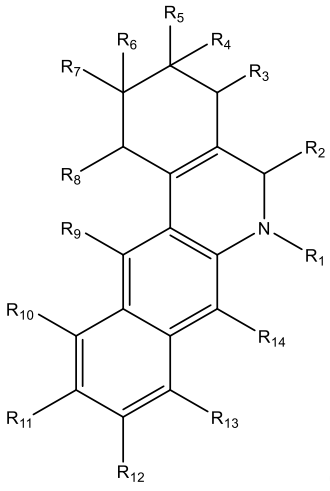
wherein R_1 is H, OH, or lower alkyl; R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; at least one of R_9 and R_{10}, R_{10} and R_{11}, or R_{11} and R_{12} together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formula (I) is optionally replaced with a nitrogen atom. In some examples, the compound of Formula (I) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, compound of Formula (I) is a compound of any one of Formula (II), (III), or (IV):



(II),



(III), or

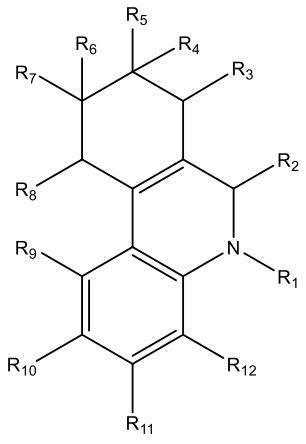


(IV)

wherein R_1 is H, OH, or lower alkyl; R_2, is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of

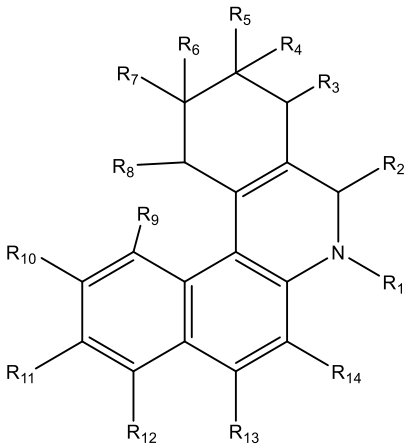
Formula (II), (III), or (IV) is optionally replaced with a nitrogen atom. In some examples, the compound of Formula (II) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, or ALT-414. In some examples, the compound of Formula (II) is ALT-59. In some examples, the compound of Formula (III) is ALT-108, ALT-317, ALT-333, or ALT-403. In some examples, the compound of Formula (IV) is ALT-205. In some examples, the pharmaceutical composition is for use in the treatment of cystic fibrosis. In some examples, composition inhibits the progression or development of cystic fibrosis. In some examples, the pharmaceutical composition is for use in the treatment of a neurodegenerative disease. In some examples, the composition inhibits the progression or development of the neurodegenerative disease. In some examples, the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, hippocampal sclerosis of aging (HS-Aging), chronic traumatic encephalopathy, or Parkinson's disease. In some examples, the compound of Formula (I) is present in an amount of 0.01 mg to 3000 mg. In some examples, the composition is formulated for oral or parenteral administration.

[0007] Some examples provided herein relate to methods of reducing or inhibiting TAR DNA-binding protein 43 (TDP-43) in a subject. In some examples, the methods include selecting a subject in need of a compound that reduces or inhibits TDP-43 and administering to the subject a composition comprising a therapeutically effective amount of a compound of any one of Formula (I), an analogue, derivative, or a pharmaceutically acceptable salt thereof:

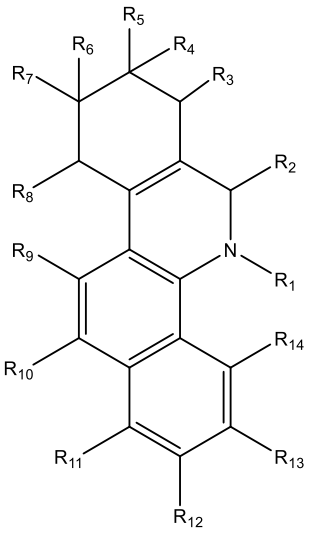


(I)

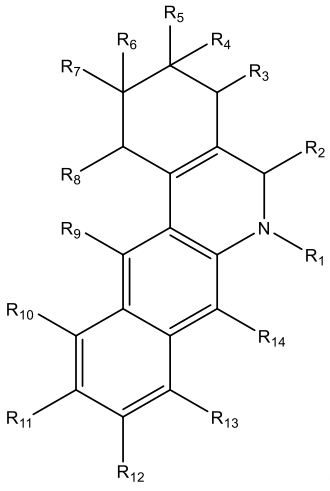
wherein R_1 is H, OH, or lower alkyl; R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; at least one of R_9 and R_{10}, R_{10} and R_{11}, or R_{11} and R_{12} together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formula (I) is optionally replaced with a nitrogen atom. In some examples, the compound of Formula (I) is a compound of any one of Formula (II), (III), or (IV):



(II),



(III), or

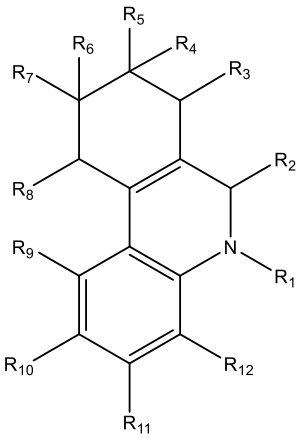


(IV)

wherein R_1 is H, OH, or lower alkyl; R_2, is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of

Formulas (II), (III), or (IV) is optionally replaced with a nitrogen atom. In some examples, the subject is identified as having a disease or condition associated with TDP-43 toxicity. In some examples, the disease is cystic fibrosis or a neurodegenerative disease. In some examples, the method inhibits or delays the progression or development of cystic fibrosis or of the neurodegenerative disease. In some examples, the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, hippocampal sclerosis of aging (HS-Aging), chronic traumatic encephalopathy, or Parkinson's disease. In some examples, the compound of Formula (I) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, the compound of Formula (I) is ALT-59. In some examples, the composition is administered to the subject orally or parenterally. In some examples, TDP-43 is reduced by at least 10%.

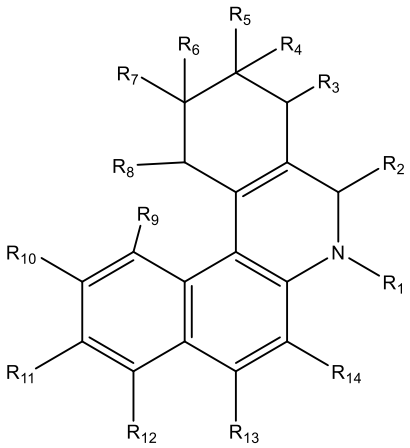
[0008] Some examples provided herein relate to methods of treating a subject suffering from a disease or condition associated with TAR DNA-binding protein 43 (TDP-43) toxicity. In some examples, the methods including identifying a subject in need of a compound that reduces, inhibits, delays, ameliorates, or prevents TDP-43 toxicity and administering to the subject a composition comprising a therapeutically effective amount of a compound of Formula (I), an analogue, derivative, or a pharmaceutically acceptable salt thereof:



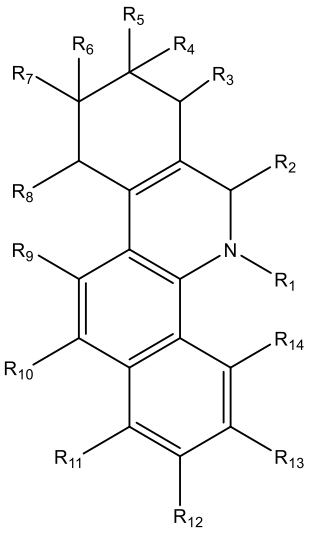
(I)

wherein R_1 is H, OH, or lower alkyl; R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2,

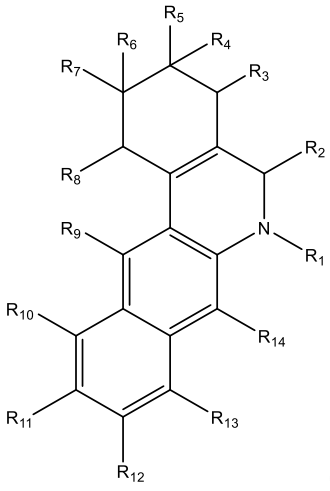
lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; at least one of R_9 and R_{10}, R_{10} and R_{11}, or R_{11} and R_{12} together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formula (I) is optionally replaced with a nitrogen atom. In some examples, the compound of Formula (I) is a compound of any one of a compound of Formula (II), (III), or (IV):



(II),



(III), or

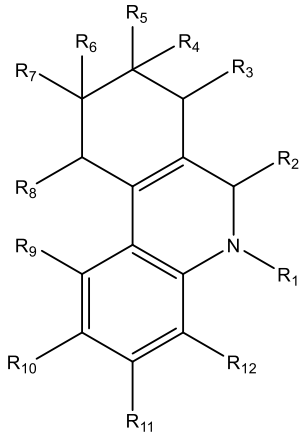


(IV)

wherein R_1 is H, OH, or lower alkyl; R_2, is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of

Formulas (II), (III), or (IV) is optionally replaced with a nitrogen atom. In some examples, the disease is cystic fibrosis or a neurodegenerative disease. In some examples, the method inhibits or delays the progression or development of cystic fibrosis or of the neurodegenerative disease. In some examples, the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, hippocampal sclerosis of aging (HS-Aging), chronic traumatic encephalopathy, or Parkinson's disease. In some examples, the compound of Formula (I) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-208, ALT-207, ALT-208, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, the compound of Formula (I) is ALT-59. In some examples, the composition is administered to the subject orally or parenterally. In some examples, the method reduces TDP-43 toxicity.

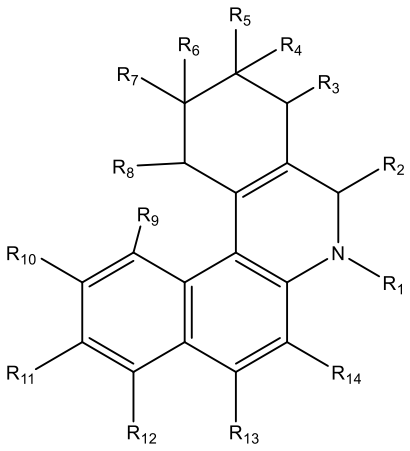
[0009] Some examples provided herein relate to uses of a compound of Formula (I) in the manufacture of a medicament for the treatment of a disease or condition associated with TAR DNA-binding protein 43 (TDP-43) toxicity in a subject, wherein the compound of Formula (I) has the structure:



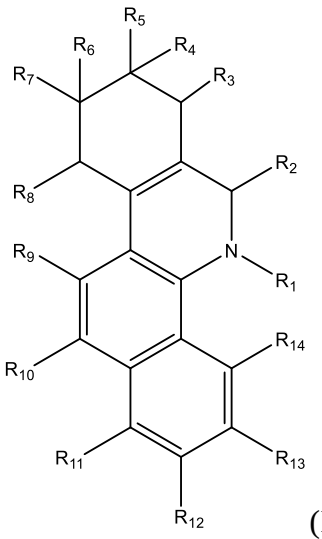
(I)

wherein R_1 is H, OH, or lower alkyl; R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the

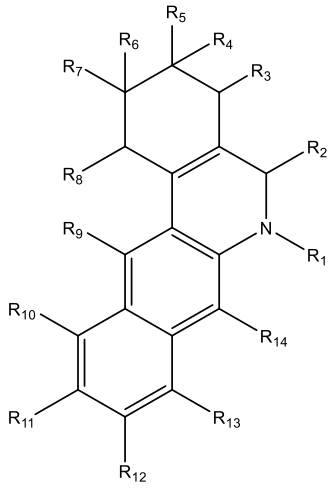
group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; at least one of R_9 and R_{10}, R_{10} and R_{11}, or R_{11} and R_{12} together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formula (I) is optionally replaced with a nitrogen atom. In some examples, the compound of Formula (I) is a compound of any one of Formula (II), (III), or (IV):



(II),



(III), or

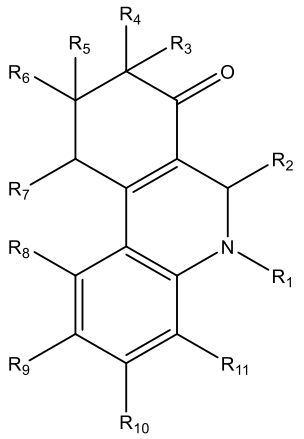


(IV)

wherein R_1 is H, OH, or lower alkyl; R_2, is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2,

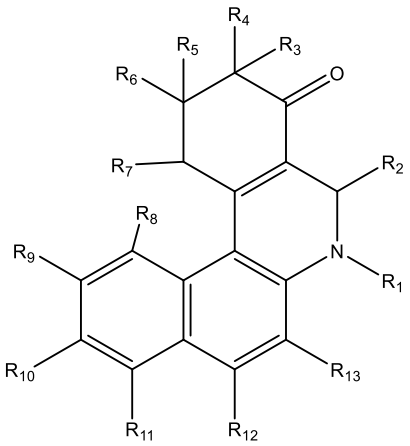
lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formulas (II), (III), or (IV) is optionally replaced with a nitrogen atom. In some examples, the disease is cystic fibrosis or a neurodegenerative disease. In some examples, the medicament inhibits or delays the progression or development of cystic fibrosis or of the neurodegenerative disease. In some examples, the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, hippocampal sclerosis of aging (HS-Aging), chronic traumatic encephalopathy, or Parkinson's disease. In some examples, the compound of Formula (I) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-207, ALT-208, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, the compound of Formula (I) is ALT-59.

[0010] In some examples, the compound of Formula (I) is a compound of any one of Formula (V), (VI), (VII), or (VIII). Some examples provided herein relate to pharmaceutical compositions. In some examples, the pharmaceutical composition is for use in the treatment of a disease or condition associated with TAR DNA-binding protein 43 (TDP-43) toxicity. In some examples, the composition comprises a therapeutically effective amount of a compound of Formula (V), an analogue, derivative, or a pharmaceutically acceptable salt thereof:

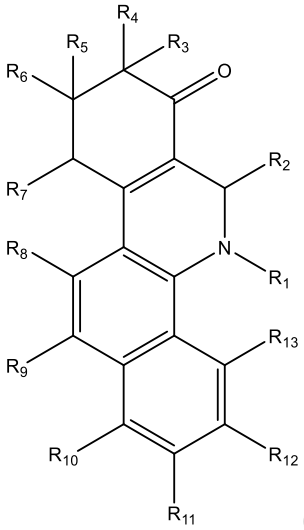


(V)

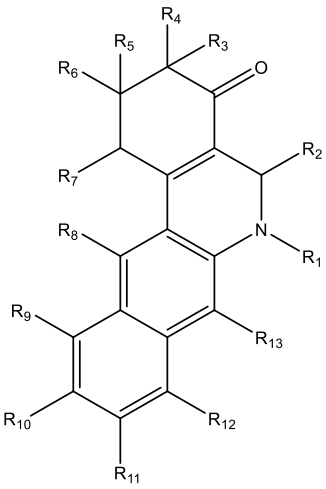
wherein R_1 is H, OH, or lower alkyl; R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3, R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; at least one of R_8 and R_9, R_9 and R_{10}, or R_{10} and R_{11} together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formula (V) is optionally replaced with a nitrogen atom. In some examples, the compound of Formula (V) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, the compound of Formula (V) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, compound of Formula (V) is a compound of any one of Formula (VI), (VII), or (VIII):



(VI),



(VII), or

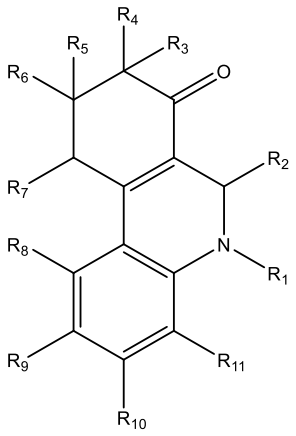


(VIII)

wherein R_1 is H, OH, or lower alkyl; R_2, is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3, R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are each independently H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formula (VI), (VII), or (VIII) is optionally replaced with a nitrogen atom. In some examples, the compound of Formula (VI) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-

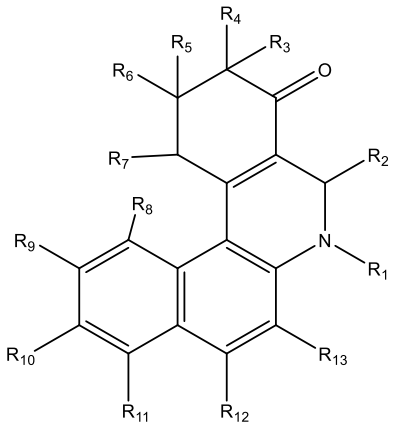
211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, or ALT-414. In some examples, the compound of Formula (VI) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, or ALT-414. In some examples, the compound of Formula (VI) is ALT-59. In some examples, the compound of Formula (VII) is ALT-108, ALT-317, ALT-333, or ALT-403. In some examples, the compound of Formula (VIII) is ALT-205. In some examples, the pharmaceutical composition is for use in the treatment of cystic fibrosis. In some examples, composition inhibits the progression or development of cystic fibrosis. In some examples, the pharmaceutical composition is for use in the treatment of a neurodegenerative disease. In some examples, the composition inhibits the progression or development of the neurodegenerative disease. In some examples, the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, hippocampal sclerosis of aging (HS-Aging), chronic traumatic encephalopathy, or Parkinson's disease. In some examples, the compound of Formula (V) is present in an amount of 0.01 mg to 3000 mg. In some examples, the composition is formulated for oral or parenteral administration.

[0011] Some examples provided herein relate to methods of reducing or inhibiting TAR DNA-binding protein 43 (TDP-43) in a subject. In some examples, the methods include selecting a subject in need of a compound that reduces or inhibits TDP-43 and administering to the subject a composition comprising a therapeutically effective amount of a compound of any one of Formula (V), an analogue, derivative, or a pharmaceutically acceptable salt thereof:

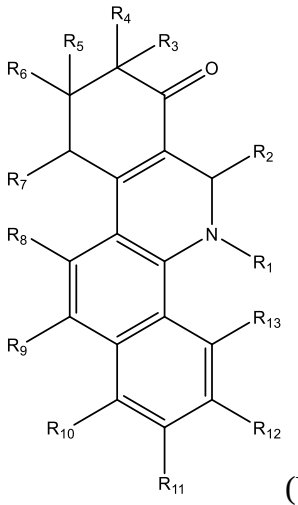


(V)

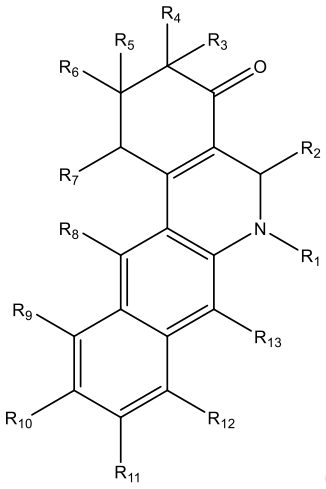
wherein R_1 is H, OH, or lower alkyl; R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3, R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; at least one of R_8 and R_9, R_9 and R_{10}, or R_{10} and R_{11} together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formula (V) is optionally replaced with a nitrogen atom. In some examples, the compound of Formula (V) is a compound of any one of Formula (VI), (VII), or (VIII):



(VI),



(VII), or

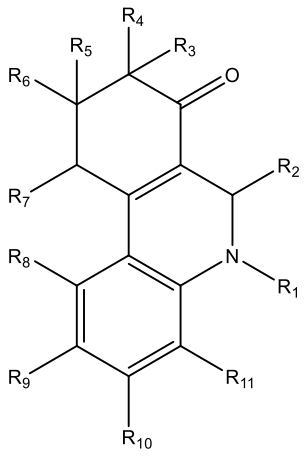


(VIII)

wherein R_1 is H, OH, or lower alkyl; R_2, is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3, R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are each independently H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formulas (VI), (VII), or (VIII) is optionally replaced with a nitrogen atom. In some examples, the subject is identified as having a disease or condition associated with TDP-43 toxicity. In some examples, the disease is cystic fibrosis or a neurodegenerative disease. In

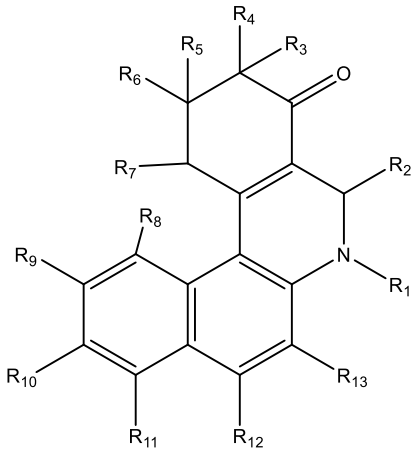
some examples, the method inhibits or delays the progression or development of cystic fibrosis or of the neurodegenerative disease. In some examples, the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, hippocampal sclerosis of aging (HS-Aging), chronic traumatic encephalopathy, or Parkinson's disease. In some examples, the compound of Formula (V) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, the compound of Formula (V) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, the compound of Formula (V) is ALT-59. In some examples, the composition is administered to the subject orally or parenterally. In some examples, TDP-43 is reduced by at least 10%.

[0012] Some examples provided herein relate to methods of treating a subject suffering from a disease or condition associated with TAR DNA-binding protein 43 (TDP-43) toxicity. In some examples, the methods including identifying a subject in need of a compound that reduces, inhibits, delays, ameliorates, or prevents TDP-43 toxicity and administering to the subject a composition comprising a therapeutically effective amount of a compound of Formula (V), an analogue, derivative, or a pharmaceutically acceptable salt thereof:

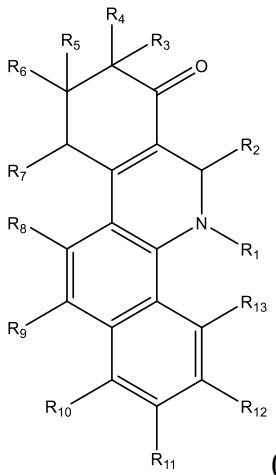


(V)

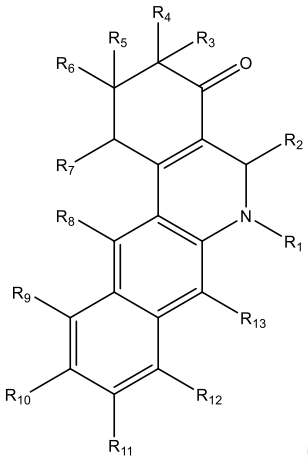
wherein R_1 is H, OH, or lower alkyl; R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3, R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; at least one of R_8 and R_9, R_9 and R_{10}, or R_{10} and R_{11} together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formula (V) is optionally replaced with a nitrogen atom. In some examples, the compound of Formula (V) is a compound of any one of a compound of Formula (VI), (VII), or (VIII):



(VI),



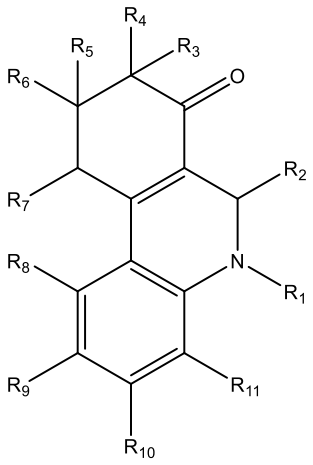
(VII), or



(VIII)

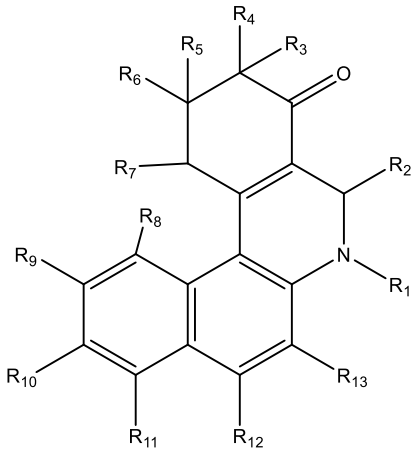
wherein R_1 is H, OH, or lower alkyl; R_2, is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3, R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are each independently H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formulas (VI), (VII), or (VIII) is optionally replaced with a nitrogen atom. In some examples, the disease is cystic fibrosis or a neurodegenerative disease. In some examples, the method inhibits or delays the progression or development of cystic fibrosis or of the neurodegenerative disease. In some examples, the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, hippocampal sclerosis of aging (HS-Aging), chronic traumatic encephalopathy, or Parkinson's disease. In some examples, the compound of Formula (V) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-208, ALT-207, ALT-208, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, the compound of Formula (V) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-202, ALT-204, ALT-208, ALT-207, ALT-208, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, the compound of Formula (V) is ALT-59. In some examples, the composition is administered to the subject orally or parenterally. In some examples, the method reduces TDP-43 toxicity.

[0013] Some examples provided herein relate to uses of a compound of Formula (V) in the manufacture of a medicament for the treatment of a disease or condition associated with TAR DNA-binding protein 43 (TDP-43) toxicity in a subject, wherein the compound of Formula (V) has the structure:

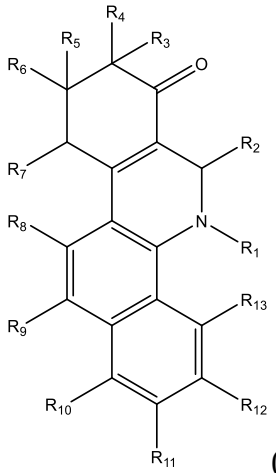


(V)

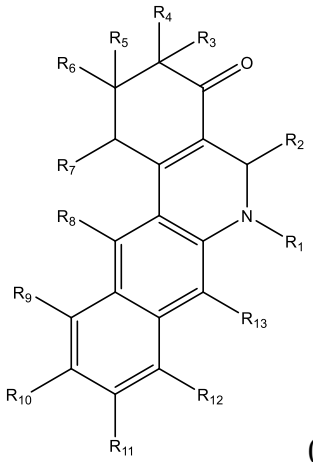
wherein R_1 is H, OH, or lower alkyl; R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3, R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; at least one of R_8 and R_9, R_9 and R_{10}, or R_{10} and R_{11} together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formula (V) is optionally replaced with a nitrogen atom. In some examples, the compound of Formula (V) is a compound of any one of Formula (VI), (VII), or (VIII):



(VI),



(VII), or



(VIII)

wherein R_1 is H, OH, or lower alkyl; R_2, is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring; R_3, R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino; R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are each independently H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and wherein any one of the carbon atoms on any one of fused rings of Formulas (VI), (VII), or (VIII) is optionally replaced with a nitrogen atom. In some examples, the disease is cystic fibrosis or a neurodegenerative disease. In some examples, the medicament inhibits or delays the progression or development of cystic fibrosis or of the neurodegenerative disease. In some examples, the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, hippocampal sclerosis of aging (HS-Aging), chronic traumatic encephalopathy, or Parkinson's disease. In some examples, the compound of Formula (V) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-207, ALT-208, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, the compound of Formula (V) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-202, ALT-204, ALT-207, ALT-208, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307,

ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205. In some examples, the compound of Formula (V) is ALT-59.

BRIEF DESCRIPTION OF THE DRAWINGS

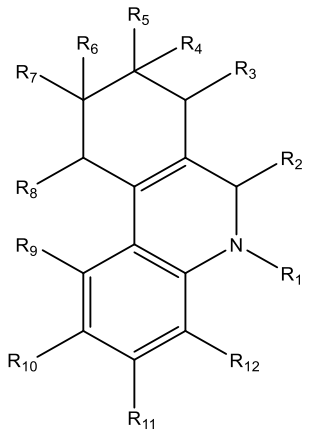
[0014] FIG. 1 depicts a blot showing isolation of ALT-59 binding proteins. Solid phase affinity precipitation was performed using cell lysates from PLC/PRF/5 and MDA-MB-231 cells. Precipitated proteins were resolved by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) gel and silver stained. A major band with an apparent molecular weight of 43 kDa were visualized from both samples.

[0015] FIG. 2 is a table showing a list of potential ALT-59 binding proteins identified by mass spectrometry. ALT-59 precipitated protein samples were subjected to mass spectrometry for protein identification. TDP-43 (boxed) was ranked as the top hit and is likely the 43 kDa band visualized in FIG. 1.

[0016] FIG. 3 depicts expression of histidine-tagged TDP-43 in *E. coli* whole cell lysates. Transformant Rosetta (DE3) cells with pRETb/TDP43-His were un-induced, induced with isopropyl β-D-1-thiogalactopyranoside (IPTG) alone, or together with ALT-59 (30 or 60 μM) or polymyxin B nonapeptide (PMBN) or both. PMBN increases the permeability of the outer membrane of Gram-negative bacteria for increased entry of ALT-59. In the presence of PMBN, ALT-59 at a concentration of 60 μM increased expression of TDP43-His, suggesting that ALT-59 can reduce toxicity caused by TDP-43 expression in bacteria. However, the

WHAT IS CLAIMED IS:

1. Use of a pharmaceutical composition in the manufacture of a medicament for use in the treatment of a disease or condition associated with TAR DNA-binding protein 43 (TDP-43) toxicity, wherein the composition comprises a therapeutically effective amount of a compound of Formula (I), an analogue, derivative, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1 is H, OH, or lower alkyl;

R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring;

R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino

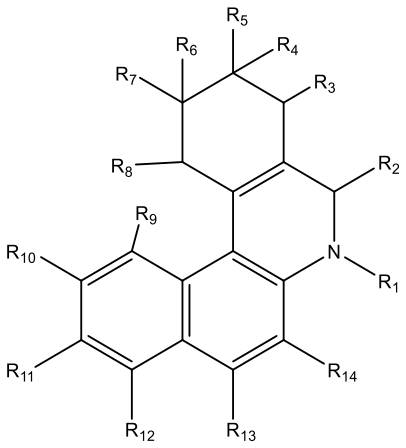
R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino;

at least one of R_9 and R_{10}, R_{10} and R_{11}, or R_{11} and R_{12}, together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and

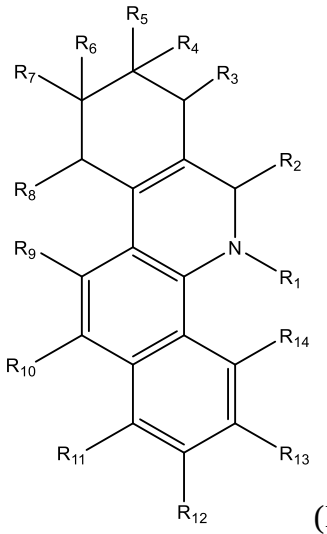
wherein any one of the carbon atoms on any one of fused rings of Formula (I) is optionally replaced with a nitrogen atom.

2. The use of claim 1, wherein the compound of Formula (I) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, ALT-414, ALT-108, ALT-317, ALT-333, ALT-403, or ALT-205.

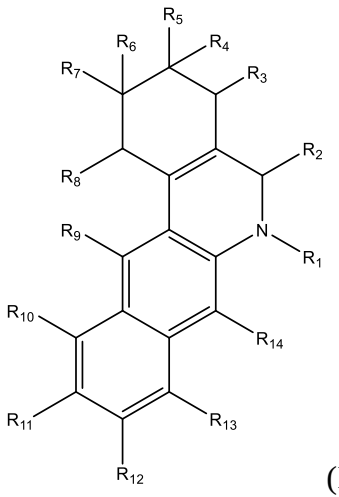
3. The use of claim 1, wherein the compound of Formula (I) is a compound of any one of Formula (II), (III), or (IV):



(II),



(III), or



(IV)

wherein:

R_1 is H, OH, or lower alkyl;

R_2, is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring;

R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino;

R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino;

R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14} are each independently H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and

wherein any one of the carbon atoms on any one of fused rings of Formula (II), (III), or (IV) is optionally replaced with a nitrogen atom.

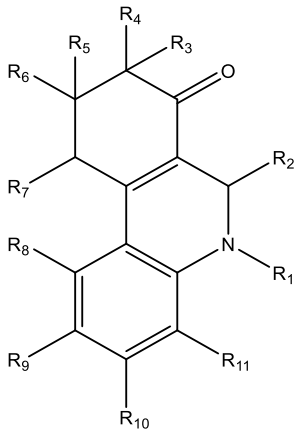
4. The use of claim 3, wherein the compound of Formula (II) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-201, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, or ALT-414.

5. The use of any one of claims 3-4, wherein the compound of Formula (II) is ALT-59.

6. The use of claim 3, wherein the compound of Formula (III) is ALT-108, ALT-317, ALT-333, or ALT-403.

7. The use of claim 3, wherein the compound of Formula (IV) is ALT-205.

8. The use of claim 1, wherein the compound of Formula (I) is a compound of Formula (V):



(V)

wherein:

R_1 is H, OH, or lower alkyl;

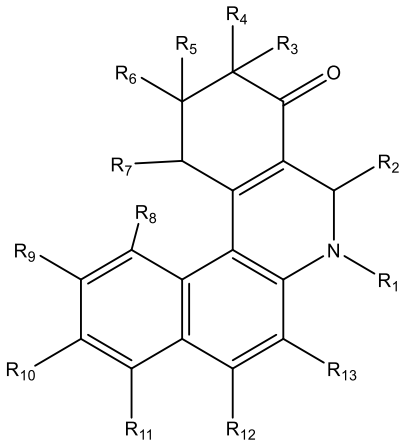
R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring;

R_3, R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino;

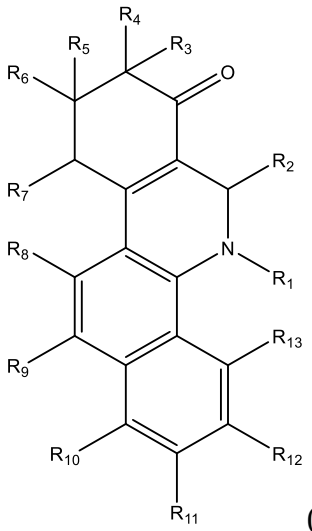
at least one of R_8 and R_9, R_9 and R_{10}, or R_{10} and R_{11} together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and

wherein any one of the carbon atoms on any one of fused rings of Formula (V) is optionally replaced with a nitrogen atom.

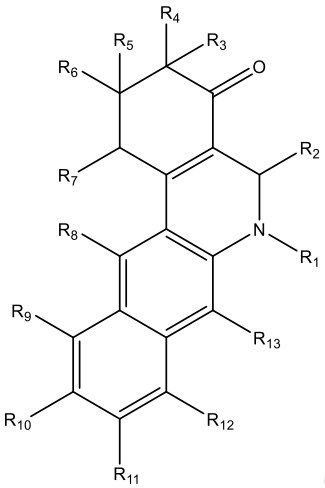
9. The use of claim 8, wherein the compound of Formula (V) is a compound of any one of Formula (VI), (VII), or (VIII):



(VI),



(VII), or



(VIII)

wherein:

R_1 is H, OH, or lower alkyl;

R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring;

R_3, R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino;

R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are each independently H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and

wherein any one of the carbon atoms on any one of fused rings of Formula (VI), (VII), or (VIII) is optionally replaced with a nitrogen atom.

10. The use of claim 9, wherein the compound of Formula (VI) is ALT-212, ALT-215, ALT-308, ALT-309, ALT-408, ALT-411, ALT-59, ALT-110, ALT-202, ALT-204, ALT-208, ALT-207, ALT-210, ALT-211, ALT-302, ALT-306, ALT-307, ALT-311, ALT-318, ALT-322, ALT-324, ALT-402, ALT-404, ALT-406, ALT-409, ALT-410, ALT-413, or ALT-414.

11. The use of any one of claims 9-10, wherein the compound of Formula (VI) is ALT-59.

12. The use of claim 9, wherein the compound of Formula (VII) is ALT-108, ALT-317, ALT-333, or ALT-403.

13. The use of claim 9, wherein the compound of Formula (VIII) is ALT-205.

14. The use of any one of claims 1-13, wherein the disease is cystic fibrosis.

15. The use of claim 14, wherein the composition inhibits or delays the progression or development of cystic fibrosis.

16. The use of any one of claim 1-15, wherein the disease is a neurodegenerative disease.

17. The use of claim 16, wherein the composition inhibits or delays the progression or development of the neurodegenerative disease.

18. The use of any one of claims 16-17, wherein the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, hippocampal sclerosis of aging (HS-Aging), chronic traumatic encephalopathy, or Parkinson's disease.

19. The use of any one of claims 1-18, wherein the compound of Formula (I) is present in an amount of 0.01 mg to 3000 mg.

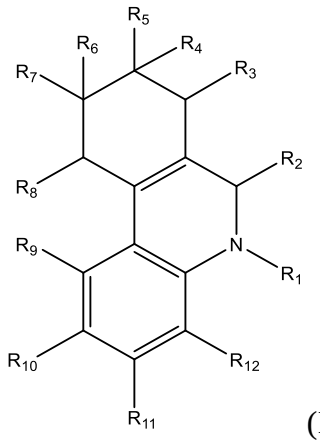
20. The use of any one of claims 1-19, wherein the composition is formulated for oral or parenteral administration.

21. The use of any one of claims 1-20, wherein the composition further comprises a pharmaceutically acceptable carrier or excipient.

22. Use of a pharmaceutical composition in the manufacture of a medicament for use in reducing or inhibiting TAR DNA-binding protein 43 (TDP-43) in a subject,

wherein the subject is in need of a compound that reduces or inhibits TDP-43; and

wherein the pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula (I), an analogue, derivative, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1 is H, OH, or lower alkyl;

R_2 is an optionally substituted aromatic ring of four, five, or six carbons, wherein the aromatic ring is carbocyclic or heterocyclic, and wherein each position on the aromatic ring is independently H, halo, lower alkyl, OH, lower alkoxy, NH_2, lower alkylamino, di(lower alkyl)amino, SH, lower alkylthio, NO_2, or two residues together form a heterocyclic ring;

R_3 and R_8 are each independently H, lower alkyl, =O, =S, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino

R_4, R_5, R_6, and R_7 are each independently H, lower alkyl, OH, NH_2, aryl, or aralkyl, where aryl and aralkyl are substituted with 0-3 moieties selected from the group consisting of halo, OH, NH_2, lower alkyl, lower alkoxy, SH, lower alkylthio, and lower alkylamino;

at least one of R_9 and R_{10}, R_{10} and R_{11}, or R_{11} and R_{12}, together form an optionally substituted benzene ring, wherein the benzene ring is optionally substituted with H, halo, lower alkyl, OH, lower alkoxy, or NO_2; and

wherein any one of the carbon atoms on any one of fused rings of Formula (I) is optionally replaced with a nitrogen atom.

23. The use of claim 22, wherein the subject is identified as having a disease or condition associated with TDP-43 toxicity.

24. The use of claim 23, wherein the disease is cystic fibrosis or a neurodegenerative disease.

25. The use of claim 24, wherein the composition inhibits or delays the progression or development of cystic fibrosis or of the neurodegenerative disease.

26. The use of any one of claims 24-25, wherein the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, hippocampal sclerosis of aging (HS-Aging), chronic traumatic encephalopathy, or Parkinson's disease.

27. The use of any one of claims 22-26, wherein the composition is to be administered to the subject orally or parenterally.

28. The use of any one of claims 22-27, wherein TDP-43 is reduced by at least 10%.

29. The use of any one of claims 1-21, wherein the composition reduces TDP-43 toxicity.