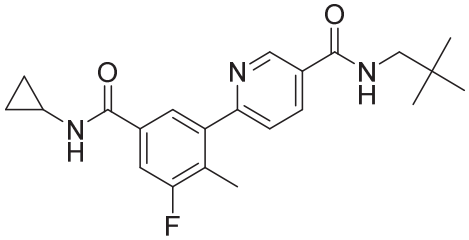
disease unique among muscular dystrophies. FSHD's primary manifestations are weakness and wasting of muscles of the face, shoulder girdle, upper arms, and trunk, and impacts lower extremities in more severe cases.

[006] Genetic mutations associated with FSHD lead to a partial decompaction of the *D4Z4* chromatin structure and a resulting failure to repress DUX4, a transcription factor encoded by the *D4Z4* unit, in skeletal muscle. FSHD1, representing about 95% of FSHD cases reported, is associated with deletions of macrosatellite *D4Z4* repeats in the subtelomeric region of chromosome 4q35, leaving 1–10 *D4Z4* repeats (reviewed in Tawil et. al., 2014). FSHD2 is caused by mutations in Structural Maintenance of Chromosomes Flexible Hinge Domain Containing 1 gene (*SMCHD1*) on chromosome 18 (reviewed in van der Maarel et. al., 2007). Both FSHD1 and FSHD2 mutations lead to loss of repression at the 4q35 *D4Z4* repeat array, allowing aberrant transcription in muscle of a full-length form of Double homeobox 4, DUX4, mRNA (*DUX4-fl*), which encodes the double homeobox 4 (DUX4) transcription factor (Tawil et. al., 2014). *DUX4-fl* RNA isoforms found associated with FSHD vary only in the 3′ untranslated region and have no identified functional distinction.

[007] There is currently no approved treatment that can halt or reverse the effects of FSHD, although nonsteroidal anti-inflammatory drug are often prescribed to improve comfort and mobility. Clearly, therefore, there is a need in the art for new methods for reducing the expression levels of DUX4, e.g., *DUX4-fl* mRNA and/or DUX4 protein, e.g., to treat FSHD and other diseases. The present invention meets this need.

SUMMARY

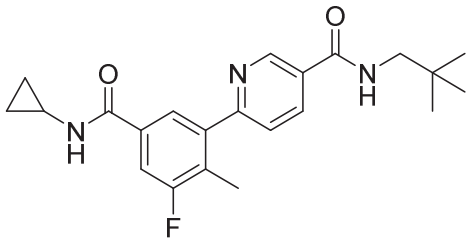
[008] In one example, a method for treating a disorder responsive to p38 kinase inhibition is provided. The method includes administering to a subject in need thereof, an effective amount of a p38 kinase inhibitor of Formula V′:



(V′),

or a stereoisomer thereof, an isotopically-enriched compound thereof, a prodrug thereof, a solvate thereof, or a pharmaceutically acceptable salt thereof. The method includes the treatment of disorders associated with DUX4 gene expression, wherein the inhibition of p38 kinase with a p38 kinase inhibitor may reduce DUX4 expression levels and/or the expression of one or more downstream genes in cells of the subject.

[008a] In one aspect, the present disclosure refers to use of a p38 kinase inhibitor in the manufacture of a medicament for treating facioscapulohumeral muscular dystrophy (FSHD) in a subject in need thereof, wherein the p38 kinase inhibitor is characterized by Formula (V′):

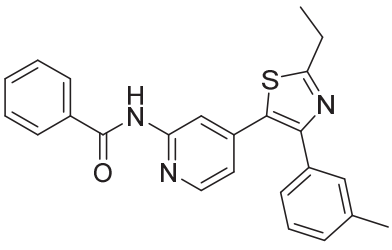


(V′),

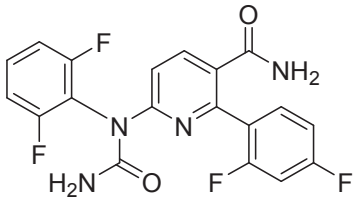
or a pharmaceutically acceptable salt thereof; and wherein administration of the p38 kinase inhibitor reduces expression levels of a DUX4 polypeptide and/or a polypeptide encoded by a DUX4 downstream gene in muscle cells of the subject.

[009] In another example, a method for treating facioscapulohumeral muscular dystrophy (FSHD) is provided. The method includes administering to a subject in need thereof, an effective amount of a p38 kinase inhibitor of Formula V′, or a stereoisomer thereof, an isotopically-enriched compound thereof, a prodrug thereof, a solvate thereof, or a pharmaceutically acceptable salt thereof.

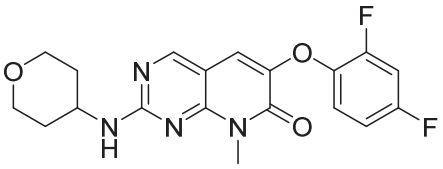
[0010] In one example, a method for treating a disorder responsive to p38 kinase inhibition is provided. The method includes administering to a subject in need thereof, an effective amount of a p38 kinase inhibitor selected from one or more of the following Formulae I′-XXIX′:



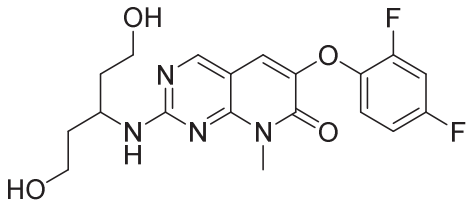
(I′),



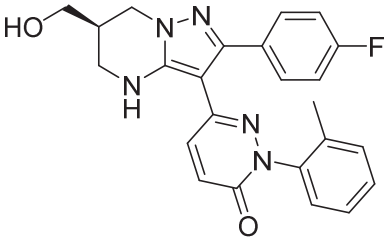
(II′),



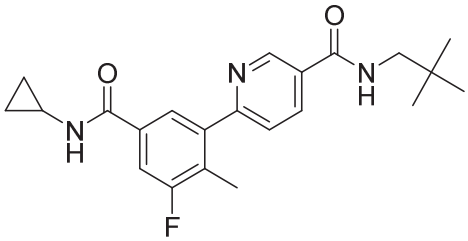
(III′a),



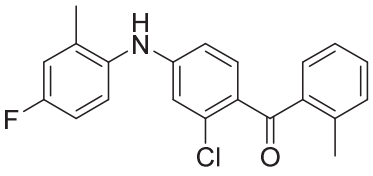
(III′b),



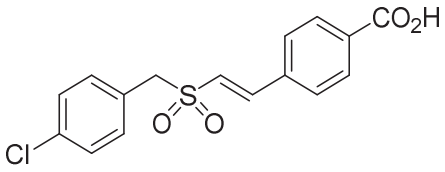
(IV′),



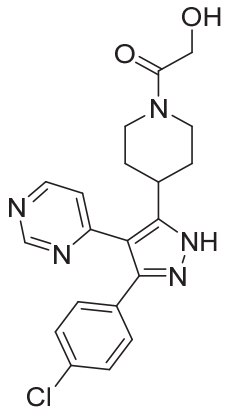
(V′),



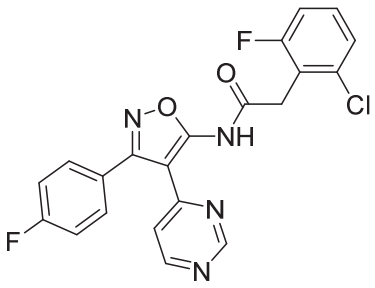
(XXII′),



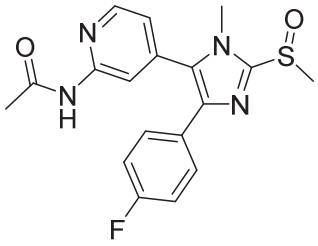
(XXIII′),



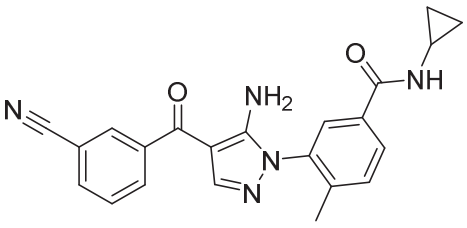
(XXIV′),



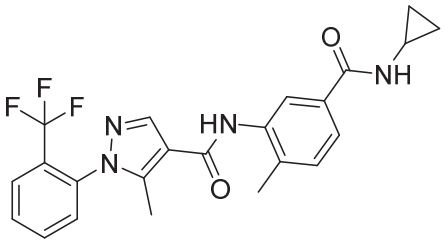
(XXV′),



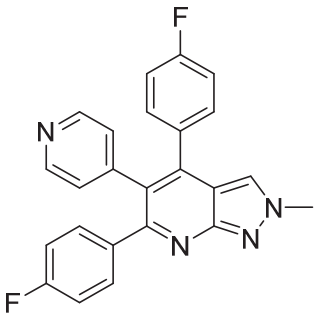
(XXVI′),



(XXVII′),



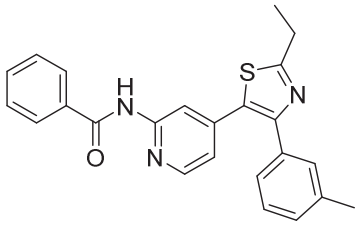
(XXVIII′), and



(XXIX′),

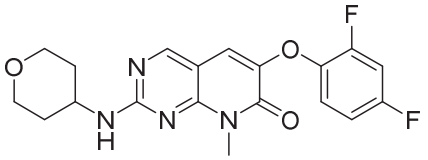
or a stereoisomer thereof, an isotopically-enriched compound thereof, a prodrug thereof, a solvate thereof, or a pharmaceutically acceptable salt thereof. The method includes the treatment of disorders associated with DUX4 gene expression, wherein the inhibition of p38 kinase with a p38 kinase inhibitor may reduce DUX4 expression levels and/or the expression of one or more downstream genes in cells of the subject.

[0010a] In one aspect, the present disclosure refers to use of a p38 kinase inhibitor in the manufacture of a medicament for treating facioscapulohumeral muscular dystrophy (FSHD) in a subject in need thereof, wherein the p38 kinase inhibitor is selected from:



(I')
"TAK-715"

,



(IIIa')
"R1487"

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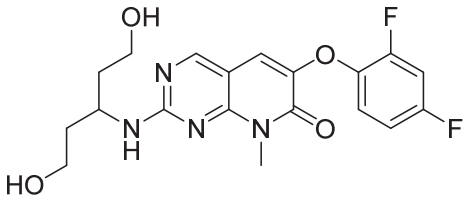
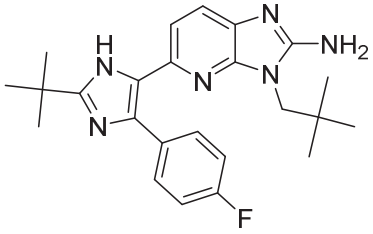


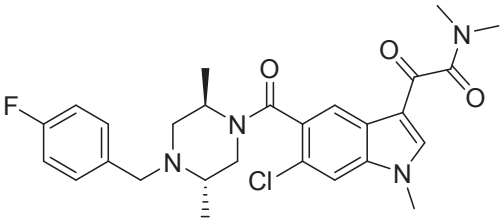
(IIIb')
"pamapimod" or "RO 4492257"

,



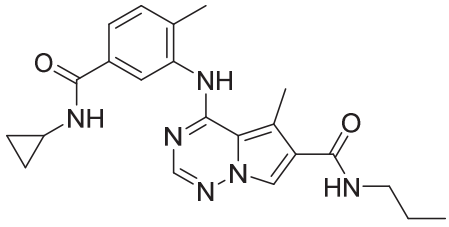
(VI')
"LY2228820" or "ralimetinib"

,



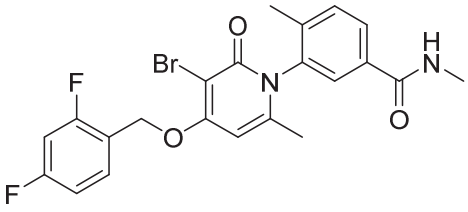
(VII')
"SCIO-469" or "talmapimod"

,



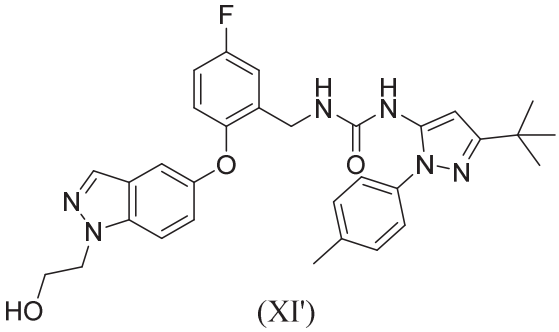
(IX")
"BMS-582949" or "PS-5404446"

,



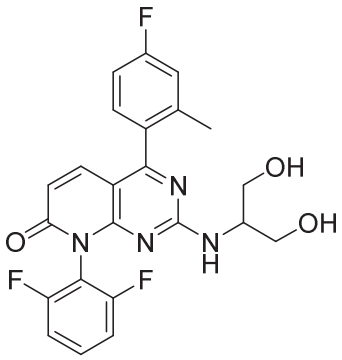
(X')
"PH-797804"

,

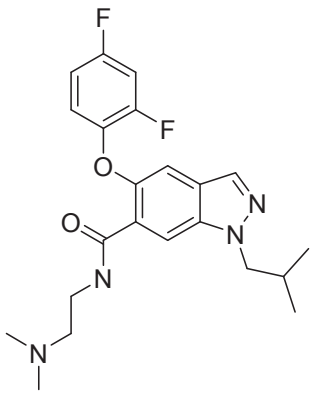


(XI')
"pexmetinib" or "ARRY-614"

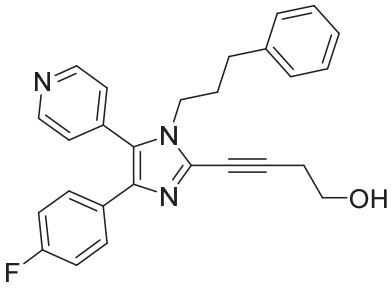
,



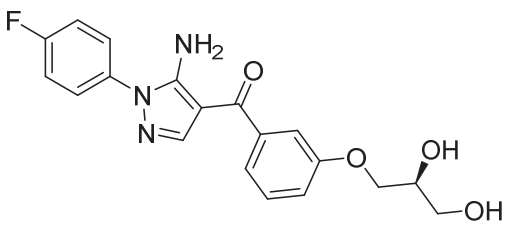
(XII')
"dilmapimod" or "SB-681323" ,



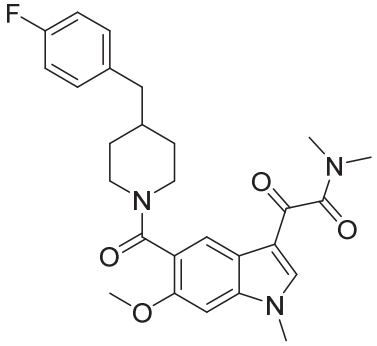
(XIV')
"ARRY-797" or "ARRY-371797" ,



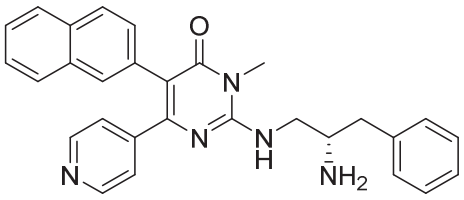
(XVI')
"RWJ-67657" ,



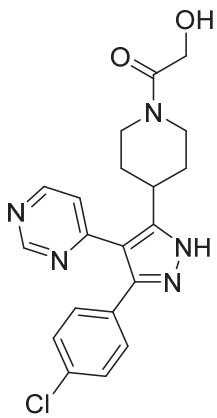
(XVIII')
"RO-3201195" ,



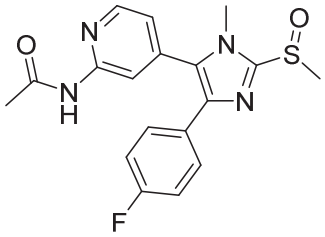
(XX')
"SCIO-323" ,



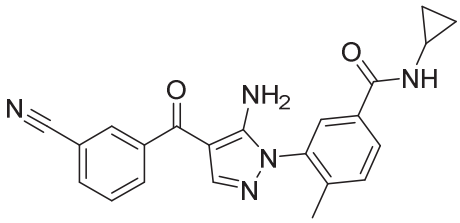
(XXI')
"AMG-548" ,



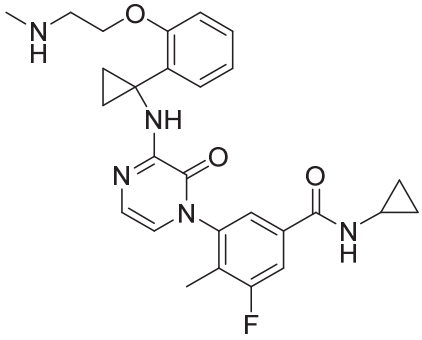
(XXIV')
"SD-0006" or "SD-06" ,



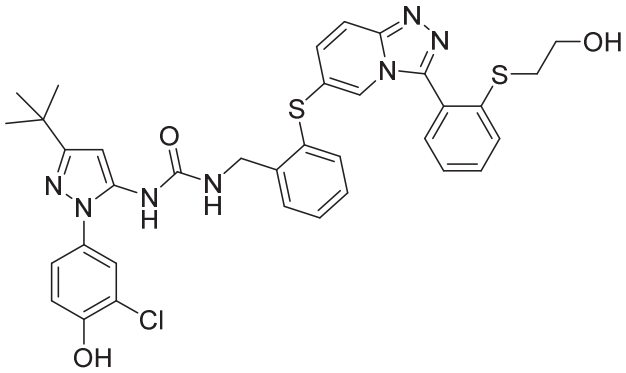
(XXVI')
"CBS-3595" or "ML-3595",



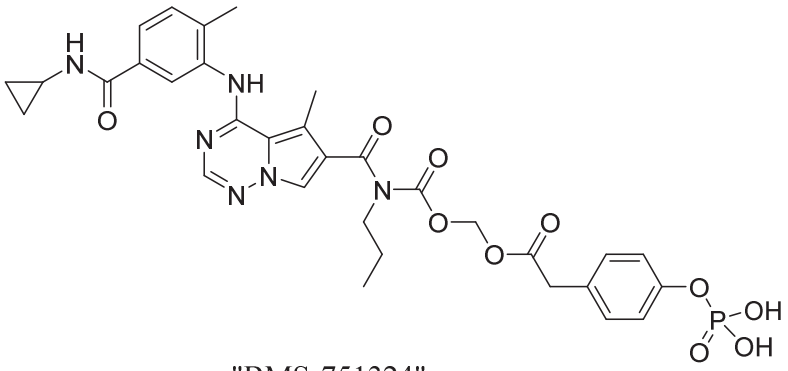
(XXVII')
"acumapimod" or "BCT-197",



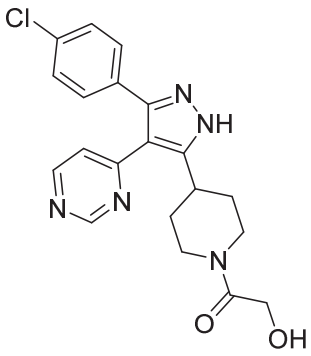
"AZD-7624",



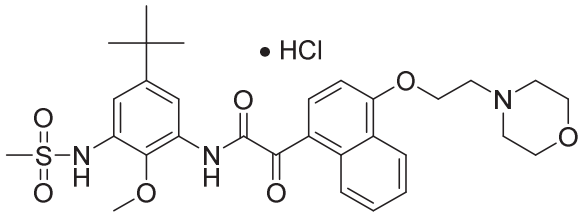
"PF-03715455",



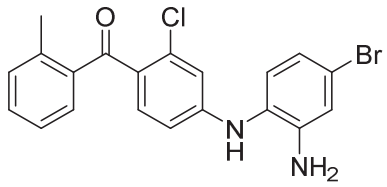
"BMS-751324"



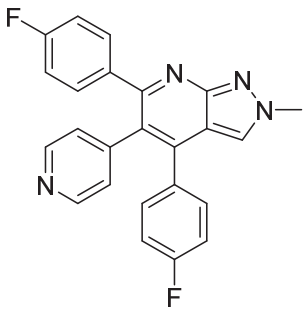
SC80036 ,



ITX-5061 ,



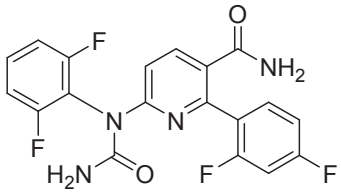
EO-1428 , and



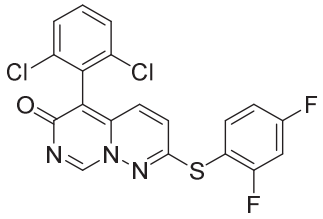
UR-13870 ,

or a pharmaceutically acceptable salt thereof; and wherein administration of the p38 kinase inhibitor reduces expression levels of a DUX4 polypeptide and/or a polypeptide encoded by a DUX4 downstream gene in muscle cells of the subject.

[0010b] In one aspect, the present disclosure refers to use of a p38 kinase inhibitor in the manufacture of a medicament for reducing expression levels of a DUX4 polypeptide and/or a polypeptide encoded by a DUX4 downstream gene in muscle cells in a subject in need thereof, wherein the p38 kinase inhibitor is selected from:

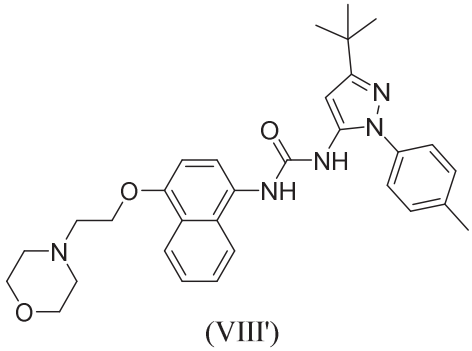


(II')
"VX-702"



(XIII')
"neflamapimod" or "VX-745"

, and



(VIII')
"doramapimod" or "BIRB-796"

,

or a pharmaceutically salt thereof; and wherein administration of the p38 kinase inhibitor reduces expression levels of a DUX4 polypeptide and/or a polypeptide encoded by a DUX4 downstream gene in muscle cells of the subject.

[0011] In another example, a method for treating facioscapulohumeral muscular dystrophy (FSHD) is provided. The method includes administering to a subject in need thereof, an

effective amount of a p38 kinase inhibitor selected from one or more of Formulae I′-XXIX′, or a stereoisomer thereof, an isotopically-enriched compound thereof, a prodrug thereof, a solvate thereof, or a pharmaceutically acceptable salt thereof.

[0012] In one example, a method for treating a disorder responsive to p38 kinase inhibition is provided. The method includes administering to a subject in need thereof, an effective amount of a p38 kinase inhibitor selected from one or more of Formulae I-XIII (of Genuses I-XIII described herein), or a stereoisomer thereof, an isotopically-enriched compound thereof, a prodrug thereof, a solvate thereof, or a pharmaceutically acceptable salt thereof. The method includes the treatment of disorders associated with DUX4 gene expression, wherein the inhibition of p38 kinase with a p38 kinase inhibitor may reduce DUX4 expression levels and/or the expression of one or more downstream genes in cells of the subject.

[0013] In another example, a method for treating facioscapulohumeral muscular dystrophy (FSHD) is provided. The method includes administering to a subject in need thereof, an effective amount of a p38 kinase inhibitor selected from one or more of Formulae I-XIII (of Genuses I-XIII described herein), or a stereoisomer thereof, an isotopically-enriched compound thereof, a prodrug thereof, a solvate thereof, or a pharmaceutically acceptable salt thereof.

[0014] In one example, a method for treating a disorder responsive to p38 kinase inhibition is provided. The method includes administering to a subject in need thereof, an effective amount of a p38 kinase inhibitor, or a stereoisomer thereof, an isotopically-enriched compound thereof, a prodrug thereof, a solvate thereof, or a pharmaceutically acceptable salt thereof. The method includes the treatment of disorders associated with DUX4 gene expression, wherein the inhibition of p38 kinase with a p38 kinase inhibitor may reduce DUX4 expression levels and/or the expression of one or more downstream genes in cells of the subject.

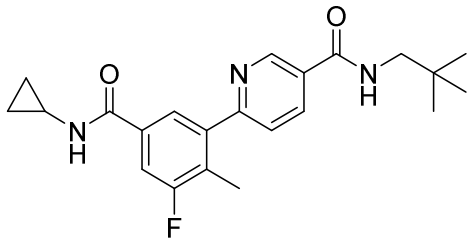
[0015] In several examples, a method for treating facioscapulohumeral muscular dystrophy (FSHD) is provided. The method includes administering to a subject in need thereof, an effective amount of a p38 kinase inhibitor described herein, or a stereoisomer thereof, an isotopically-enriched compound thereof, a prodrug thereof, a solvate thereof, or a pharmaceutically acceptable salt thereof.

CLAIMS

What is claimed is:

1. Use of a p38 kinase inhibitor in the manufacture of a medicament for treating facioscapulohumeral muscular dystrophy (FSHD) in a subject in need thereof,

wherein the p38 kinase inhibitor is characterized by Formula (V′):



(V′),

or a pharmaceutically acceptable salt thereof; and

wherein administration of the p38 kinase inhibitor reduces expression levels of a DUX4 polypeptide and/or a polypeptide encoded by a DUX4 downstream gene in muscle cells of the subject.

2. The use of claim 1, wherein the DUX4 downstream gene is selected from the group consisting of: ZSCAN4, LEUTX, PRAMEF2, TRIM43, MBD3L2, KHDC1L, RFPL2, CCNA1, SLC34A2, TPRX1, PRAMEF20, TRIM49, PRAMEF4, PRAME6, PRAMEF15, and ZNF280A.

3. The use of claim 1, wherein the muscle cells are terminally differentiated muscle cells.

4. The use of claim 1, wherein the muscle cells comprise a dysregulated *D4Z4* array at chromosome 4q35.

5. The use of claim 1, wherein the facioscapuloumeral muscular dystrophy is FSHD type 1 (FSHD1).

6. The use of claim 5, wherein the muscle cells comprise a deletion of one or more macrosatellite *D4Z4* repeats in the subtelomeric region of chromosome 4q35.

7. The use of claim 6, wherein the muscle cell comprises less than 11 macrosatellite *D4Z4* repeats in the subtelomeric region of chromosome 4q35.

8. The use of claim 1, wherein the facioscapuloumeral muscular dystrophy is FSHD type 2 (FSHD2).

9. The use of claim 8, wherein the muscle cells comprise one or more mutations in a *Structural Maintenance Of Chromosomes Flexible Hinge Domain Containing 1 (SMCHD1) gene.*

10. The use of claim 1, wherein the muscle cells comprise at least one non-deleted 4qA allele.

11. The use of claim 1, wherein administration of the p38 kinase inhibitor causes a decrease in muscle degeneration in the subject.

12. The use of claim 1, wherein administration of the p38 kinase inhibitor causes a reduction in apoptosis of muscle cells in the subject.

13. The use of claim 1, wherein the compound of Formula V′ or the pharmaceutically acceptable salt thereof is to be administered at a dose of 7.5 mg or 15 mg.

14. The use of claim 1, wherein the compound of Formula V′ or the pharmaceutically acceptable salt thereof is to be administered at a dose of 7.5 mg.

15. The use of claim 13, wherein the compound of Formula V′ or the pharmaceutically acceptable salt thereof is to be administered at a dose of 15 mg.

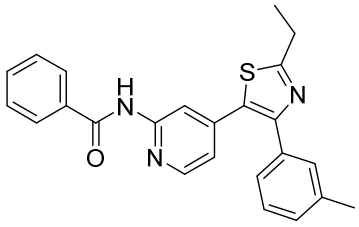
16. The use of claim 13, wherein the compound of Formula V′ or the pharmaceutically acceptable salt thereof is to be administered two times per day.

17. The use of claim 1, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered to the subject parenterally.

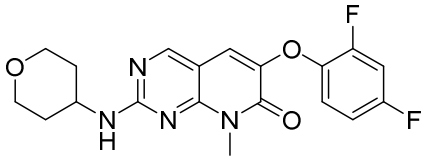
18. The use of claim 1, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered to the subject orally.

19. The use of claim 1, wherein another p38 kinase inhibitor agent is to be further administered to the subject.

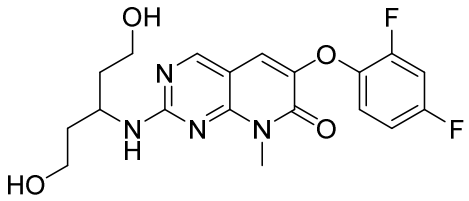
20. Use of a p38 kinase inhibitor in the manufacture of a medicament for treating facioscapulohumeral muscular dystrophy (FSHD) in a subject in need thereof, wherein the p38 kinase inhibitor is selected from:



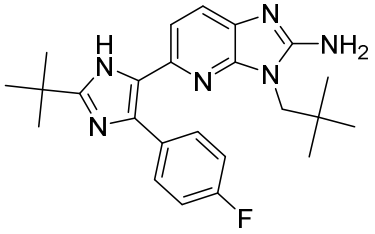
(I')
"TAK-715"



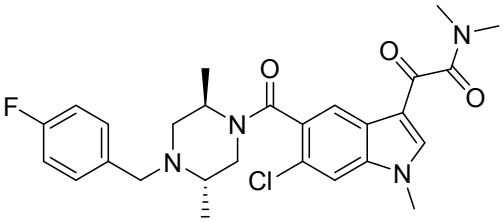
(IIIa')
"R1487"



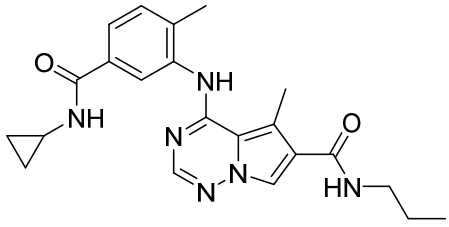
(IIIb')
"pamapimod" or "RO 4492257"



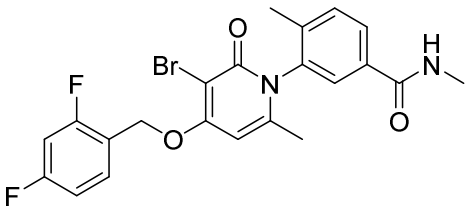
(VI')
"LY2228820" or "ralimetinib"



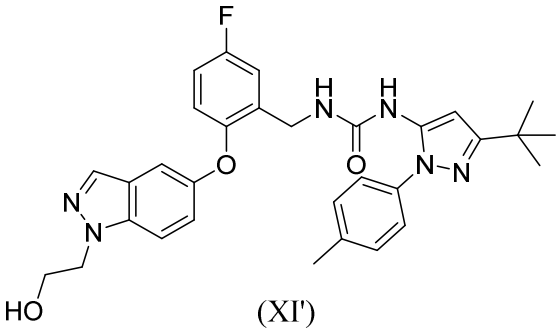
(VII')
"SCIO-469" or "talmapimod"



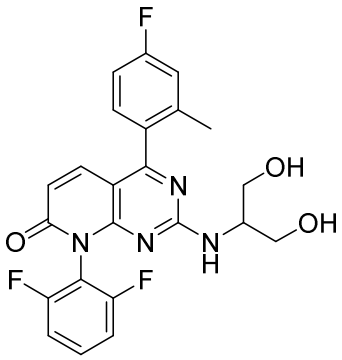
(IX")
"BMS-582949" or "PS-5404446"



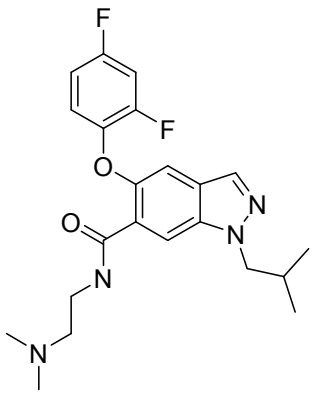
(X')
"PH-797804"



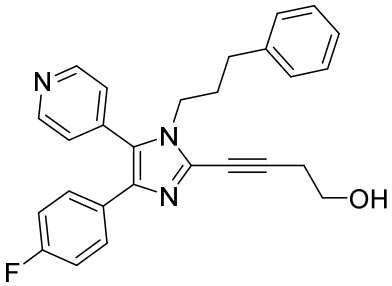
(XI')
"pexmetinib" or "ARRY-614"



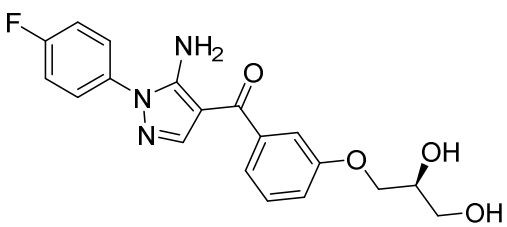
(XII')
"dilmapimod" or "SB-681323",



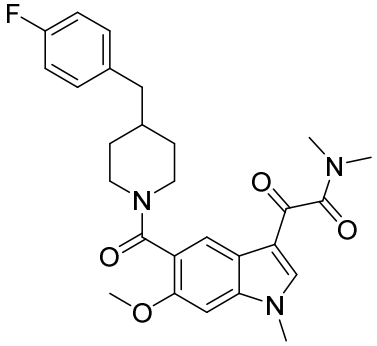
(XIV')
"ARRY-797" or "ARRY-371797",



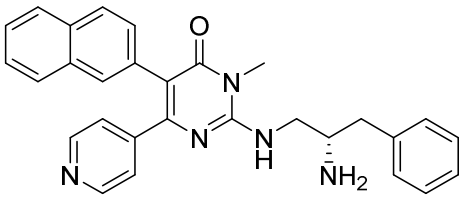
(XVI')
"RWJ-67657",



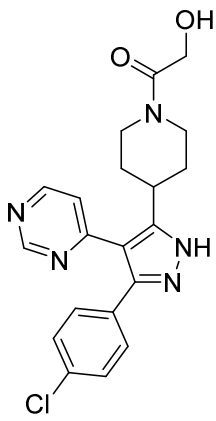
(XVIII')
"RO-3201195",



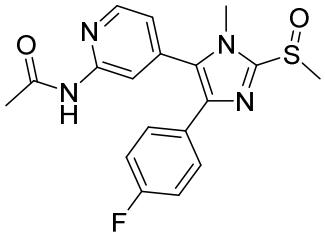
(XX')
"SCIO-323",



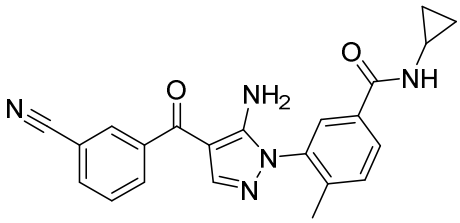
(XXI')
"AMG-548",



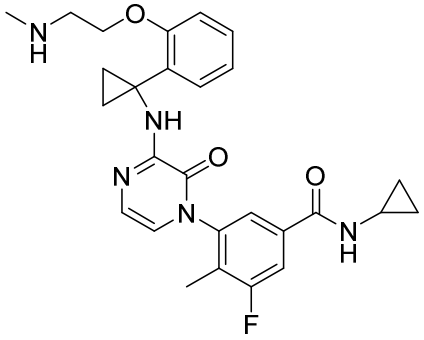
(XXIV')
"SD-0006" or "SD-06",



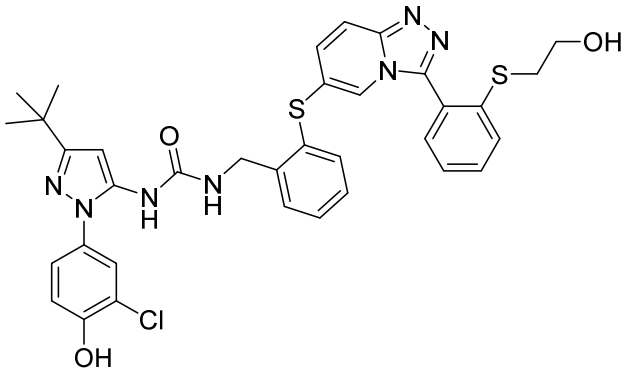
(XXVI')
"CBS-3595" or "ML-3595",



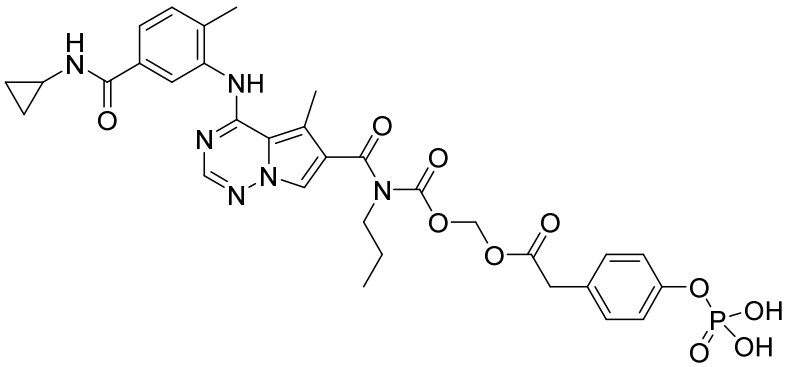
(XXVII')
"acumapimod" or "BCT-197",



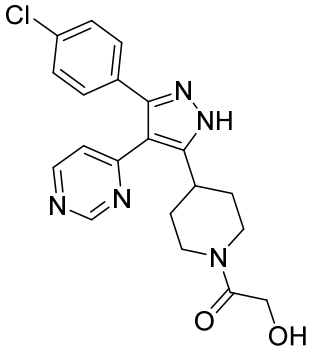
"AZD-7624",



"PF-03715455",



"BMS-751324"



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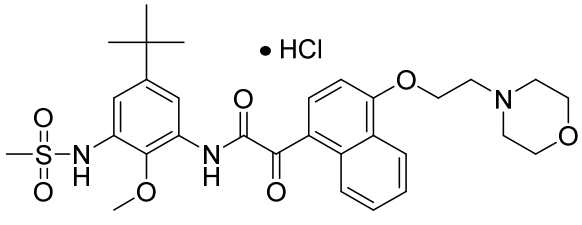
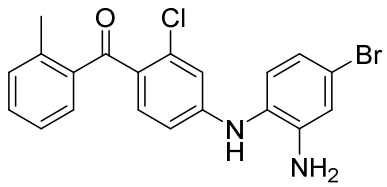
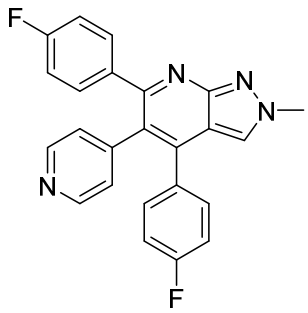


ITX-5061,



EO-1428

, and



UR-13870

,

or a pharmaceutically acceptable salt thereof; and

wherein administration of the p38 kinase inhibitor reduces expression levels of a DUX4 polypeptide and/or a polypeptide encoded by a DUX4 downstream gene in muscle cells of the subject.

21. The use of claim 20, wherein the DUX4 downstream gene is selected from the group consisting of: ZSCAN4, LEUTX, PRAMEF2, TRIM43, MBD3L2, KHDC1L, RFPL2, CCNA1, SLC34A2, TPRX1, PRAMEF20, TRIM49, PRAMEF4, PRAME6, PRAMEF15, and ZNF280A.

22. The use of claim 20, wherein the muscle cells are terminally differentiated muscle cells.

23. The use of claim 20, wherein the muscle cells comprise a dysregulated *D4Z4* array at chromosome 4q35.

24. The use of claim 20, wherein the facioscapuloumeral muscular dystrophy is FSHD type 1 (FSHD1).

25. The use of claim 24, wherein the muscle cells comprise a deletion of one or more macrosatellite *D4Z4* repeats in the subtelomeric region of chromosome 4q35.

26. The use of claim 25, wherein the muscle cell comprises less than 11 macrosatellite *D4Z4* repeats in the subtelomeric region of chromosome 4q35.

27. The use of claim 20, wherein the facioscapuloumeral muscular dystrophy is FSHD type 2 (FSHD2).

28. The use of claim 27, wherein the muscle cells comprise one or more mutations in a *Structural Maintenance Of Chromosomes Flexible Hinge Domain Containing 1 (SMCHD1) gene.*

29. The use of claim 20, wherein the muscle cells comprise at least one non-deleted 4qA allele.

30. The use of claim 20, wherein administration of the p38 kinase inhibitor causes a decrease in muscle degeneration in the subject.

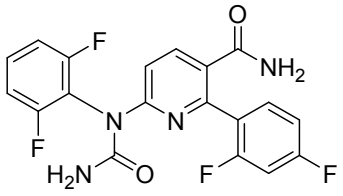
31. The use of claim 20, wherein administration of the p38 kinase inhibitor causes a reduction in apoptosis of muscle cells in the subject.

32. The use of claim 20, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered to the subject parenterally.

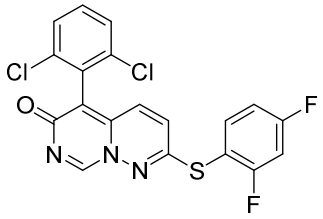
33. The use of claim 20, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered to the subject orally.

34. The use of claim 20, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered to the subject via inhalation.

35. Use of a p38 kinase inhibitor in the manufacture of a medicament for reducing expression levels of a DUX4 polypeptide and/or a polypeptide encoded by a DUX4 downstream gene in muscle cells in a subject in need thereof, wherein the p38 kinase inhibitor is selected from:

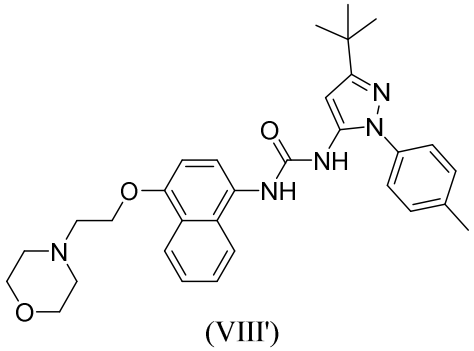


(II')
"VX-702"



(XIII')
"neflamapimod" or "VX-745"

, and



(VIII')
"doramapimod" or "BIRB-796"

,

or a pharmaceutically salt thereof; and

wherein administration of the p38 kinase inhibitor reduces expression levels of a DUX4 polypeptide and/or a polypeptide encoded by a DUX4 downstream gene in muscle cells of the subject.

36. The use of claim 35, wherein the DUX4 downstream gene is selected from the group consisting of: ZSCAN4, LEUTX, PRAMEF2, TRIM43, MBD3L2, KHDC1L, RFPL2, CCNA1, SLC34A2, TPRX1, PRAMEF20, TRIM49, PRAMEF4, PRAME6, PRAMEF15, and ZNF280A.

37. The use of claim 35, wherein the muscle cells are terminally differentiated muscle cells.

38. The use of claim 35, wherein the muscle cells comprise a dysregulated D4Z4 array at chromosome 4q35.

39. The use of claim 35, wherein the muscle cells comprise a deletion of one or more macrosatellite D4Z4 repeats in the subtelomeric region of chromosome 4q35.

40. The use of claim 39, wherein the muscle cell comprises less than 11 macrosatellite D4Z4 repeats in the subtelomeric region of chromosome 4q35.

41. The use of claim 35, wherein the muscle cells comprise one or more mutations in a *Structural Maintenance Of Chromosomes Flexible Hinge Domain Containing 1 (SMCHD1) gene.*

42. The use of claim 35, wherein the muscle cells comprise at least one non-deleted 4qA allele.

43. The use of claim 35, wherein administration of the p38 kinase inhibitor causes a decrease in muscle degeneration in the subject.

44. The use of claim 35, wherein administration of the p38 kinase inhibitor causes a reduction in apoptosis of muscle cells in the subject.

45. The use of claim 35, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered to the subject parenterally.

46. The use of claim 35, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered to the subject orally.

47. The use of claim 35, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered to the subject via inhalation.