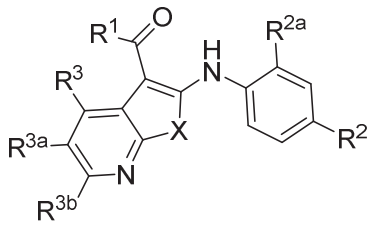
MEK1 and MEK2, are closely related and participate in this signaling pathway cascade. Inhibitors of MEK1 and MEK2 have been shown to effectively inhibit MEK signaling downstream of Ras, and thus provide a rationale for targeting MEK in the treatment of NF1. (Rice *et al. Medicinal Chemistry Letters* 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, uticaria, 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.

[0006a] In one aspect, the present disclosure refers to a compound of Formula (I):



(I)

where

R^1 is $-OR^4$ or $-NR^5R^{5a}$;

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 is -S- or -O-; and when X is -S- and R^3, R^{3a}, and R^{3b} are hydrogen, then R^2 is C_2-C_6 alkenyl, C_2-C_6 alkynyl, or -S-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, 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 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-alkyl), -N(C_1-C_6-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;

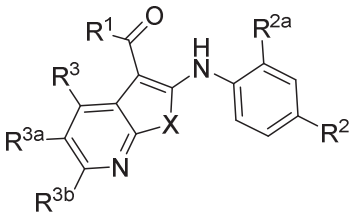
each R^{8a} and R^{9a} is independently H or $C_{1\text{-}6}$ alkyl; and

each R^8 and R^9 is independently C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_8 cycloalkyl, or heterocycloalkyl;

or an N-oxide, a stereoisomer, mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

[0006b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a Compound of the present disclosure and a pharmaceutically acceptable carrier. In yet another aspect, the present disclosure refers to the use of the compound of the present disclosure or a pharmaceutical composition of the present disclosure in the manufacture of a medicament for treating a MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder.

[0007] In one example, disclosed herein is a Compound of Formula (IA):



(IA)

where

each R^{10} is independently hydrogen, halo, hydroxy, oxo, C_1-C_6 alkyl, C_1-C_6-hydroxyalkyl, halo- C_1-C_6-alkyl, 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.

[0008] In another example, 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 (IA), Formula (I), Formula (I-P), Formula (Ia)-(Iu), or Formula (II), as described herein, and the claims, and compounds in Embodiment A.

[0009] In another example, there is also disclosed 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 (IA), Formula (I), Formula (I-P), Formula (Ia)-(Iu), or Formula (II), as described herein and the claims, and compounds in Embodiment A.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figure 1. shows suppression of p-ERK in human cutaneous neurofibroma explants after treatment with Compound of Example 8 in a topical gel formulation (1%).

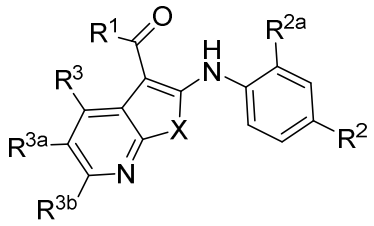
[0011] Figure 2. shows suppression of p-ERK in human cutaneous neurofibroma explants after treatment with Compound of Example 8 in a Topical Gel Formulation (1%) .

DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0012] 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. Also provided herein are methods of 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 in a mammal comprising administering a therapeutically or prophylactically effective amount of a compound or composition to a mammal. In an embodiment, the mammal is a human.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

where

R^1 is $-OR^4$ or $-NR^5R^{5a}$;

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 is -S- or -O-; and when X is -S- and R^3, R^{3a}, and R^{3b} are hydrogen, then R^2 is C_2-C_6 alkenyl, C_2-C_6 alkynyl, or -S-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, 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 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-alkyl), $-N(C_1$-C_6-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; and

each R^8 and R^9 is independently C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_8 cycloalkyl, or heterocycloalkyl;

or an N-oxide, a stereoisomer, mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein X is -O-.

3. The compound of claim 1 wherein X is -S-.

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^{3b} is methyl and R^3 and R^{3a} 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^{3b} is methoxy and R^3 and R^{3a} 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^{3b} is fluoro and R^3 and R^{3a} are each hydrogen.

11. The compound of any one of claims 1-4 wherein R^3, R^{3a}, and R^{3b} are hydrogen.

12. The compound of any one of claims 1-4 where R^3 and R^{3a} are each hydrogen and R^{3b} is C_1-C_6 alkyl, halo, or C_1-C_6 alkoxy.

13. 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.

14. The compound of any one of claims 1-4 and 13 wherein R^3 and R^{3b} are each hydrogen and R^{3a} is methyl, fluoro, or methoxy.

15. The compound of any one of claims 1-5 wherein R^{3a} is methyl and R^3 and R^{3b} are each hydrogen.

16. The compound of any one of claims 1-4 and 7 wherein R^{3a} is methoxy and R^3 and R^{3b} are each hydrogen.

17. The compound of any one of claims 1-4 and 9 wherein R^{3a} is fluoro and R^3 and R^{3b} are each hydrogen.

18. 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.

19. The compound of any one of claims 1-18 wherein R^2 is -S-C_1-C_6 alkyl.

20. The compound of any one of claims 1-19 wherein R^2 is -SCH_3.

21. The compound of any one of claims 1-18 wherein R^2 is C_1-C_6 alkyl.

22. The compound of any one of claims 1-18 and 21 wherein R^2 is -CH_3.

23. The compound of any one of claims 1-18 wherein R^2 is C_2-C_6 alkenyl.

24. The compound of any one of claims 1-18 and 23 wherein R^2 is C_2-C_4 alkenyl.

25. The compound of any one of claims 1-18 wherein R^2 is C_2-C_6 alkynyl.

26. The compound of any one of claims 1-18 and 25 wherein R^2 is C_2-C_3 alkynyl.

27. The compound of any one of claims 1-18 wherein R^2 is halo.

28. The compound of any one of claims 1-18 and 27 wherein R^2 is iodo.

29. The compound of any one of claims 1-28 wherein R^{2a} is C_1-C_6 alkyl.

30. The Compound of any one of claims 1-29 wherein R^{2a} is methyl.

31. The compound of any one of claims 1-28 wherein R^{2a} is halo.

32. The Compound of any one of claims 1-28 and 31 wherein R^{2a} is fluoro.

33. The compound of any one of claims 1-32 wherein R^1 is -OR^4.

34. The compound of any one of claims 1-33 wherein R^1 is -OR^4 and R^4 is C_1-C_6 alkyl.

35. The compound of any one of claims 1-33 wherein R^1 is -OR^4 and R^4 is branched C_1-C_6 alkyl.

36. The compound of any one of claims 1-33 wherein R^1 is -OR^4 and R^4 is C_3-C_8 cycloalkyl-C_1-C_6-alkyl.

37. The compound of any one of claims 1-33 wherein R^1 is -OR^4 and R^4 is C_1-C_6 hydroxyalkyl.

38. The compound of any one of claims 1-33 wherein R^1 is -OR^4 and R^4 is C_1-C_6 alkoxyalkyl.

39. The compound of any one of claims 1-31 wherein R^1 is -NR^5R^{5a}.

40. The compound of any one of claims 1-32 and 39 wherein R^1 is $-NR^5R^{5a}$ and R^5 is C_1-C_6 alkyl.

41. The compound of any one of claims 1-32 and 39 wherein R^1 is $-NR^5R^{5a}$ and R^5 is C_3-C_8 cycloalkyl.

42. The compound of any one of claims 1-32 and 39 wherein R^1 is $-NR^5R^{5a}$ and R^5 is C_3-C_8 cycloalkyl-C_1-C_6-alkyl-.

43. The compound of any one of claims 1-32 and 39 wherein R^1 is $-NR^5R^{5a}$ and R^5 is C_1-C_6 hydroxyalkyl.

44. The compound of any one of claims 1-32 and 39 wherein R^1 is $-NR^5R^{5a}$ and R^5 is C_1-C_6 alkoxy-C_1-C_6-alkyl.

45. The compound of any one of claims 1-32 and 39 wherein R^1 is $-NR^5R^{5a}$ and R^5 is $-OR^{5b}$.

46. The compound of any one of claims 1-32, 39, and 45 wherein R^1 is $-NR^5R^{5a}$, R^5 is $-OR^{5b}$, and R^{5b} is C_1-C_6 alkyl.

47. The compound of any one of claims 1-32, 39, and 45 wherein R^1 is $-NR^5R^{5a}$, R^5 is $-OR^{5b}$, and R^{5b} is C_3-C_8 cycloalkyl.

48. The compound of any one of claims 1-32, 39, and 45 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.

49. The compound of any one of claims 1-32, 39, and 45 wherein R^1 is $-NR^5R^{5a}$, R^5 is $-OR^{5b}$, and R^{5b} is C_1-C_6 hydroxyalkyl.

50. The compound of any one of claims 1-32, 39, and 45 wherein R^1 is $-NR^5R^{5a}$, R^5 is $-OR^{5b}$, and R^{5b} is an unbranched C_1-C_6 hydroxyalkyl.

51. The compound of any one of claims 1-32, 39, and 45 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.

52. The compound of any one of claims 1-32, 39, and 45 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.

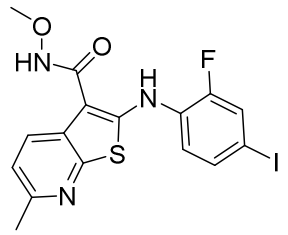
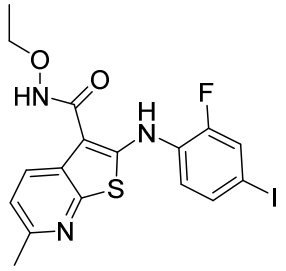
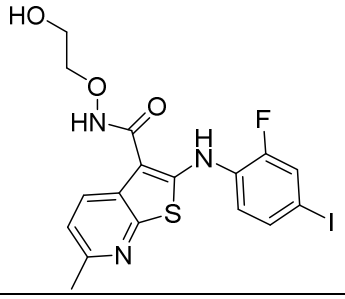
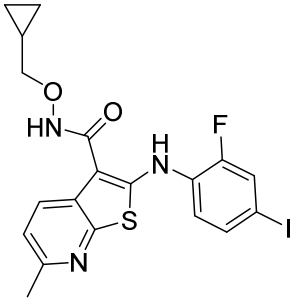
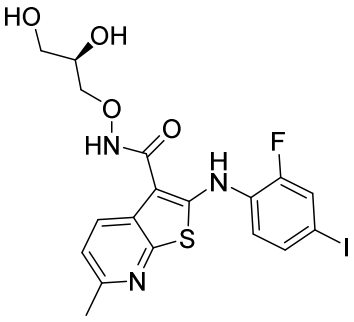
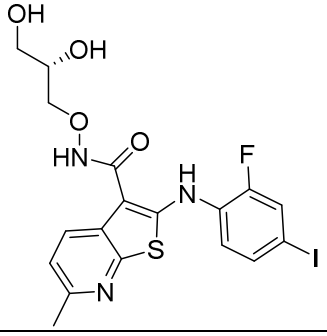
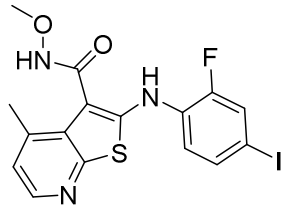
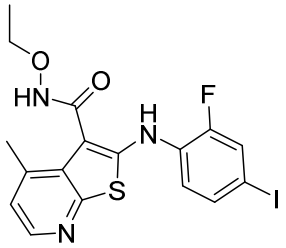
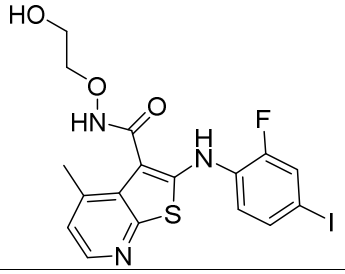
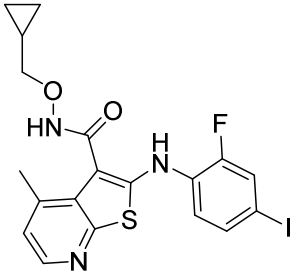
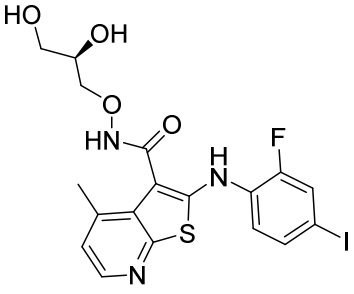
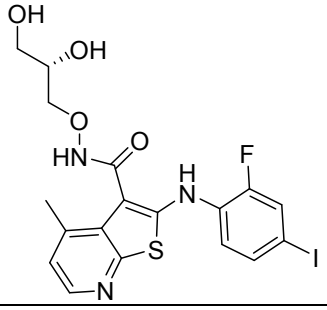
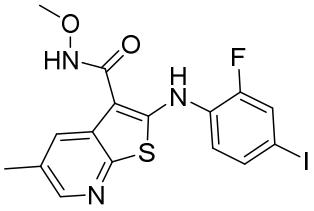
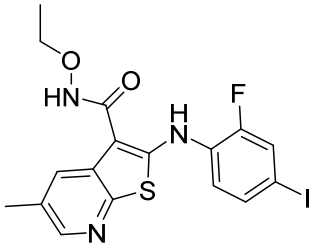
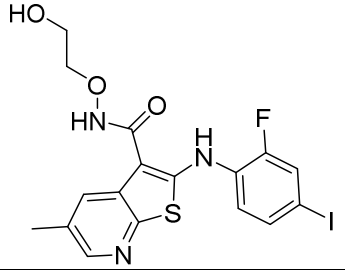
53. The compound of any one of claims 1-23, 25, 27, and 33-43 wherein R^1 is $-NR^5R^{5a}$ and R^{5a} is hydrogen.

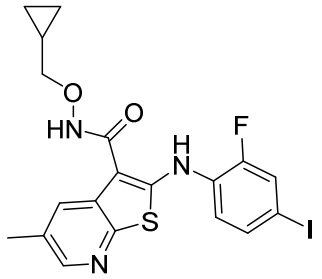
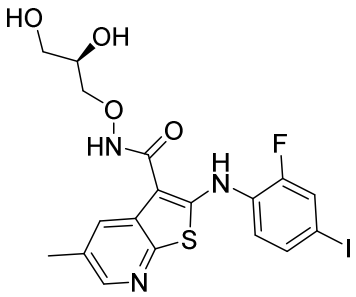
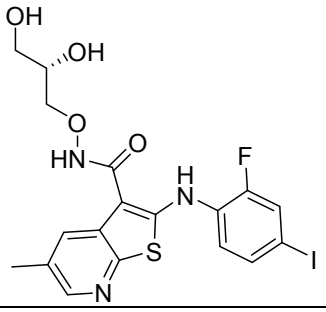
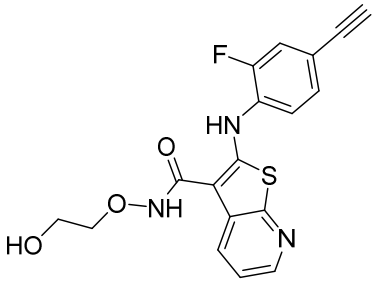
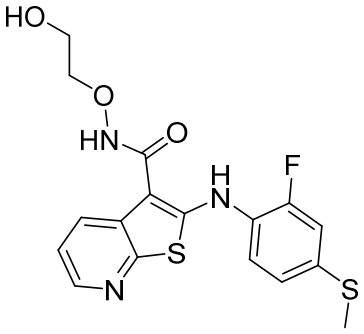
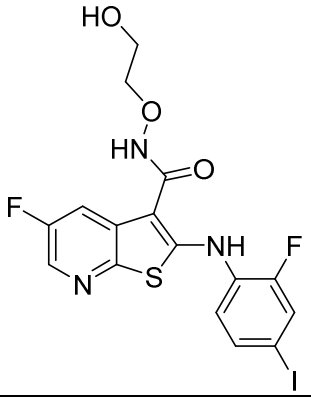
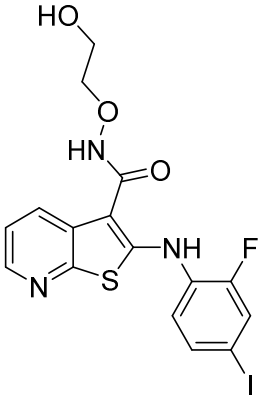
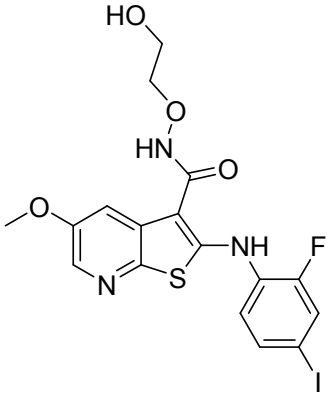
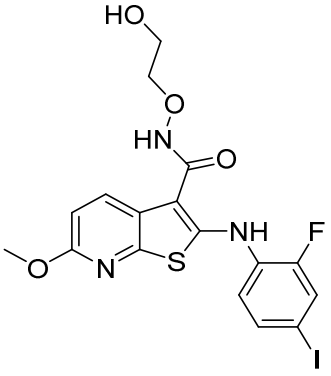
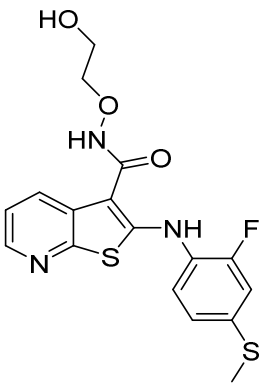
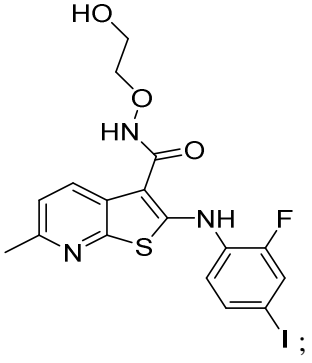
54. The compound of any one of claims 1-23, 25, 27, and 33-43 wherein R^1 is $-NR^5R^{5a}$ and R^{5a} is C_1-C_6 alkyl.

55. The compound of any one of claims 1-32 wherein R^1 is $–NH\text{-}O\text{-}CH_2CH_2OH$.

56. The compound of any one of claims 1-32 wherein R^1 is $–NH\text{-}O\text{-}CH_2$(cyclopropyl).

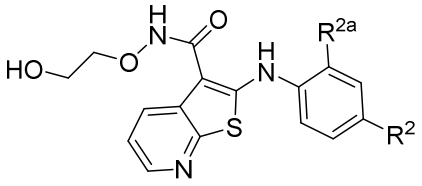
57. The Compound of claim 1 which is selected from the group consisting of:

		
		
		
 and	 ;	

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

58. A Compound of Formula (II):



(II)

where

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

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;

or an N-oxide, a stereoisomer, mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

59. The compound of claim 58 wherein R^2 is C_1-C_6 alkyl, C_2-C_6 alkynyl, or halo.

60. The compound of claim 58 or 59 wherein R^2 and R^{2a} are independently halo.

61. The compound of any one of claims 58-60 wherein R^2 is iodo and R^{2a} is fluoro; or an N-oxide, a stereoisomer, mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

62. The Compound of any one of claims 1-61, 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.

63. A pharmaceutical composition comprising a Compound of any one of claims 1-62 and a pharmaceutically acceptable carrier.

64. Use of the compound of any one of claims 1-62 or a pharmaceutical composition of claim 63 in the manufacture of a medicament for treating a MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder.

65. The use of claim 64 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 dermal neurofibroma, a subdermal neurofibroma, and a superficial plexiform neurofibroma.

66. The use of claim 64 wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is neurofibromatosis type 1.

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

68. The use of claim 64 wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is a subdermal neurofibroma.

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

70. The use of claim 64 or 65 wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is a dermal rasopathy.

71. The use of claim 70 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, and Multiple lentigines syndrome (formerly called Leopard syndrome).

72. The use of any one of claims 64-70 wherein in the compound or composition is to be administered topically, subcutaneously, transdermally, intradermally, or intralesionally.