

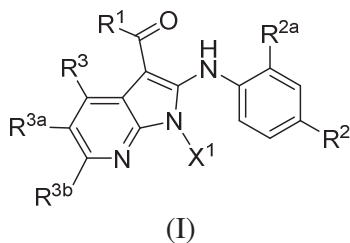
targets in each of the four MAP kinase signaling pathways. Two of these MEK proteins, MEK1 and MEK2, are closely related and participate in this signaling pathway cascade. Inhibitors of MEK1 and MEK2 have been shown to effectively inhibit MEK signaling downstream of Ras, and thus provide a rationale for targeting MEK in the treatment of NF1. (Rice *et al. Medicinal Chemistry Letters* 3:416-421, 2012).

**[0005]** Currently available MEK inhibitors are designed to have oral bioavailability for systemic delivery, and are associated with significant side effects including decreased left ventricular ejection fraction, elevated creatine phosphokinase, pneumonitis, renal failure, diarrhea, infection, urticaria, and maculo-papular rash, all of which are dose limiting or require permanent discontinuation. Moreover, clinical trials have shown side effects with prolonged high-dose administration of MEK inhibitors. (Huang *et al. J. Ocul. Pharmacol. Ther.* 25:519–530, 2009). For example, PD0325901, a clinically-tested MEK inhibitor, has exhibited neurological side effects associated with ataxia, confusion, and syncope. In addition, a number of other side effects have been observed with systemic exposure to MEK inhibitors including: acneiform rash, CPK elevation, nausea, vomiting, diarrhea, abdominal pain, and fatigue. Thus, there is a need for therapies that inhibit MEK to treat NF1 associated dermal neurofibromas or cutaneous neurofibromas, which limit one or more of these serious side effects.

## SUMMARY

**[0006]** Disclosed herein are compounds, pharmaceutical compositions comprising the compounds, and methods of using the compounds and compositions for treating dermal diseases or dermal disorders associated therewith. Also disclosed herein are methods of treating diseases or disorders in a mammal comprising administering a therapeutically or prophylactically effective amount of a compound or composition disclosed herein to a mammal. In an example, the mammal is a human.

**[0007]** In one aspect, the present disclosure refers to a Compound of Formula (I):



where

each R<sup>10</sup> is independently hydrogen, halo, hydroxy, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>-hydroxyalkyl, halo- C<sub>1</sub>-C<sub>6</sub>-alkyl, amino-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>6</sub>-alkyl, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, heterocycloalkyl, or heteroaryl; or an N-oxide, a stereoisomer, mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

**[0007a]** In another aspect, the present disclosure refers to a pharmaceutical composition comprising a Compound as disclosed herein and a pharmaceutically acceptable carrier. In yet another aspect, the present disclosure refers to the use of the Compound as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a MEK-inhibitor responsive disorder, MEK-inhibitor responsive dermal disorder, MEK-mediated disorder, or a MEK-mediated dermal disorder.

**[0008]** In an example, also disclosed herein are pharmaceutical compositions, single unit dosage forms, and kits suitable for use in treating a MEK-inhibitor responsive disorder or disease, MEK-inhibitor responsive dermal disorder or disease, MEK-mediated disorder or disease, or a MEK-mediated dermal disorder or disease which comprise a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments, of Formula (I)-(Iu) and the claims, and compounds in Embodiment A.

**[0009]** In an example, also disclosed herein is a method of treatment of MEK-inhibitor responsive disorder or disease, MEK-inhibitor responsive dermal disorder or disease, MEK-mediated disorder or disease, or a MEK-mediated dermal disorder or disease is provided comprising administering to an individual in need thereof a therapeutically or prophylactically effective amount of a compound described herein, *e.g.*, of some or any of the embodiments, of Formula (I)-(Iu) and the claims, and compounds in Embodiment A.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0010] Figure 1a and 1b.** demonstrate the suppression of pERK by the compound of Ex. 2 in human cutaneous neurofibroma (cNF) explants, obtained according to Biological Example 7.

**[0011] Figure 2.** demonstrates the suppression of p-ERK in human cNF explants with 500 nM of the compound of Ex. 2, obtained according to Biological Example 7.

**[0012] Figure 3.** demonstrates the dose-dependent suppression of p-ERK with the compound of Ex. 2 in human cNF explants, obtained according to Biological Example 7.

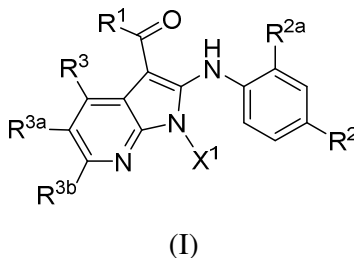
**[0013]** **Figure 4.** demonstrates that p-ERK was suppressed after application of a topical gel comprising Compound of Ex. 2 in Human cNF Explants, obtained according to Biological Example 7.

#### DESCRIPTION OF EXEMPLARY EMBODIMENTS

**[0014]** Provided herein are compounds, pharmaceutical compositions comprising the compounds, and methods of using the compounds and compositions in the treatment of a MEK-inhibitor responsive disorder or disease, MEK-inhibitor responsive dermal disorder or disease, MEK-mediated disorder or disease, or a MEK-mediated dermal disorder or disease.

## WHAT IS CLAIMED IS:

1. A compound of Formula (I):



where

$R^1$  is  $-OR^4$ ,  $-NR^5R^{5a}$ , or an N-linked heterocycloalkyl where the N-linked heterocycloalkyl is optionally substituted with one or two  $R^{10}$ ;

$R^{2a}$  is halo or  $C_1$ - $C_6$  alkyl;

$R^2$  is  $-S$ - $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl, or halo;

$X^1$  is  $C_1$ - $C_6$  alkyl;

$R^3$ ,  $R^{3a}$ , and  $R^{3b}$  are independently hydrogen,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $-S$ - $C_1$ - $C_6$  alkyl, halo,  $C_1$ - $C_6$  alkoxy,  $C_3$ - $C_8$ -cycloalkyloxy, heterocycloalkyloxy, heteroaryloxy, or phenoxy where each phenyl and heteroaryl is independently optionally substituted with 1, 2, or 3  $R^6$ ;

$R^4$  is  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_8$  cycloalkyl,  $C_3$ - $C_8$  cycloalkylalkyl,  $C_1$ - $C_6$  hydroxyalkyl, or  $C_1$ - $C_6$  alkoxyalkyl;

$R^5$  is hydrogen;  $C_1$ - $C_6$  alkyl optionally substituted with one heterocycloalkyl;  $C_3$ - $C_8$  cycloalkyl;  $C_3$ - $C_8$  cycloalkyl- $C_1$ - $C_6$ -alkyl;  $C_1$ - $C_6$  hydroxyalkyl;  $C_1$ - $C_6$  alkoxy- $C_1$ - $C_6$ -alkyl; or  $-OR^{5b}$ ;

$R^{5a}$  is hydrogen or  $C_1$ - $C_6$  alkyl;

$R^{5b}$  is hydrogen,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_8$  cycloalkyl,  $C_3$ - $C_8$  cycloalkyl- $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$  hydroxyalkyl, or  $C_1$ - $C_6$  alkoxy- $C_1$ - $C_6$ -alkyl;

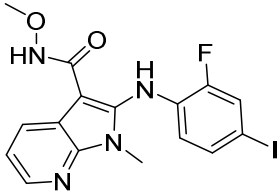
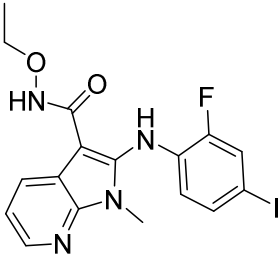
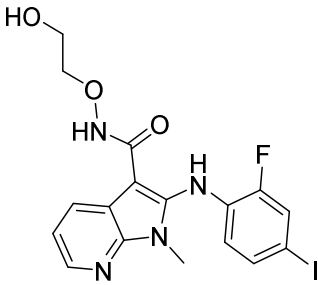
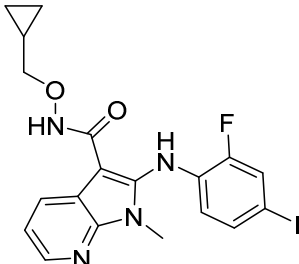
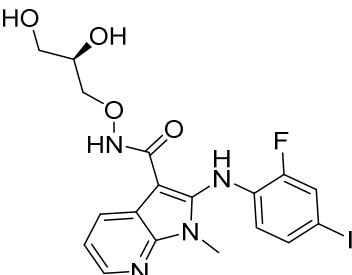
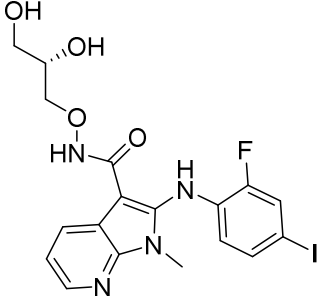
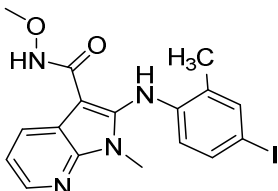
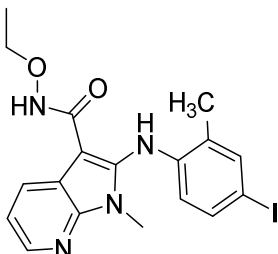
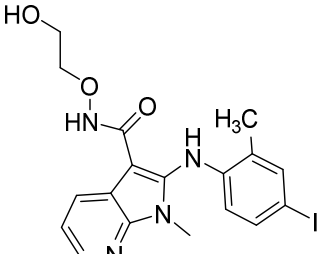
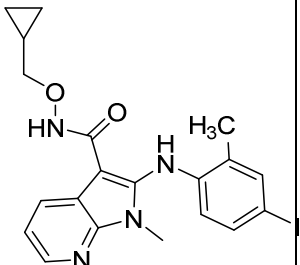
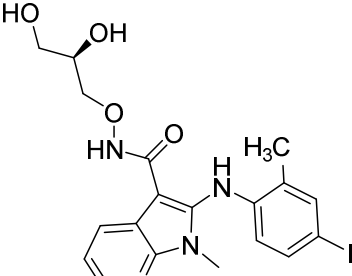
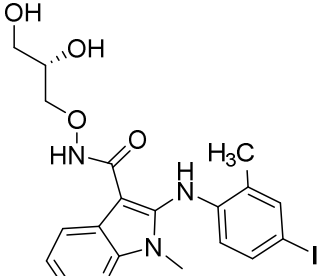
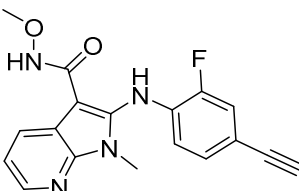
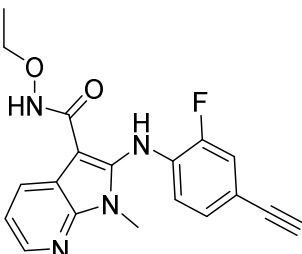
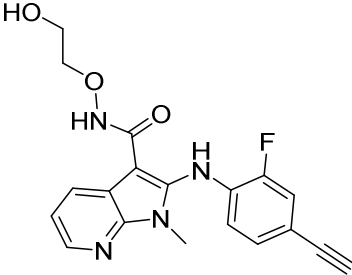
each  $R^6$  is independently selected from the group consisting of carboxy,  $C_1$ - $C_6$ -alkoxycarbonyl,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -haloalkyl,  $C_1$ - $C_6$ -alkoxy- $C_1$ - $C_6$ -alkyl,  $C_3$ - $C_8$  cycloalkyl, heterocycloalkyl,  $-OC(O)R^7$ ,  $-OS(O)_2R^7$ ,  $-O$ - $C_1$ - $C_6$ -haloalkyl,  $C_3$ - $C_8$  cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, amino,  $C_1$ - $C_6$ -alkylamino, di- $C_1$ - $C_6$ -alkylamino,  $-NR^{8a}S(O)_2R^8$ ,  $-NR^{8a}C(O)R^8$ ,  $-S(O)_2R^8$ ,  $-S(O)_2NR^{8a}R^8$ ,  $-C(O)R^8$ ,  $-C(O)NR^{8a}R^8$ , and  $-C_1$ - $C_6$ -alkylene- $R^{6a}$ ;

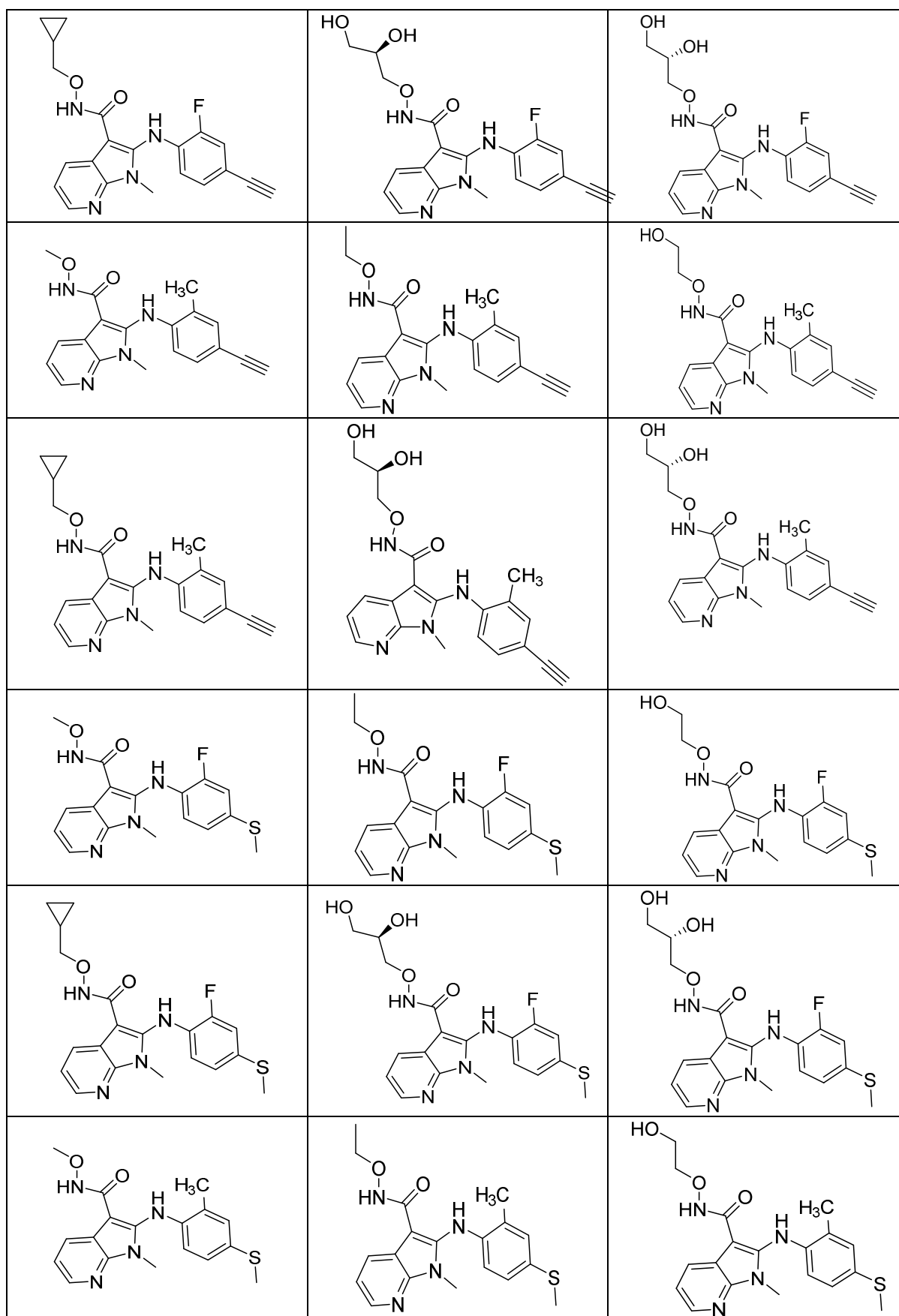
- each  $R^{6a}$  is independently selected from the group consisting of  $C_3$ - $C_8$  cycloalkyl, heterocycloalkyl,  $-NH_2$ ,  $-NH(C_1-C_6\text{-alkyl})$ ,  $-N(C_1-C_6\text{-alkyl})_2$ ,  $-NR^{9a}S(O)_2R^9$ ,  $-NR^{9a}C(O)R^9$ ,  $-S(O)_2R^9$ ,  $-S(O)_2NR^{9a}R^9$ ,  $-C(O)R^9$ , and  $-C(O)NR^{9a}R^9$ ;
- each  $R^7$  is independently selected from the group consisting of amino,  $C_1$ - $C_6$ -alkylamino, di- $C_1$ - $C_6$ -alkylamino,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_8$  cycloalkyl,  $C_1$ - $C_6$ -alkoxy, heterocycloalkyl, aryl, and heteroaryl;
- each  $R^{8a}$  and  $R^{9a}$  is independently H or  $C_{1-6}$  alkyl;
- each  $R^8$  and  $R^9$  is independently  $C_1$ - $C_6$  alkyl, aryl, heteroaryl,  $C_3$ - $C_8$  cycloalkyl, or heterocycloalkyl; and
- each  $R^{10}$  is independently hydrogen, halo, hydroxy, oxo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  hydroxyalkyl,  $C_1$ - $C_6$  haloalkyl, amino- $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_6$ -alkyl, di- $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -alkoxy,  $C_3$ - $C_8$  cycloalkyl, heterocycloalkyl, or heteroaryl;
- or an N-oxide, a stereoisomer, mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.
2. The compound of claim 1 wherein  $X^1$  is  $C_1$ - $C_3$  alkyl.
  3. The compound of claim 1 or 2 wherein  $X^1$  is  $-CH_3$ .
  4. The compound of any one of claims 1-3 wherein at least one of  $R^3$ ,  $R^{3a}$ , and  $R^{3b}$  is  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $-S-C_1$ - $C_6$  alkyl, halo,  $C_1$ - $C_6$  alkoxy,  $C_3$ - $C_8$  cycloalkyloxy, heterocycloalkyloxy, heteroaryloxy, or phenoxy, where each phenyl and heteroaryl is independently optionally substituted with 1, 2, or 3  $R^6$ .
  5. The compound of any one of claims 1-4 wherein one of  $R^3$ ,  $R^{3a}$ , and  $R^{3b}$  is methyl.
  6. The compound of any one of claims 1-5 wherein  $R^{3a}$  is methyl and  $R^3$  and  $R^{3b}$  are each hydrogen.
  7. The compound of any one of claims 1-4 wherein one of  $R^3$ ,  $R^{3a}$ , and  $R^{3b}$  is methoxy.
  8. The compound of any one of claims 1-4 and 7 where  $R^{3a}$  is methoxy and  $R^3$  and  $R^{3b}$  are each hydrogen.
  9. The compound of any one of claims 1-4 wherein one of  $R^3$ ,  $R^{3a}$ , and  $R^{3b}$  is fluoro.
  10. The compound of any one of claims 1-4 and 9 where  $R^{3a}$  is fluoro and  $R^3$  and  $R^{3b}$  are each hydrogen.
  11. The compound of any one of claims 1-4 wherein  $R^3$  and  $R^{3b}$  are each hydrogen and  $R^{3a}$  is  $C_1$ - $C_6$  alkyl, halo, or  $C_1$ - $C_6$  alkoxy.
  12. The compound of any one of claims 1-4 wherein  $R^3$  and  $R^{3b}$  are each hydrogen and  $R^{3a}$  is methyl, fluoro, or methoxy.

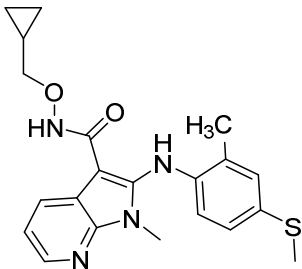
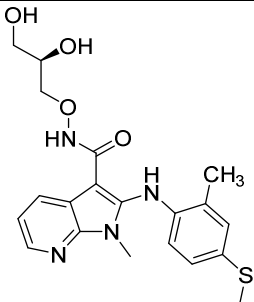
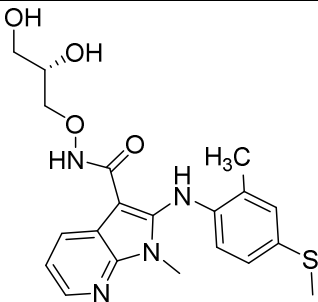
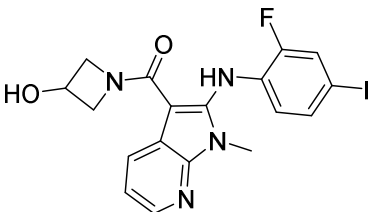
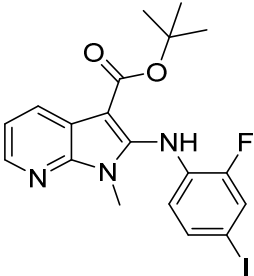
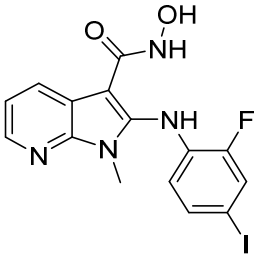
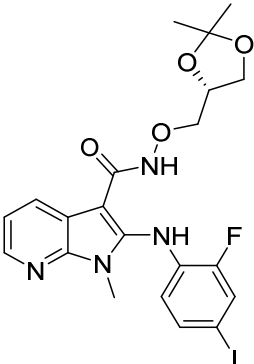
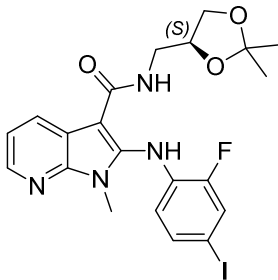
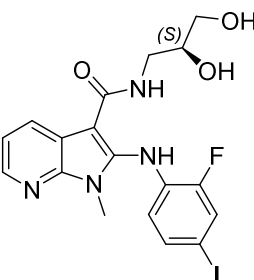
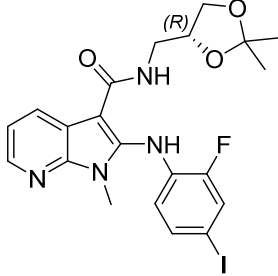
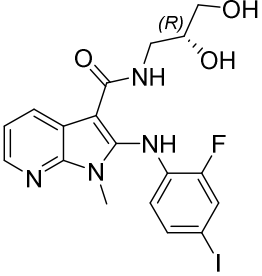
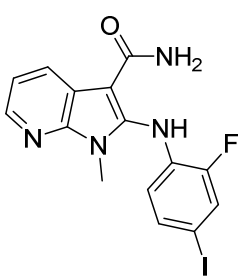
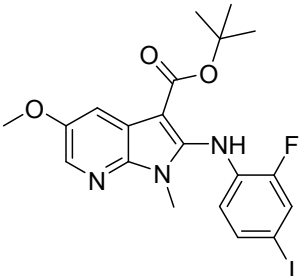
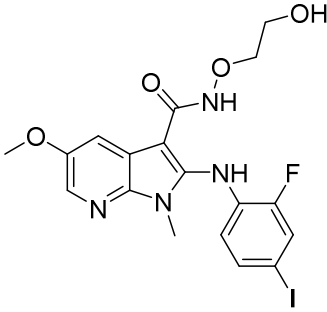
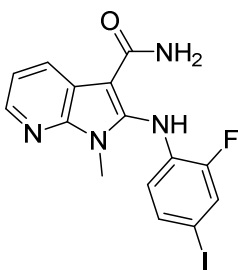
13. The compound of any one of claims 1-3 wherein  $R^3$ ,  $R^{3a}$ , and  $R^{3b}$  are hydrogen.
14. The compound of any one of claims 1-13 wherein  $R^2$  is -S-C<sub>1</sub>-C<sub>6</sub> alkyl.
15. The compound of any one of claims 1-14 wherein  $R^2$  is -SCH<sub>3</sub>.
16. The compound of any one of claims 1-13 wherein  $R^2$  is C<sub>1</sub>-C<sub>6</sub> alkyl.
17. The compound of any one of claims 1-13 and 16 wherein  $R^2$  is CH<sub>3</sub>.
18. The compound of any one of claims 1-13 wherein  $R^2$  is C<sub>2</sub>-C<sub>6</sub> alkenyl.
19. The compound of any one of claims 1-13 and 18 wherein  $R^2$  is C<sub>2</sub>-C<sub>4</sub> alkenyl.
20. The compound of any one of claims 1-13 wherein  $R^2$  is C<sub>2</sub>-C<sub>6</sub> alkynyl.
21. The compound of any one of claims 1-13 and 20 wherein  $R^2$  is C<sub>2</sub>-C<sub>3</sub> alkynyl.
22. The compound of any one of claims 1-13 wherein  $R^2$  is halo.
23. The compound of any one of claims 1-13 and 22 wherein  $R^2$  is iodo.
24. The compound of any one of claims 1-23 wherein  $R^{2a}$  is C<sub>1</sub>-C<sub>6</sub> alkyl.
25. The Compound of any one of claims 1-24 wherein  $R^{2a}$  is methyl.
26. The compound of any one of claims 1-23 wherein  $R^{2a}$  is halo.
27. The Compound of any one of claims 1-23 and 26 where  $R^{2a}$  is fluoro.
28. The compound of any one of claims 1-27 wherein  $R^1$  is an N-linked heterocycloalkyl optionally substituted with one or two  $R^{10}$ .
29. The compound of any one of claims 1-27 wherein  $R^1$  is -OR<sup>4</sup> or -NR<sup>5</sup>R<sup>5a</sup>.
30. The compound of any one of claims 1-27 and 29 wherein  $R^1$  is -OR<sup>4</sup>.
31. The compound of any one of claims 1-27 and 29 wherein  $R^1$  is -NR<sup>5</sup>R<sup>5a</sup>.
32. The compound of any one of claims 1-27, 29, and 30 wherein  $R^1$  is -OR<sup>4</sup> and  $R^4$  is C<sub>1</sub>-C<sub>6</sub> alkyl.
33. The compound of any one of claims 1-27, 29, and 30 wherein  $R^1$  is -OR<sup>4</sup> and  $R^4$  is C<sub>3</sub>-C<sub>8</sub> cycloalkyl.
34. The compound of any one of claims 1-27, 29, and 30 wherein  $R^1$  is -OR<sup>4</sup> and  $R^4$  is C<sub>3</sub>-C<sub>8</sub> cycloalkyl-C<sub>1</sub>-C<sub>6</sub>-alkyl.
35. The compound of any one of claims 1-27, 29, and 30 wherein  $R^1$  is -OR<sup>4</sup> and  $R^4$  is C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl.
36. The compound of any one of claims 1-27, 29, and 30 wherein  $R^1$  is -OR<sup>4</sup> and  $R^4$  is C<sub>1</sub>-C<sub>6</sub> alkoxyalkyl.
37. The compound of any one of claims 1-27, 29, and 31 wherein  $R^1$  is -NR<sup>5</sup>R<sup>5a</sup> and  $R^5$  is unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl.
38. The compound of any one of claims 1-27, 29, and 31 wherein  $R^1$  is -NR<sup>5</sup>R<sup>5a</sup> and  $R^5$  is C<sub>3</sub>-C<sub>8</sub> cycloalkyl.

39. The compound of any one of claims 1-27, 29, and 31 wherein  $R^1$  is  $-NR^5R^{5a}$  and  $R^5$  is  $C_3-C_8$  cycloalkyl- $C_1-C_6$ -alkyl-.
40. The compound of any one of claims 1-27, 29, and 31 wherein  $R^1$  is  $-NR^5R^{5a}$  and  $R^5$  is  $C_1-C_6$  hydroxyalkyl.
41. The compound of any one of claims 1-27, 29, and 31 wherein  $R^1$  is  $-NR^5R^{5a}$  and  $R^5$  is  $C_1-C_6$  alkoxy- $C_1-C_6$ -alkyl.
42. The compound of any one of claims 1-27, 29, and 31 wherein  $R^1$  is  $-NR^5R^{5a}$  and  $R^5$  is  $-OR^{5b}$ .
43. The compound of any one of claims 1-27, 29, 31, and 42 wherein  $R^1$  is  $-NR^5R^{5a}$ ,  $R^5$  is  $-OR^{5b}$ , and  $R^{5b}$  is  $C_1-C_6$  alkyl.
44. The compound of any one of claims 1-27, 29, 31, and 42 wherein  $R^1$  is  $-NR^5R^{5a}$ ,  $R^5$  is  $-OR^{5b}$ , and  $R^{5b}$  is  $C_3-C_8$  cycloalkyl.
45. The compound of any one of claims 1-27, 29, 31, and 42 wherein  $R^1$  is  $-NR^5R^{5a}$ ,  $R^5$  is  $-OR^{5b}$ , and  $R^{5b}$  is  $C_3-C_8$  cycloalkyl- $C_1-C_6$ -alkyl.
46. The compound of any one of claims 1-27, 29, 31, and 42 wherein  $R^1$  is  $-NR^5R^{5a}$ ,  $R^5$  is  $-OR^{5b}$ , and  $R^{5b}$  is cyclopropylmethyl.
47. The compound of any one of claims 1-27, 29, 31, and 42 wherein  $R^1$  is  $-NR^5R^{5a}$ ,  $R^5$  is  $-OR^{5b}$ , and  $R^{5b}$  is  $C_1-C_6$  hydroxyalkyl.
48. The compound of any one of claims 1-27, 29, 31, and 47 wherein  $R^1$  is  $-NR^5R^{5a}$ ,  $R^5$  is  $-OR^{5b}$ , and  $R^{5b}$  is an unbranched  $C_1-C_6$  hydroxyalkyl.
49. The compound of any one of claims 1-27, 29, 31, 42, 47, and 48 wherein  $R^1$  is  $-NR^5R^{5a}$ ,  $R^5$  is  $-OR^{5b}$ , and  $R^{5b}$  is  $C_1-C_6$  hydroxyalkyl where the  $C_1-C_6$  alkyl in  $C_1-C_6$  hydroxyalkyl is substituted with one hydroxy.
50. The compound of any one of claims 1-27, 29, 31, and 42 wherein  $R^1$  is  $-NR^5R^{5a}$ ,  $R^5$  is  $-OR^{5b}$ , and  $R^{5b}$  is  $C_1-C_6$  alkoxy- $C_1-C_6$ -alkyl.
51. The compound of any one of claims 1-27, 29, and 31 wherein  $R^1$  is  $-NR^5R^{5a}$  and  $R^5$  is  $C_1-C_6$  alkyl substituted with one heterocycloalkyl.
52. The compound of any one of claims 1-27, 29, 31, and 37-51 wherein  $R^1$  is  $-NR^5R^{5a}$  and  $R^{5a}$  is hydrogen.
53. The compound of any one of claims 1-27, 29, 31, and 37-51 wherein  $R^1$  is  $-NR^5R^{5a}$  and  $R^{5a}$  is  $C_1-C_6$  alkyl.
54. The compound of any one of claims 1-27 wherein  $R^1$  is  $-NH-O-CH_2CH_2OH$ .
55. The compound of any one of claims 1-27 wherein  $R^1$  is  $-NH-O-CH_2$ (cyclopropyl).

56. The Compound of claim 1 which is selected from the group consisting of:

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or a stereoisomer, mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

57. The Compound of any one of claims 1-56, exhibiting a half-life of less than or equal to about 60 minutes, less than or equal to about 45 minutes, less than or equal to about 30 minutes, or less than or equal to about 20 minutes; optionally wherein the half-life is measured using an assay substantially as described in Biological Example 3, optionally using human liver S9 fraction.

58. A pharmaceutical composition comprising a Compound of any one of claims 1-57 and a pharmaceutically acceptable carrier.

59. Use of the Compound of any one of claims 1-57 or the pharmaceutical composition of claim 58 in the manufacture of a medicament for treating a MEK-inhibitor responsive disorder, MEK-inhibitor responsive dermal disorder, MEK-mediated disorder, or a MEK-mediated dermal disorder .

60. The use of claim 59 wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is selected from the group consisting of a dermal rasopathy, a neurofibromatosis type 1, a cutaneous neurofibroma, a subdermal neurofibroma, and a superficial plexiform neurofibroma.

61. The use of claim 59 wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is neurofibromatosis type 1.

62. The use of claim 59 wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is a cutaneous neurofibroma.

63. The use of claim 59 wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is a subdermal neurofibroma.

64. The use of claim 59 wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is a superficial plexiform neurofibroma.

65. The use of claim 58 or 59 wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is a dermal rasopathy.

66. The use of claim 65 wherein the dermal rasopathy is selected from the group consisting of psoriasis, keratocanthoma (KA), hyperkeratosis, papilloma, Noonan syndrome (NS), cardiofaciocutaneous syndrome (CFC), Costello syndrome (faciocutaneoskeletal syndrome or FCS syndrome), oculoectodermal syndrome, cafe au lait spots, pyogenic granuloma, sebaceous gland hyperplasia, cutaneous neurofibromas, seborrheic keratosis, sebaceous hyperplasia, seborrheic keratosis, and Multiple lentigines syndrome (formerly called Leopard syndrome).

67. The use of any one of claims 59-66 wherein in the compound or composition is to be administered topically, subcutaneously, transdermally, intradermally, or intralesionally.