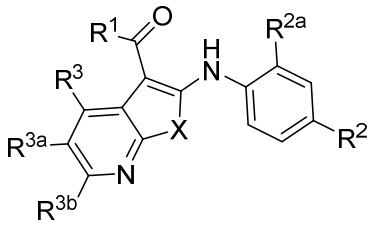
MEK1 and MEK2, are closely related and participate in this signaling pathway cascade. Inhibitors of MEK1 and MEK2 have been shown to effectively inhibit MEK signaling downstream of Ras, and thus provide a rationale for targeting MEK in the treatment of NF1. (Rice *et al. Medicinal Chemistry Letters*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

wherein

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

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-; and when 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, halo, or C_1-C_6 alkoxy;

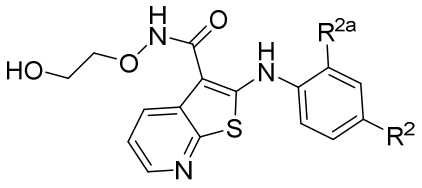
R^5 is $-OR^{5b}$;

R^{5a} is hydrogen; and

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

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 compound of Formula (II):



(II)

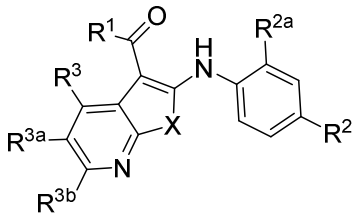
wherein:

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. In yet 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 selected from the group consisting of a dermal rasopathy, a neurofibromatosis type 1, a dermal neurofibroma, a subdermal neurofibroma, and a superficial plexiform neurofibroma.

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

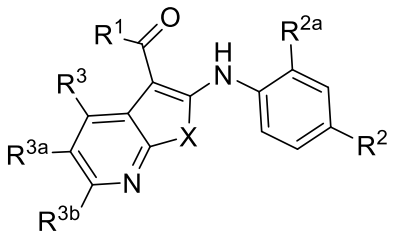


(IA)

where

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

wherein:

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

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-; and when 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, halo, or C_1-C_6 alkoxy;

R^5 is $-OR^{5b}$;

R^{5a} is hydrogen; and

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

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

2. The compound of claim 1, wherein at least one of R^3, R^{3a}, and R^{3b} is C_1-C_6 alkyl, halo, or C_1-C_6 alkoxy.

3. The compound of claim 1 or 2, wherein one of R^3, R^{3a}, and R^{3b} is methyl.

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

5. The compound of claim 1 or 2, wherein one of R^3, R^{3a}, and R^{3b} is methoxy.

6. The compound of any one of claims 1-2 and 5, wherein R^{3b} is methoxy and R^3 and R^{3a} are each hydrogen.

7. The compound of claim 1 or 2, wherein one of R^3, R^{3a}, and R^{3b} is fluoro.

8. The compound of any one of claims 1-2 and 7, wherein R^{3b} is fluoro and R^3 and R^{3a} are each hydrogen.

9. The compound of claim 1, wherein R^3, R^{3a}, and R^{3b} are hydrogen.

10. The compound of claim 1 or 2, wherein R^3 and R^{3a} are each hydrogen and R^{3b} is C_1-C_6 alkyl, halo, or C_1-C_6 alkoxy.

11. The compound of claim 1 or 2, 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 1-2 and 11, 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^{3a} is methyl and R^3 and R^{3b} are each hydrogen.

14. The compound of any one of claims 1-2 and 5, wherein R^{3a} is methoxy and R^3 and R^{3b} are each hydrogen.

15. The compound of any one of claims 1-2 and 7, wherein R^{3a} is fluoro and R^3 and R^{3b} are each hydrogen.

16. The compound of any one of claims 1-15, wherein R^2 is -S-C_1-C_6 alkyl.

17. The compound of any one of claims 1-16, wherein R^2 is -SCH_3.

18. The compound of any one of claims 1-15, wherein R^2 is C_1-C_6 alkyl.

19. The compound of any one of claims 1-15 and 18, wherein R^2 is -CH_3.

20. The compound of any one of claims 1-15, wherein R^2 is C_2-C_6 alkenyl.

21. The compound of any one of claims 1-15 and 20, wherein R^2 is C_2-C_4 alkenyl.

22. The compound of any one of claims 1-15, wherein R^2 is C_2-C_6 alkynyl.

23. The compound of any one of claims 1-15 and 22, wherein R^2 is C_2-C_3 alkynyl.

24. The compound of any one of claims 1-15, wherein R^2 is halo.

25. The compound of any one of claims 1-15 and 24, wherein R^2 is iodo.

26. The compound of any one of claims 1-25, wherein R^{2a} is C_1-C_6 alkyl.

27. The compound of any one of claims 1-26, wherein R^{2a} is methyl.

28. The compound of any one of claims 1-25, wherein R^{2a} is halo.

29. The compound of any one of claims 1-25 and 28, wherein R^{2a} is fluoro.

30. The compound of any one of claims 1-29, wherein R^{5b} is C_3-C_8 cycloalkyl-C_1-C_6-alkyl.

31. The compound of any one of claims 1-29, wherein R^{5b} is C_1-C_6 hydroxyalkyl.

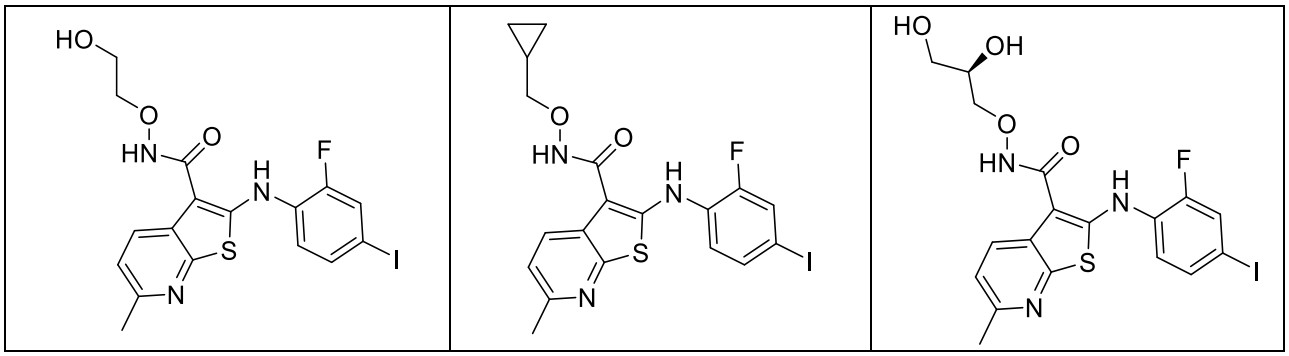
32. The compound of any one of claims 1-29 and 31, wherein R^{5b} is an unbranched C_1-C_6 hydroxyalkyl.

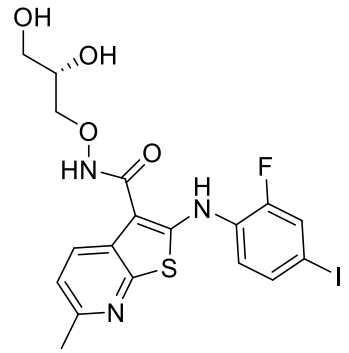
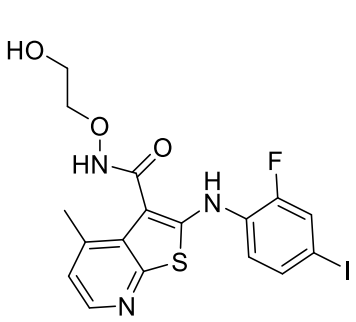
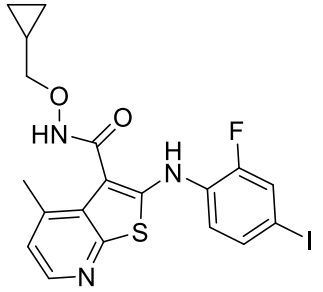
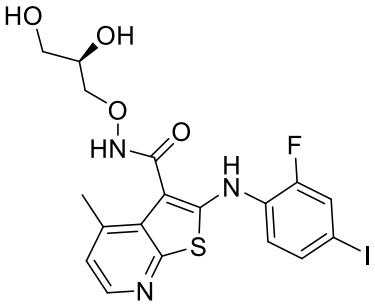
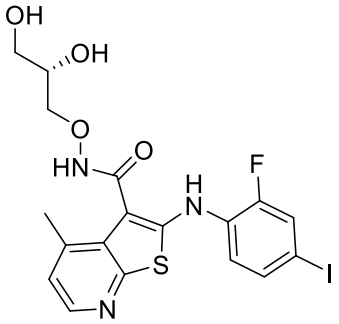
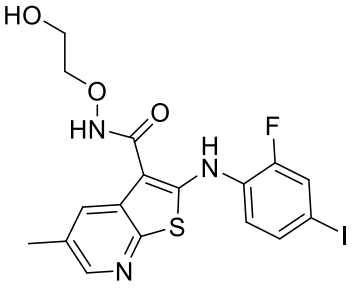
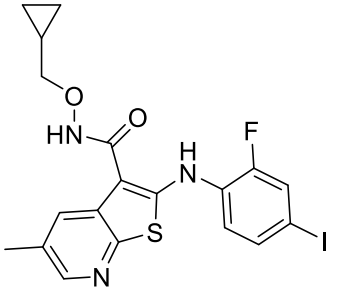
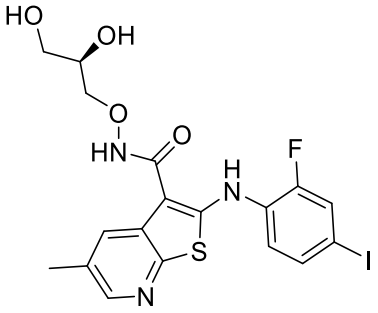
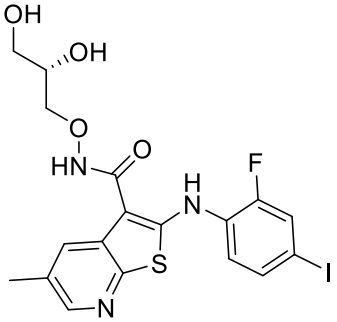
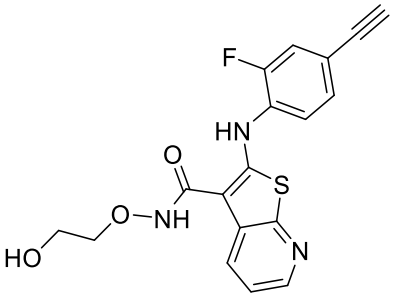
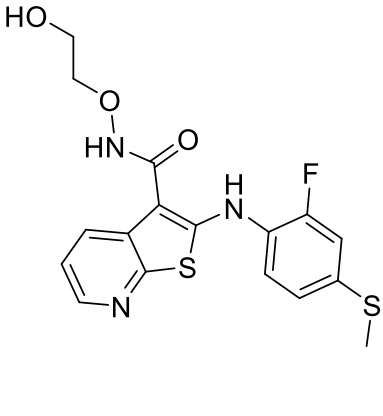
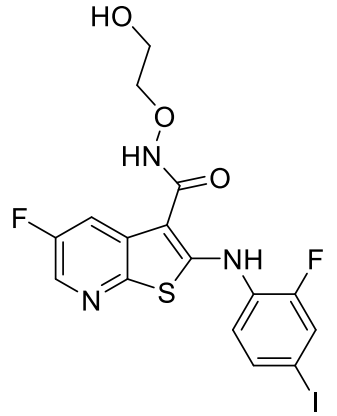
33. The compound of any one of claims 1-29 and 31-32, wherein the C_1-C_6 alkyl in C_1-C_6 hydroxyalkyl is substituted with one hydroxy.

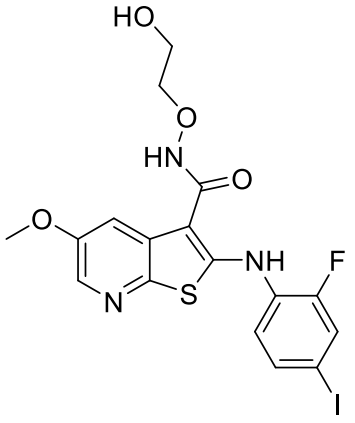
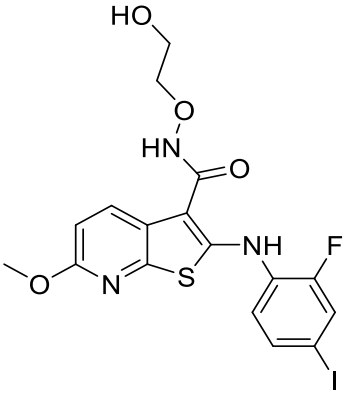
34. The compound of any one of claims 1-29, wherein R^1 is –NH-O-CH_2CH_2OH.

35. The compound of any one of claims 1-29, wherein R^1 is –NH-O-CH_2(cyclopropyl).

36. The compound of claim 1, which is selected from the group consisting of:

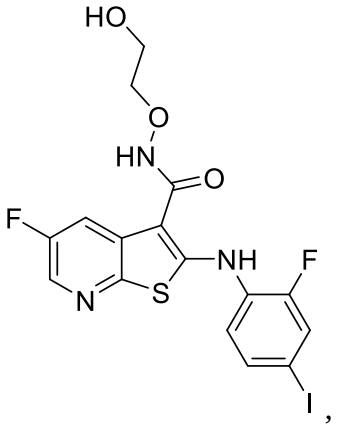


 and	 ;	

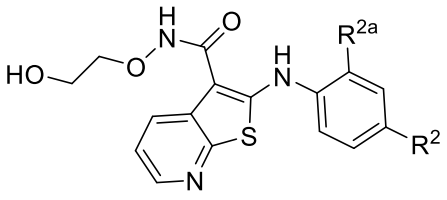
or a stereoisomer, mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

37. The compound of claim 1, represented by the formula:

 ,

or a pharmaceutically acceptable salt thereof.

38. A compound of Formula (II):



(II)

wherein:

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;

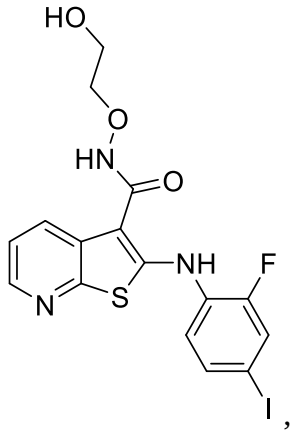
or an N-oxide, a stereoisomer, mixture of stereoisomers, and/or a pharmaceutically acceptable salt thereof.

39. The compound of claim 38, wherein R^2 is -S-C_1-C_6 alkyl, C_2-C_6 alkynyl, or halo.

40. The compound of claim 38 or 39, wherein R^2 and R^{2a} are independently halo.

41. The compound of any one of claims 38-40, wherein R^2 is iodo and R^{2a} is fluoro.

42. The compound of claim 38, represented by formula:



or a pharmaceutically acceptable salt thereof.

43. The compound of any one of claims 1-42, 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 as described in Biological Example 3, optionally using human liver S9 fraction.

44. A pharmaceutical composition comprising a compound of any one of claims 1-43 and a pharmaceutically acceptable carrier.

45. Use of the compound of any one of claims 1-43 or a pharmaceutical composition of claim 44 in the manufacture of a medicament for treating a MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder selected from the group consisting of a dermal rasopathy, a neurofibromatosis type 1, a dermal neurofibroma, a subdermal neurofibroma, and a superficial plexiform neurofibroma.

46. The use of claim 45, wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is neurofibromatosis type 1.

47. The use of claim 45, wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is a dermal neurofibroma.

48. The use of claim 45, wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is a subdermal neurofibroma.

49. The use of claim 45, wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is a superficial plexiform neurofibroma.

50. The use of claim 45, wherein the MEK-inhibitor responsive dermal disorder or a MEK-mediated dermal disorder is a dermal rasopathy.

51. The use of claim 50, 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).

52. The use of any one of claims 45-51, wherein the compound or composition is to be administered topically, subcutaneously, transdermally, intradermally, or intralesionally.